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

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, July 28, 2016 1:00 - 5:00 PM
HP Conference Room
4070 27th Ct. SE
Salem, OR 97302

MEETING AGENDA

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

Public Comment: Public comment will be limited to 3 minutes per person or organization, with a maximum of 10 minutes allotted for public comment period in each section.

Time		
	I. CALL TO ORDER	
1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Approval of Agenda and Minutes	B. Origer (Chair)
	D. Department Update	D. Weston (OHA)
	II. DUR ACTIVITIES	
1:10 PM	A. Quarterly Utilization Reports	R. Citron (OSU)
	B. ProDUR Report	R. Holsapple (HPE)
	C. RetroDUR Report	T. Williams (OSU)
	D. Oregon State Drug Review	K. Sentena (OSU)
	1. "Autism Spectrum Disorder Still Not Linked to the MMR Vaccine: A Review of the Studies since the 1998 Wakefield Study"	
1:20 PM	III. DUR OLD BUSINESS	
	A. Ivacaftor/Lumacaftor (Orkambi™) Concerns	R. Citron (OSU)
	1. Conflict of Interest Declarations	
	a. Updated Form and Process	
	2. Process Recommendations	
	IV. DUR NEW BUSINESS	
1:50 PM	A. ADHD Drug Policy Evaluation	M. Herink (OSU)
	1. Policy Evaluation	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	
	V. PREFERRED DRUG LIST NEW BUSINESS	

2:10 PM	A. Smoking Cessation Drug Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
2:20 PM	B. Drug Class Literature Scans	
	1. Antidepressants	D. Moretz (OSU)
	2. Erythropoiesis Stimulating Agents	D. Moretz (OSU)
	3. Antivirals for Herpes Simplex Virus	K. Sentena (OSU)
	4. Drugs for Benign Prostatic Hypertrophy (BPH)	K. Sentena (OSU)
	5. Anti-Parkinson's Agents	D. Engen (OSU)
	6. Bone Resorption Inhibitors and Related Agents	A. Gibler (OSU)
	7. Public Comment 8. Discussion of Clinical Recommendations to OHA	
3:00 PM	BREAK	
3:10 PM	C. Antiepileptic Drug Class Update 1. Briviact® (brivaracetam) New Drug Evaluation 2. Antiepileptic Drug Literature Scan 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
3:35 PM	D. Direct-acting Oral Anticoagulants Class Update 1. DERP Summary Review 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
3:50 PM	E. Zurampic® (lesinurad) New Drug Evaluation 1. New Drug Evaluation 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Engen (OSU)
4:05 PM	F. Monoclonal Antibodies for Asthma Class Review 1. Class Review/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	M. Herink/ A. Gibler (OSU)
4:20 PM	VI. EXECUTIVE SESSION	
	VII. RECONVENE for PUBLIC RECOMMENDATIONS	
	VIII. ADJOURN	

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Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Residency Faculty	Albany	December 2017
Caryn Mickelson, Pharm.D.	Pharmacist	Pharmacy Director	Coos Bay	December 2017
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2017
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2017
Dave Pass, M.D.	Physician	Medical Director	West Linn	December 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
Kelley Burnett, D.O.	Physician	Pediatric Medical Director	Grants Pass	December 2019

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, May 26, 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; Phillip Levine, PhD; Caryn Mickelson, PharmD; Tracy Klein, PhD, FNP;

Members Present by Phone:

Staff Present: Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD; Dee Weston; Dave Engen, PharmD; Andrew Gibler, PharmD; Kathy Ketchum, RPh. MPA:HA; Kim Wentz, MD; Deanna Moretz, PharmD; Elizabeth Le, PharmD Candidate

Staff Present by Phone: Kathy Sentena, PharmD;

Audience: Lyle Laird (Sunovion Pharmaceuticals)*; Kim Laubmeier (Sunovion Pharmaceuticals)*; Mary Kemhus (Novartis); Joe Schreck (Allergan); Karen Nishihara (Alkermes)*; Laura Litzenberger (Janssen)*; Laurence Ikeda (Pfizer)*; Mike Willett (Pfizzer); Bobbi Jo Drumm (BMS); Jennifer Svec (MedImpact); Barry Benson (Merck); Ann Neilson (ZS Pharma); Bob Gustafson (Lundbeck); John Schillo (Lundbeck); Steven Hill (Relypsa); Beth Clark (Relypsa)*; Samantha Sweeney (Otsuka); Jacob White (UCB); Mindy Schimpf (UCB); Melissa Snider (Biomarin)*; Jill Kerrick Walker, PharmD (Acorda); Heather Williams-Downing (Acorda); Rick Frees (Vertex); Kelli Strother (Otsuka); Don Stecher (Novartis); Jennifer McElravey, RPh (OHSU); Courtney Strouse (OSU COP); Johnathan Nyo (OSU COP); Dean Haxby (OSU); Amy Burns (AllCare Health); Tony Jelinek (Reckitt Benckiser); Jeana Colabianchi, PharmD (Sunovion); Willram Kennon, Rph (Cascadia Health Alliance); Lisa Boyle, Rph (WVP Health Authority); Jennifer Stout Leyden, Rph (WVP); Rayan Shadralch; Paul Monham (Novo Nordisk); Kerry Bonilla (AstraZeneca); Pierre Thoumsin (Pfizer);

(*) Provided verbal testimony

I. CALL TO ORDER

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

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

c. Approval of agenda and minutes presented by Dr. Origer. (pages 4 - 9)

ACTION: Motion, 2nd, All in Favor.

d. Department updates for OHA.

II. DUR ACTIVITIES

a. Quarterly Utilization Reports (pages 27 – 29)
Presented by Mr. Citron.

b. ProDUR Report (pages 15 – 17)
Presented by Mr. Holsapple.

c. RetroDUR Report (pages 18- 22)
Presented by Dr. Williams.

d. Oregon State Drug Reviews (pages 23 – 26)
Presented by Dr. Sentena.

1. 2015 in Review: Relevant Safety Updates and Ongoing Safety Concerns (23 – 24)
2. Antidiabetic Treatments and Cardiovascular Implications (25 – 26)

III. DUR NEW BUSINESS

Abbreviated Clinical Prior Authorization Reviews

a. Ampyra® (dalfampridine) (pages 27 – 29)
Dr. Moretz presented the clinical authorization review.

1. No further research is needed at this time.
2. Maintain current PA policy.

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

b. Kynamro® (mipomersen) and Juxtapid® (lomitapide) (pages 30 – 33)
Dr. Moretz presented the clinical authorization review.

1. No further research is needed at this time.
2. Maintain current PA policy.

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

c. Kuvan® (saproterin) (pages 34 – 36)
Dr. Moretz presented the clinical authorization review.

1. No further research is needed at this time.
2. Maintain PA criteria and update target Phe levels per guideline.

Public Comment:
Melissa Snider from Biomarin gave public comment.

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

IV. PREFERRED DRUG LIST NEW BUSINESS

a. New Drug Evaluations for COPD

1. Utibron™ Neohaler® (indacaterol/ glycopyrrolate) (pages 37 – 49)
   Dr. Sentena presented the new drug evaluation.

   a. Designate GLY as non-preferred due to insufficient evidence.
   b. Designate IND/ GLY as non-preferred and subject to LAMA/LABA PA criteria.
   c. Evaluate comparative costs in executive session.

   No Changes to PMPDP.

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

2. Seebri™ Neohaler® (glycopyrrolate) (pages 37 – 49)
   Dr. Sentena presented the new drug evaluation.

   a. Designate GLY as non-preferred due to insufficient evidence.
   b. Designate IND/ GLY as non-preferred and subject to LAMA/ LABA PA criteria.
   c. Evaluate comparative costs in executive session.

   No Changes to PMPDPD.

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

b. Antipsychotics Drug Class Update (pages 50 – 88)
   Dr. Gibler presented the following class updates.

   1. No changes to the PDL based on the clinical evidence.
   2. Perform and present DUE.
   3. Evaluate comparative costs in executive session.

Public Comment:
Lyle K. Laid, PharmD from Sunovion Pharmaceuticals Inc. gave public comment.
Kim Laubmeier from Sunovion Pharmaceuticals Inc. gave public comment.
Karen Nishihara from Alkermes gave public comment.
Laura Litzenberger from Janssen gave public comment.

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

c. Long-acting Opioids Drug Class Update (pages 89 – 120)
   Dr. Gibler presented the following class update.

   1. No changes to the PDL based on the clinical evidence.
   2. Approve proposed opioid analgesics PA criteria as amended, including:

a. Ask if the opioid prescription is for pain diagnosis associated with back or spine conditions as defined by the OHP list of Prioritized Services, or for migraine headache.
b. Add examples of validated tools that assess functions as outlined in Guideline Note 60 of the OHP List of Prioritized Services

3. Discontinue PAs for Methadone, Opioid/non-opioid fixed dose combination products, and short-acting fentanyl products.
4. Present plan to P&T of how to reach ultimate coverage goal, monitor impact and perform provider education.
5. Evaluate comparative costs in executive session

Public Comment:
Laurence Ikeda from Pfizer gave public comment.

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

d. Smoking Cessation Drug Class Update (pages 121 – 144)
Deferred to future meeting.

e. Cough and Cold Drug Class Update (pages 145 – 156)
Ms. Ketchum presented the following class update.

1. Prefer no expectorants and remove all guaifenesin single ingredient products (HSN = 000271) from the PMPDP.
2. Ensure there is a minimum of 1 product with codeine and 1 with dextromethorphan preferred on the PDL for refractory cough.
3. Expand the pediatric restriction (children 13 years of age and older) to all cough and cold products.
4. Restrict codeine cough products to adults (19 years of age and older) and update Codeine PA criteria to reflect.
5. Evaluate comparative costs in executive session.

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

f. Vyvanse™ (lisdexamfetamine) New Indication Evaluation (pages 157 – 165)
Ms. Ketchum presented the following new indication.

Updated the current PA criteria to include BED indication.

The committee deferred taking action on the proposed changes to the ADHD PA criteria until July when the ADHD DUE will be presented. The committee asked that options be considered for restricting use of Vyvanse for BED to second line therapy in the PA criteria.

ACTION: Deferred to July.

g. Veltassa® (patiromer) New Drug Evaluation (pages 166 – 180)
Dr. Herink presented the following new drug evaluation.

1. Defer PDL decisions until a review of sodium polystyrene sulfonate and zirconium cyclosilicate (awaiting FDA approval) at future P&T meeting.
2. Approve proposed PA criteria to prevent use in the emergent setting or in scenarios not supported by the medical literature.

Public Comment:
Elizabeth Clark from Relypsa gave public comment.

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

h. Zurampic® (lesinurad) New Drug Evaluation (pages 181 – 190)
Deferred to future meeting.

i. Briviact® (brivaracetam) New Drug Evaluation (pages 191 – 200)
Deferred to future meeting.

j. Drug Class Literature Scans

1. Erythropoiesis Stimulating Agents (pages 201 – 207)
Scan deferred to future meeting.

2. Antivirals for Herpes Simplex Virus (pages 208 – 217)
Scan deferred to future meeting.

V. EXECUTIVE SESSION

VI. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

a. New Drug Evaluations for COPD (pages 37 - 49)
***ACTION:** recommend no changes to the PMPDP
Motion, 2nd, All in Favor. Approved.

b. Antipsychotics Drug Class Update (pages 50 – 88)
***ACTION:** Make Latuda™ preferred contingent upon SR.
Make Saphris™ preferred contingent upon SR.
Make Abilify Maintenna preferred contingent upon SR.
Monitor market shift.
Make chlorpromazine voluntary non-preferred (no PA required)
Perform change form request.
Maintain brexpiprazole Voluntary non-preferred.
Maintain cariprazine Voluntary non-preferred.
Motion, 2nd, All in Favor. Approved.

c. Long-acting Opioids Drug Class Update (pages 89 – 120)
ACTION: ~~Approved PA criteria changes~~.
Recommend no changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

d. Cough and Cold Drug Class Update (pages 145 – 156)
***ACTION:** Make benzonatate non-preferred.
Motion, 2nd, All in Favor. Approved.

VII. ADJOURN

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Pharmacy Utilization Summary Report: January 2015 - December 2015

Eligibility	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Avg Monthly
Total Members (FFS & Encounter)	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	1,055,600	1,018,999	1,033,098	1,048,609
FFS Members	157,174	140,889	134,463	130,455	132,476	126,047	135,197	145,013	138,135	143,529	146,793	125,393	137,964
OHP Basic with Medicare	29,283	29,328	29,255	29,480	29,794	29,983	30,262	30,466	30,646	30,825	30,889	30,968	30,098
OHP Basic without Medicare	18,429	17,581	16,680	16,978	16,784	16,112	15,354	14,992	14,714	14,234	14,190	13,045	15,758
ACA	109,462	93,980	88,528	83,997	85,898	79,952	89,581	99,555	92,775	98,470	101,714	81,380	92,108
Encounter Members	870,481	902,590	925,036	950,789	946,363	923,597	894,902	908,964	913,045	912,071	872,206	907,705	910,646
OHP Basic with Medicare	39,105	39,244	39,267	39,566	39,496	39,527	39,574	39,754	39,815	40,037	39,946	39,951	39,607
OHP Basic without Medicare	120,645	116,957	116,321	116,337	113,941	97,164	92,850	90,593	85,877	84,019	73,277	73,440	98,452
ACA	710,731	746,389	769,448	794,886	792,926	786,906	762,478	778,617	787,353	788,015	758,983	794,314	772,587

Gross Cost Figures for Drugs	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	YTD Sum
Total Amount Paid (FFS & Encounter)	$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	$66,447,679	$63,711,667	$69,368,732	$781,121,493
Mental Health Carve-Out Drugs	$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	$10,911,014	$10,466,317	$11,529,032	$130,959,403
OHP Basic with Medicare	$10,229	$10,140	$10,995	$12,864	$11,878	$13,598	$11,082	$8,812	$3,611	$1,048	$778	$1,762	$96,796
OHP Basic without Medicare	$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	$4,857,822	$4,678,572	$5,196,184	$60,854,361
ACA	$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	$6,013,231	$5,729,953	$6,265,953	$69,598,899
FFS Physical Health Drugs	$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	$3,299,096	$3,258,164	$3,004,259	$38,727,184
OHP Basic with Medicare	$249,872	$227,174	$239,842	$228,025	$230,736	$232,816	$263,038	$225,706	$218,199	$212,525	$207,563	$211,099	$2,746,595
OHP Basic without Medicare	$1,294,806	$1,152,932	$1,167,338	$1,049,568	$949,612	$1,008,770	$991,645	$989,033	$953,819	$1,045,522	$996,771	$900,139	$12,499,954
ACA	$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	$1,949,300	$1,976,591	$1,797,537	$22,586,543
FFS Physician Administered Drugs	$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	$1,477,271	$1,299,907	$1,325,372	$18,747,725
OHP Basic with Medicare	$284,529	$245,748	$227,308	$291,911	$253,746	$267,061	$282,746	$273,243	$276,877	$270,912	$243,594	$316,105	$3,233,779
OHP Basic without Medicare	$368,768	$303,421	$344,732	$406,258	$247,313	$385,423	$244,257	$312,171	$280,485	$240,283	$216,877	$286,929	$3,636,917
ACA	$964,378	$819,761	$1,002,613	$697,970	$874,688	$728,455	$865,415	$776,570	$699,925	$771,655	$579,491	$526,759	$9,307,679
Encounter Physical Health Drugs	$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	$43,728,089	$41,861,448	$45,949,060	$503,791,005
OHP Basic with Medicare	$256,990	$242,596	$247,628	$275,801	$267,863	$280,483	$202,208	$212,016	$145,132	$152,195	$141,102	$138,151	$2,562,165
OHP Basic without Medicare	$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	$12,091,542	$11,381,465	$12,435,204	$146,011,199
ACA	$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	$31,278,075	$30,055,920	$33,051,458	$352,868,738
Encounter Physician Administered Drugs	$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	$7,032,209	$6,825,831	$7,561,009	$88,896,176
OHP Basic with Medicare	$232,150	$195,919	$180,188	$186,892	$169,577	$164,069	$162,748	$124,937	$169,114	$121,616	$90,054	$138,295	$1,935,557
OHP Basic without Medicare	$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	$1,868,250	$1,857,513	$1,907,602	$25,372,312
ACA	$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	$4,952,467	$4,753,805	$5,418,430	$60,050,014

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

Last Updated: July 20, 2016

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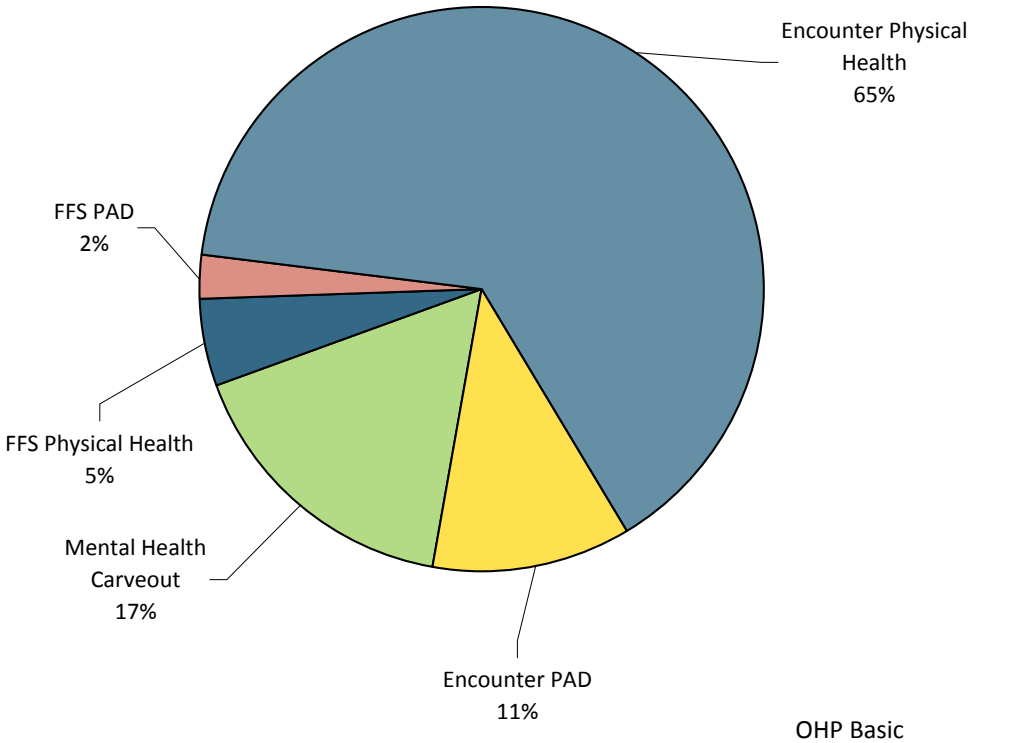
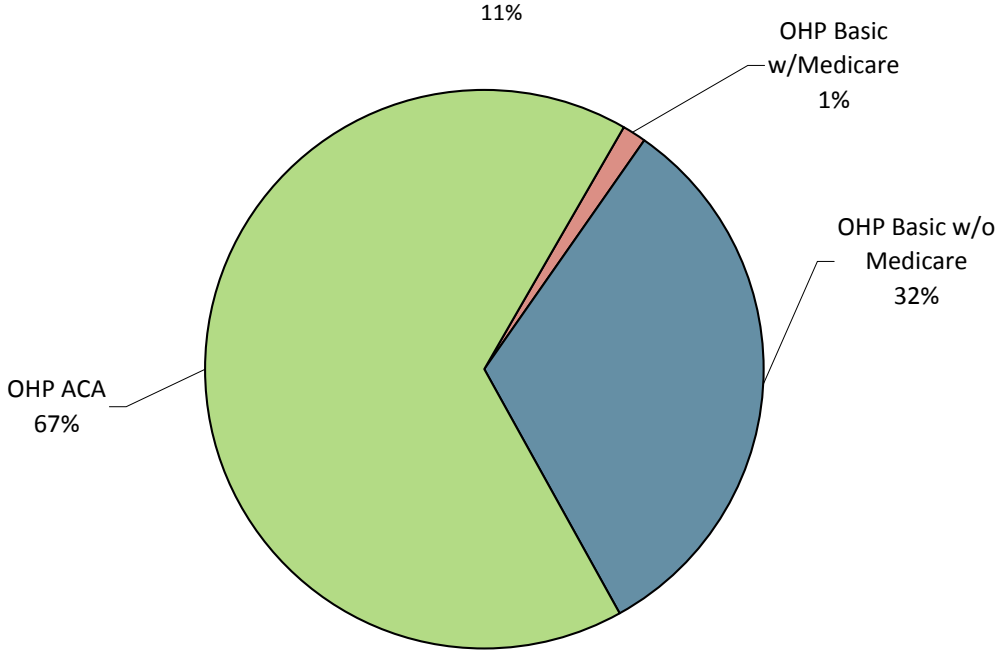
Pharmacy Utilization Summary Report: January 2015 - December 2015

YTD Percent Paid Amounts





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

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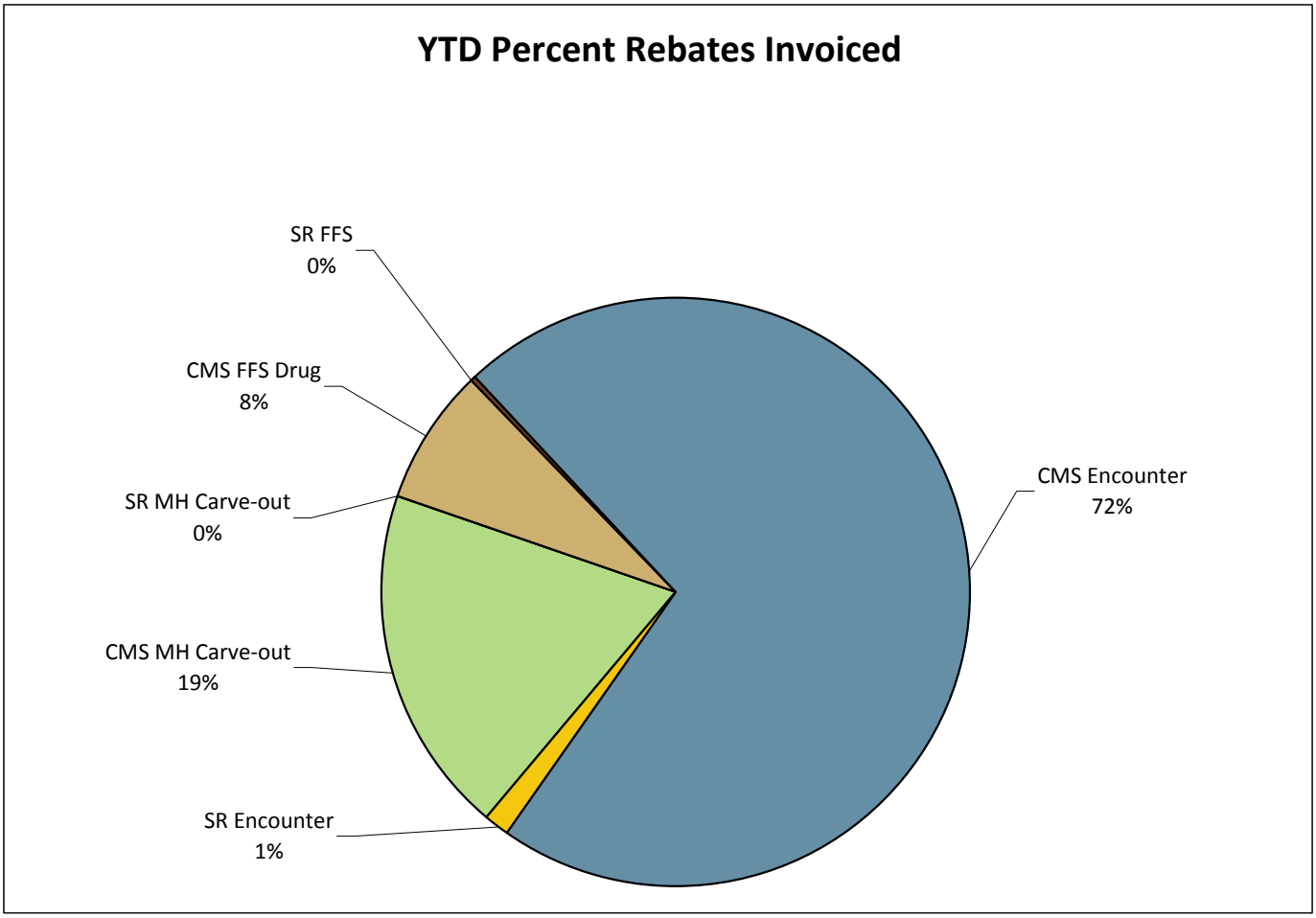
Pharmacy Utilization Summary Report: January 2015 - December 2015

Quarterly Rebates Invoiced	2015-Q1	2015-Q2	2015-Q3	2015-Q4	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$90,317,848	$96,965,410	$96,702,587	$98,892,415	$382,878,259
CMS MH Carve-out	$18,443,216	$18,968,489	$17,383,620	$18,392,498	$73,187,822
SR MH Carve-out					$0
CMS FFS Drug	$7,218,763	$6,124,949	$9,439,245	$6,594,137	$29,377,094
SR FFS	$254,210	$222,397	$292,108	$296,151	$1,064,866
CMS Encounter	$63,520,362	$70,366,887	$68,016,528	$72,222,289	$274,126,067
SR Encounter	$881,296	$1,282,688	$1,571,086	$1,387,339	$5,122,410

Quaterly Net Drug Costs	2015-Q1	2015-Q2	2015-Q3	2015-Q4	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$98,959,348	$98,750,591	$99,897,632	$100,635,663	$398,243,234
Mental Health Carve-Out Drugs	$14,418,629	$13,961,208	$14,877,878	$14,513,865	$57,771,581
FFS Phys Health + PAD	$7,970,038	$7,635,304	$4,653,827	$6,773,781	$27,032,949
Encounter Phys Health + PAD	$76,570,680	$77,154,079	$80,365,927	$79,348,018	$313,438,704



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

Last Updated: July 20, 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: January 2015 - December 2015

PMPM Drug Costs (Rebates not Included)	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$61.18	$56.67	$63.49	$59.73	$59.74	$63.52	$64.17	$61.67	$62.31	$62.95	$62.52	$67.15	$62.09
Mental Health Carve-Out Drugs	$10.58	$9.93	$10.98	$10.46	$9.91	$10.42	$10.50	$10.13	$10.24	$10.34	$10.27	$11.16	$10.41
FFS Physical Health Drugs	$24.71	$23.25	$23.25	$23.53	$21.57	$25.57	$25.74	$20.92	$23.29	$22.99	$22.20	$23.96	$23.41
FFS Physician Administered Drugs	$11.84	$10.76	$13.25	$12.41	$11.87	$13.02	$11.83	$10.93	$10.64	$10.29	$8.86	$10.57	$11.36
Encounter Physical Health Drugs	$45.03	$41.52	$46.29	$42.97	$44.25	$46.58	$47.20	$46.39	$46.66	$47.94	$47.99	$50.62	$46.12
Encounter Physician Administered Drugs	$8.12	$7.20	$8.56	$8.14	$7.88	$8.51	$8.90	$8.29	$8.16	$7.71	$7.83	$8.33	$8.13

Claim Counts	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Avg Monthly
Total Claim Count (FFS & Encounter)	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	1,037,867	977,187	1,031,827	1,023,036
Mental Health Carve-Out Drugs	148,733	139,073	154,438	154,149	148,814	152,199	152,180	150,978	151,853	153,828	146,402	157,690	150,861
FFS Physical Health Drugs	83,918	70,340	72,809	70,967	68,496	72,311	73,666	67,651	69,915	72,180	70,902	67,797	71,746
FFS Physician Administered Drugs	16,134	13,266	13,957	14,451	14,173	15,144	15,582	14,583	14,617	13,335	11,850	12,083	14,098
Encounter Physical Health Drugs	703,071	668,393	743,803	737,507	716,143	713,608	692,850	690,397	700,265	718,215	673,982	721,607	706,653
Encounter Physician Administered Drugs	77,352	72,430	84,039	85,933	84,377	84,980	81,171	79,628	79,208	80,309	74,051	72,650	79,677

Amount Paid per Claim (Rebates not Included)	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$61.09	$61.37	$62.93	$60.76	$62.45	$64.22	$65.10	$64.79	$64.48	$64.02	$65.20	$67.23	$63.64
Mental Health Carve-Out Drugs	$73.07	$74.52	$75.31	$73.34	$71.85	$71.83	$71.11	$70.72	$70.88	$70.93	$71.49	$73.11	$72.35
FFS Physical Health Drugs	$46.28	$46.56	$42.93	$43.26	$41.71	$44.58	$47.23	$44.85	$46.02	$45.71	$45.95	$44.31	$44.95
FFS Physician Administered Drugs	$115.38	$114.25	$127.64	$112.00	$110.97	$108.35	$102.63	$108.68	$100.59	$110.78	$109.70	$109.69	$110.89
Encounter Physical Health Drugs	$55.75	$56.07	$57.56	$55.40	$58.47	$60.29	$60.96	$61.08	$60.83	$60.88	$62.11	$63.68	$59.42
Encounter Physician Administered Drugs	$91.34	$89.72	$94.20	$90.04	$88.37	$92.46	$98.10	$94.63	$94.03	$87.56	$92.18	$104.07	$93.06

Amount Paid per Claim - Multi Source Drugs (Rebates not Included)	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$28.51	$28.93	$28.97	$27.64	$28.11	$28.15	$27.85	$27.59	$27.72	$27.59	$27.40	$27.38	$27.99
Mental Health Carve-Out Drugs	$56.12	$57.38	$57.78	$55.49	$54.13	$53.49	$51.87	$51.26	$50.98	$50.72	$51.07	$51.29	$53.46
FFS Physical Health Drugs	$23.42	$22.62	$22.37	$21.54	$21.57	$21.00	$22.13	$21.41	$21.74	$22.54	$21.26	$21.07	$21.89
Encounter Physical Health Drugs	$23.07	$23.49	$23.45	$22.22	$23.16	$23.30	$23.01	$22.84	$23.07	$22.93	$22.72	$22.58	$22.98

Amount Paid per Claim - Single Source Drugs (Rebates not Included)	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$448.07	$466.02	$481.63	$476.20	$498.99	$517.15	$530.56	$524.35	$484.53	$476.63	$515.55	$551.73	$497.62
Mental Health Carve-Out Drugs	$470.29	$470.76	$478.63	$480.88	$478.31	$493.52	$510.14	$514.25	$522.36	$518.39	$521.50	$547.36	$500.53
FFS Physical Health Drugs	$319.72	$349.28	$307.30	$324.16	$302.02	$349.17	$375.40	$353.06	$354.74	$325.34	$359.08	$354.23	$339.46
Encounter Physical Health Drugs	$461.33	$478.00	$499.16	$490.44	$520.58	$537.05	$549.43	$541.70	$491.96	$486.11	$530.33	$569.51	$512.97

Multi-Source Drug Use Percentage	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Avg Monthly
Multi-Source Drug Use Percentage	93.1%	93.3%	93.3%	93.4%	93.4%	93.3%	93.3%	93.2%	92.6%	92.5%	92.8%	93.0%	93.1%
Mental Health Carve-Out Drugs	95.9%	95.9%	95.8%	95.8%	95.8%	95.8%	95.8%	95.8%	95.8%	95.7%	95.7%	95.6%	95.8%
FFS Physical Health Drugs	92.3%	92.7%	92.8%	92.8%	92.8%	92.8%	92.9%	92.9%	92.7%	92.3%	92.7%	93.0%	92.7%
Encounter Physical Health Drugs	92.5%	92.8%	92.8%	92.9%	92.9%	92.8%	92.8%	92.6%	91.9%	91.8%	92.2%	92.5%	92.6%

Preferred Drug Use Percentage	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Avg Monthly
Preferred Drug Use Percentage	86.72%	86.60%	86.56%	86.52%	86.45%	86.48%	86.33%	86.45%	86.45%	86.80%	86.84%	86.74%	86.6%
Mental Health Carve-Out Drugs	76.97%	76.76%	76.94%	76.81%	76.71%	76.57%	76.24%	76.38%	76.26%	76.12%	76.10%	76.20%	76.5%
FFS Physical Health Drugs	94.99%	94.80%	94.60%	94.61%	94.59%	94.89%	95.23%	95.40%	95.42%	95.17%	95.84%	95.57%	95.1%
Encounter Physical Health Drugs	87.88%	87.87%	87.83%	87.82%	87.74%	87.79%	87.54%	87.71%	87.72%	88.19%	88.15%	88.12%	87.9%

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

Last Updated: July 20, 2016

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$3,340,962	8.7%	3,537	$945	V
2	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$2,263,514	5.9%	12,011	$188	V
3	SEROQUEL XR	Antipsychotics, 2nd Gen	$1,915,185	5.0%	3,008	$637	V
4	STRATTERA	ADHD Drugs	$1,849,431	4.8%	4,789	$386	Y
5	INVEGA SUSTENNA	Antipsychotics, Parenteral	$1,292,638	3.4%	823	$1,571	V
6	DULOXETINE HCL	Antidepressants	$639,249	1.7%	25,554	$25	V
7	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$621,148	1.6%	996	$624	V
8	FLUOXETINE HCL	Antidepressants	$610,926	1.6%	31,574	$19	Y
9	SAPHRIS	Antipsychotics, 2nd Gen	$561,297	1.5%	939	$598	V
10	HARVONI	Hepatitis C - Direct Acting Antivirals	$559,509	1.5%	20	$27,975	Y
11	ABILIFY MAINTENA	Antipsychotics, Parenteral	$540,842	1.4%	352	$1,536	V
12	PRISTIQ ER	Antidepressants	$475,339	1.2%	1,645	$289	V
13	BUPROPION XL	Antidepressants	$473,105	1.2%	17,768	$27	V
14	SERTRALINE HCL	Antidepressants	$447,431	1.2%	39,254	$11	Y
15	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$424,195	1.1%	1,275	$333	V
16	RISPERDAL CONSTA	Antipsychotics, Parenteral	$411,959	1.1%	552	$746	Y
17	TRAZODONE HCL	Antidepressants	$387,822	1.0%	36,899	$11	
18	VENLAFAXINE HCL ER	Antidepressants	$373,502	1.0%	1,954	$191	V
19	DIVALPROEX SODIUM ER	Antiepileptics (oral & rectal)	$368,666	1.0%	4,224	$87	Y
20	Factor Viii Recombinant Nos	Physican Administered Drug	$345,051	0.9%	12	$28,754	
21	AMITRIPTYLINE HCL	Antidepressants	$327,851	0.9%	17,297	$19	Y
22	LAMOTRIGINE	Antiepileptics (oral & rectal)	$297,358	0.8%	20,779	$14	Y
23	VIIBRYD	Antidepressants	$286,065	0.7%	1,299	$220	V
24	Infliximab Injection	Physican Administered Drug	$281,866	0.7%	130	$2,168	
25	CITALOPRAM HBR	Antidepressants	$280,588	0.7%	29,277	$10	Y
26	VENLAFAXINE HCL ER	Antidepressants	$255,431	0.7%	14,869	$17	Y
27	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$246,833	0.6%	610	$405	Y
28	ESCITALOPRAM OXALATE	Antidepressants	$245,470	0.6%	19,778	$12	Y
29	INVEGA TRINZA	Antipsychotics, Parenteral	$242,242	0.6%	50	$4,845	V
30	BUPROPION HCL SR	Antidepressants	$231,876	0.6%	11,492	$20	Y
31	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$231,034	0.6%	13,570	$17	
32	METHYLPHENIDATE ER	ADHD Drugs	$227,723	0.6%	1,752	$130	N
33	ENBREL	Biologics for RA, Psoriasis and Crohn's Disease	$221,801	0.6%	75	$2,957	Y
34	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$219,632	0.6%	2,183	$101	
35	QUETIAPINE FUMARATE	Antipsychotics, 2nd Gen	$216,091	0.6%	12,351	$17	Y
36	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$211,886	0.6%	3,781	$56	Y
37	REXULTI	Antipsychotics, 2nd Gen	$208,937	0.5%	214	$976	V
38	LANTUS	Diabetes, Insulins	$195,375	0.5%	603	$324	
39	LORAZEPAM	Benzodiazepine Anxiolytics	$178,187	0.5%	18,576	$10	
40	SOVALDI	Hepatitis C - Direct Acting Antivirals	$174,296	0.5%	7	$24,899	Y
		Top 40 Aggregate:	**$22,682,319**		**355,879**	**$2,554**	
		All FFS Drugs Totals:	**$38,260,898**		**699,322**	**$393**	

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: July 20, 2016

ProDUR Report for April through June 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	36	12	0	24	0.10%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,925	421	0	1,504	1.57%
DD (Drug/Drug Interaction)	Set alert/Pay claim	218	62	3	153	0.10%
ER (Early Refill)	Set alert/Deny claim	83,085	14,866	104	68,079	69.20%
ID (Ingredient Duplication)	Set alert/Pay claim	23,677	6,158	24	17,474	19.67%
LD (Low Dose)	Set alert/Pay claim	906	167	0	737	0.73%
LR (Late Refill/Underutilization)	Set alert/Pay claim	47	26	0	21	0.10%
MC (Drug/Disease Interaction)	Set alert/Pay claim	113	28	0	85	0.10%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	1,430	364	14	1,051	1.13%
PG (Pregnancy/Drug Interaction)	Set alert/Deny claim	821	488	1	332	0.67%
TD (Therapeutic Duplication)	Set alert/Pay claim	7,699	2,281	2	5,409	6.33%
	Totals	**119,957**	**24,873**	**148**	**94,869**	**99.70%**

ProDUR Report for April through June 2016

Top Drugs in Early Refill

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
DC	Diazepam	101	28	73	11,079	0.9%	27.7%
	Haloperidol	276	72	204	2,999	9.2%	26.1%
	Wellbutrin (Bupropion)	919	146	773	44,661	2.1%	15.9%
DD	Geodon (Ziprasidone)	81	30	51	5,061	1.6%	37.0%
ER	Remeron (Mirtazapine)	1,170	170	1,000	10,195	11.5%	14.5%
	Hydrocodone/APAP	172	61	111	7,568	2.3%	35.5%
	Oxycodone	282	129	153	6,547	4.3%	45.7%
	Lorazepam	1,647	363	1,284	25,404	6.5%	22.0%
	Alprazolam	1,263	227	1,036	19,629	6.4%	18.0%
	Lamictal (Lamotrigine)	4,198	774	3,424	33,260	12.6%	18.4%
	Abilify (Aripiprazole)	2,776	456	2,320	23,236	11.9%	16.4%
	Seroquel (Quetiapine)	3,165	596	2,565	23,003	13.8%	18.8%
	Risperdal (Risperidone)	2,201	422	1,779	15,997	13.8%	19.2%
	Wellbutrin (Bupropion)	4,120	580	3,540	44,661	9.2%	14.1%
	Zoloft (Sertraline)	5,446	880	4,566	52,981	10.3%	16.2%
	Prozac (Fluoxetine)	3,977	590	3,387	42,864	9.3%	14.8%
	Celexa (Citalopram)	3,375	437	2,938	39,107	8.6%	12.9%
	Trazodone	5,272	804	4,468	50,709	10.4%	15.3%
	Cymbalta (Duloxetine)	3,430	494	2,935	34,824	9.8%	14.4%
ID	Lamictal (Lamotrigine)	1,501	389	1,110	33,260	4.5%	25.9%
	Seroquel (Quetiapine)	1,626	460	1,158	23,003	7.1%	28.3%
	Abilify (Aripiprazole)	1,164	240	924	23,236	5.0%	20.6%
	Risperdal (Risperidone)	1,010	261	749	15,997	6.3%	25.8%
	Zoloft (Sertraline)	1,267	333	934	52,981	2.4%	26.3%
	Prozac (Fluoxetine)	1,014	230	784	42,864	2.4%	22.7%
PG	Lorazepam	95	72	23	25,404	0.4%	75.8%
	Alprazolam	69	50	19	19,629	0.4%	72.5%
TD	Lamictal (Lamotrigine)	637	179	458	33,260	1.9%	28.1%
	Depakote (Divalproex Sodium)	377	117	260	14,597	2.6%	31.0%
	Seroquel (Quetiapine)	823	265	553	23,003	3.6%	32.2%
	Zyprexa (Olanzapine)	520	180	340	14,400	3.6%	34.6%

ProDUR Report for April through June 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)	1,170	170	10,195	6	12	73	14	65	0
	Hydrocodone/APAP	172	61	7,568	0	0	33	0	28	0
	Oxycodone	282	129	6,547	0	8	62	0	59	0
	Lorazepam	1,647	363	25,404	3	6	173	6	175	0
	Alprazolam	1,263	227	19,629	3	13	108	0	103	0
	Lamictal (Lamotrigine)	4,198	774	33,260	45	33	355	6	335	0
	Abilify (Aripiprazole)	2,776	456	23,236	15	21	168	6	246	0
	Seroquel (Quetiapine)	3,165	596	23,003	10	45	207	4	330	0
	Risperdal (Risperidone)	2,201	422	15,997	3	15	163	9	232	0
	Wellbutrin (Bupropion)	4,120	580	44,661	26	45	206	9	294	0
	Zoloft (Sertraline)	5,446	880	52,981	35	29	450	13	353	0
	Prozac (Fluoxetine)	3,977	590	42,864	24	42	239	9	276	0
	Celexa (Citalopram)	3,375	437	39,107	24	34	124	3	252	0
	Trazodone	5,272	804	50,709	15	80	317	12	372	8
	Cymbalta (Duloxetine)	3,430	494	34,824	9	36	199	4	246	0

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500 Summer Street NE, E35, Salem, Oregon 97301-1079
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Retro-DUR Intervention History by Quarter FFY 2015 - 2016

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul-Sep
Pediatric Psychotropics	ADHD New Start with Follow Up In First 30 Days	Members Identified	26	42	16	0
		Profiles Sent	10	18	7	0
		Responses Received	4	10	2	0
		Response Rate	40%	56%	29%	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

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Retro-DUR Intervention History by Quarter FFY 2015 - 2016

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul-Sep
Profile Review	Children under age 12 antipsychotic	RetroDUR_Profiles Reviewed	87	131	87	29
		RetroDUR_Letters Sent To Providers	0	0	0	1
		Provider Responses	0	0	0	0
		Provider Agreed / Found Info Useful	0	0	0	0
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	14	27	13	8
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	99	155	83	25
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	14	15	12	6
	Lock-In	RetroDUR_Profiles Reviewed	89	57	17	0
		RetroDUR_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	2	0
	Med Matrix	RetroDUR_Profiles Reviewed	97	0	0	0
	Polypharmacy	RetroDUR_Profiles Reviewed	0	56	89	0
		RetroDUR_Letters Sent To Providers	0	11	7	0
		Provider Responses	0	0	0	0
		Provider Agreed / Found Info Useful	0	0	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
Safety Net	ICS/LABA	Disqualified	13	2	4	1
		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	4	1
		Faxes Sent	7	5	5	0
		Fax Sent - SABA	0	2	2	0
		Fax Sent - Controller	2	0	2	0
		Fax Sent - Combination Inhaler	4	2	0	0
		No Subsequent Pulmonary Claims	1	1	1	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%	1,133	2,459	46%						
Five or more concurrent psychotropics	188	10,624	2%	202	11,375	2%						
Three or more concurrent psychotropics	1,985	10,624	19%	1,989	11,375	17%						
Two or More Concurrent Antipsychotics	97	10,624	1%	79	11,375	1%						
Under 18 years old on any antipsychotic	2,419	10,624	23%	2,477	11,375	22%						
Youth five years and younger on psychotropics	143	10,624	1%	163	11,375	1%						

7/25/2016

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.

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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%	313	510	61%						
Five or more concurrent psychotropics	31	2,138	1%	41	2,648	2%						
Three or more concurrent psychotropics	332	2,138	16%	357	2,648	13%						
Two or More Concurrent Antipsychotics	17	2,138	1%	18	2,648	1%						
Under 18 years old on any antipsychotic	442	2,138	21%	499	2,648	19%						
Youth five years and younger on psychotropics	35	2,138	2%	39	2,648	1%						

7/25/2016

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.

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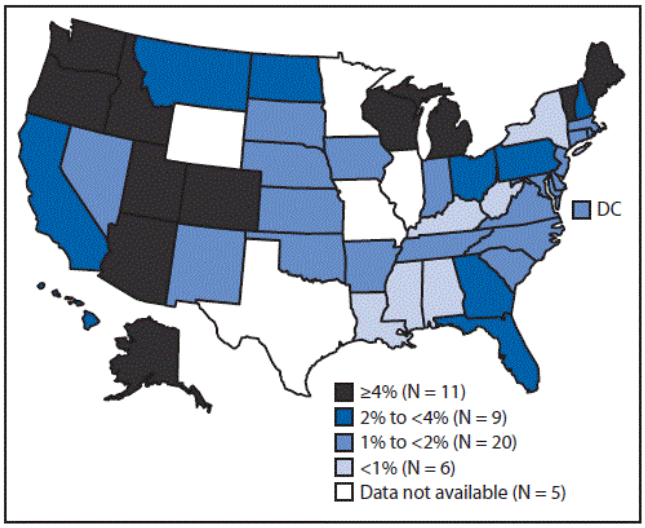
Autism Spectrum Disorder Still Not Linked to the MMR Vaccine: A Review of the Studies since the 1998 *Wakefield* Study

By Courtney Strouse, Pharm.D. Candidate 2016, OSU College of Pharmacy, and Andrew Gibler, Pharm.D., OSU College of Pharmacy Drug Use Research and Management

The Diagnostic and Statistical Manual of Mental Disorders, *5th* edition (DSM-V) has reclassified autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder (PDD) into a collective diagnosis now referred to as Autism Spectrum Disorder (ASD).[1] ASD is characterized by early-onset impairments in social interaction and restricted and repetitive physical and cognitive behaviors such as with movements, interests, and activities.[2] The prevalence of ASD diagnoses continue to increase, though it is unclear how much increase is due to increased awareness of the disorder and improved DSM-V classifications. The Centers for Disease Control and Prevention (CDC) Autism and Developmental Disabilities Monitoring (ADDM) network estimates that 1 in 68 children in the United States (U.S.) is diagnosed with ASD and disproportionately affects males.[3] The cause (or causes) of ASD remain unknown despite an abundance of research. The research has, however, provided some clarity to what is not associated with ASD.

Concerns about possible associations between vaccines and ASD remain a topic of private and public debate despite several studies that have refuted the conclusions of a small (n=12), uncontrolled and retracted 1998 study by former gastroenterologist Andrew Wakefield that attempted to show an association between ASD and the measles, mumps and rubella (MMR) vaccine.[5] The ramifications of the study, despite its retraction from the *Lancet* several years ago, are still apparent. A CDC report (see Image 1) of children in kindergarten during the 2014-2015 academic year found that Oregon has the second highest vaccine exemption rate in the nation at 6.0%.[4]

Image 1: Estimated percentage of children enrolled in kindergarten during 2014-15 academic year exempt from receiving one or more vaccines, by state.[4]



Measles, Mumps, and Rubella Vaccine and its Debunked Association to Autism Spectrum Disorder

The 1998 *Wakefield* study led to immunization hesitation and increased nonmedical vaccine exemptions despite that the study was a small case-series of 12 children (mean age 6 years [range, 3 to 10 years]) with inflammatory bowel disease (IBD) and already had a history of PDD. Parents of 8 of the children felt the onset of behavioral impairment occurred around the time of immunization with the MMR vaccine. The study speculatively concluded that there was a pattern of IBD in children with developmental disorders, and that in most cases, the onset of symptoms occurred after MMR immunization.[5]

Wakefield's findings were perpetuated by another study that found an association between measles infection and a variant of IBD found in children with developmental disorders;[6] however, an association between the MMR vaccine and ASD was never established. Immediately after Wakefield's publication, epidemiological data began to refute any link between MMR vaccination and ASD.[7,8] Indeed, the logic of a perceived association after the Wakefield study was published was immediately questioned since MMR vaccination occurs in early childhood, around the same time of life ASD is typically diagnosed. Eventually, 10 of the 12 investigators involved in the Wakefield study retracted the original conclusions as by stating in 2004,

> *We wish to make it clear that in this paper no causal link was established between MMR vaccine and autism as the data were insufficient.*[9]

In 2010, the *Lancet* retracted the publication after it had become clear that the study had provided false information and there were critical conflicts of interest and methodological concerns not previously disclosed.[10] The *British Medical Journal* has published a series of articles on the exposure of the fraudulent study, which was accomplished with journalistic investigation, and not academic vigilance.[11-13]

Clarity Lies in the Data

Several studies have been published that have found no association between the MMR vaccine and ASD. The first of these studies was an epidemiologic study, which identified 498 children with an ASD diagnosis born after 1979.[7] The study looked at trends in prevalence of ASD after the introduction of the MMR vaccine in 1988.[7] The study concluded that although there was a steady increase in ASD throughout the time period studied, there was no increased trend of reported cases around the time of introduction of the MMR vaccine; nor was there any evidence to support a sudden increase of ASD diagnoses in the years following the introduction of the MMR vaccine.[7]

In 1982, the National Board of Health and National Public Health Institute launched a long-term vaccination project directed at eliminating MMR diseases in Finland.[14] Data were collected prospectively from the vaccination project to review the development of gastrointestinal (GI) symptoms after the receipt of the MMR vaccine and its possible link to ASD. By the end of 1996, the institute had data on 3 million vaccinations and only 31 patients had gone on to develop GI symptoms.[14] Time from MMR vaccine to onset of symptoms varied from 20 hours to 15 days. These 31 patients were followed for a mean period of 9 years and none of them went on to develop ASD.[14] From these data, no association between the MMR vaccine and PDD or IBD could be found.[14]

A retrospective cohort of 535,544 Finland children vaccinated for MMR between 1982 and 1986 was also analyzed.[15] A total of 352 children from this cohort were hospitalized and discharged with a diagnosis of ASD. Of these, 309 children had been immunized with the MMR vaccine prior to admission.[15] The time from MMR vaccination to onset of symptoms of ASD in 309 of the hospitalized children varied widely, from 3 days to 12.5 years, and the data did not show any evidence of clustering.[15] None of the hospitalizations were for IBD.[15] Children not hospitalized were not captured in these data, although it is worth noting that most diagnoses in Finland were made in the hospital during this time period.[15] The study was unable to identify an association between MMR vaccine and ASD.[15]

Another retrospective cohort study analyzed pooled data of all children in Denmark born between January 1991 and December 1998 and a complete vaccination registry from 1991 to 1999 to determine if an association between MMR vaccine and ASD existed.[16] The cohort consisted of 535,393 children

with a total follow-up of over 2 million person-years.[16] Of the 440,655 (82%) children that received the MMR vaccine, no increased risk for autistic disorder (n=316; adjusted relative-risk (ARR) 0.92 (95% CI 0.68 to 1.24) or ASD (n=422; ARR 0.83 (95% CI 0.65 to 1.07) was found.[16]

A large retrospective cohort (n=95,727) was recently reviewed to determine diagnoses of ASD by MMR vaccine status in U.S. children with older siblings with and without ASD.[17] Overall, the MMR vaccination rate (≥1 dose) for children with older siblings without ASD was higher than for children with older siblings with ASD at age 2 years (84% vs. 73%) and at age 5 years (92% vs. 86%).[17] Compared to unvaccinated children, the cumulative incidence rate ratio (RR) of ASD for 1 dose of MMR at age 2 years among children with unaffected older siblings was 0.80 (95% CI, 0.44 to 1.46; p=0.57) and 0.44 (95% CI, 0.15 to 1.29; p=0.22) among children with older siblings with ASD.[17] There were also no associations found between 1 dose of MMR at ages 3, 4, and 5 years, irrespective of whether their older siblings had ASD.[17] Similarly, compared to unvaccinated children, for 2 doses of MMR at age 5 years, the cumulative incidence RR of ASD among children with unaffected older siblings was 0.74 (95% CI, 0.55 to 0.99; p=0.049) and 0.44 (95% CI, 0.26 to 0.75; p<0.01) among children with older siblings with ASD.[17] The study concluded that the MMR vaccine was not associated with increased risk of ASD in children, regardless of whether older siblings had ASD.[17]

Conclusion

Vaccine refusal has reintroduced many new cases of preventable measles cases in the U.S. each year.[18] Since 2000, there have been 1,416 reported measles cases in the U.S.[18] A total of 199 cases (14.1%) involved persons who had been vaccinated against measles, whereas 805 cases (56.8%) involved persons who had not been vaccinated (in the remaining cases, vaccine history was unknown).[18] Of the cases where detailed vaccination history was available, 59.2% of the cases occurred in unvaccinated individuals who were age-eligible to receive the vaccine, most of which had nonmedical exemptions as opposed to a contraindication to the vaccine.[18] Thus, a substantial proportion of the U.S. measles cases occurred in persons intentionally unvaccinated. Perhaps more important than the number of measles cases are the potentially very serious complications associated with its spread, both to the exposed children and to public health.

Some parents remain hesitant to vaccinate their children due to uncertainty whether vaccination is necessary for rare diseases, perceived risks associated with multiple vaccinations in a short period of time, concern over adverse effects of vaccinations (such as ASD), and the unknown long-term effects of new vaccinations. Preserving parent autonomy while developing buy-in requires great motivational interviewing skills and supporting educational material. The CDC vaccination website provides great communication tools for clinicians to inform parents about the benefits of vaccination and the potential risks of vaccination exemption to their child, and the community as a whole.[19,20] A helpful place for providers to start is the
Provider Resources for Vaccine Conversations with Parents webpage, located at http://www.cdc.gov/vaccines/hcp/conversations/index.html

Access to several additional resources from the CDC is also available:
Talking to Parents about Vaccines
http://www.cdc.gov/vaccines/hcp/conversations/conv-materials.html

For Parents: Vaccines for Your Children
http://www.cdc.gov/vaccines/parents/index.html

About Vaccine Conversations with Parents
http://www.cdc.gov/vaccines/hcp/conversations/about-vacc-conversations.html

Vaccine Resources to Share with Parents
http://www.cdc.gov/vaccines/hcp/conversations/resources-parents.html

Helpful and up-to-date clinical information on communicable disease outbreaks, rates and trends, immunization recommendations and schedules, and laws and requirements regarding vaccinations can be found at: http://www.cdc.gov/vaccines/.[21]

Peer Reviewed By:
Steven A. Wahls, MD, FAAFP, Assistant Professor, Department of Family Medicine, Oregon Health and Science University and Dave Bearden, Pharm.D., Professor, OSU College of Pharmacy.

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DUR / P & T Committee

Declaration of Compensation for Public Comment or Testimony

The P & T Committee will allow opportunity for public testimony at every meeting and accept testimony, in writing when submitted at least one week in advance of the scheduled meeting or in-person, prior to deliberating on any recommendations regarding a drug or a class of drugs. Persons offering either written or in-person testimony shall be required to state in writing and disclose publicly, prior to their testimony, if they have received or are receiving, either directly or indirectly, compensation by any other interested party or entity including the nature or amount of the compensation being given in exchange for offering testimony.

What agenda topic will you provide testimony on today? _____

Do you have a significant financial interest related to the P & T meeting topics?

Yes

No

"Significant Financial Interest" means an interest of you, your family, or your employer or sponsoring institution, which reasonably appears to be related to the P & T proceedings and meets one of the following:

- Remuneration received from any pharmaceutical manufacturer, patient advocacy group, or other stakeholder group during the past 24 months exceeding $2,000
- Equity in a pharmaceutical manufacturer exceeding $5,000, excluding investment vehicles for which you do not have direct control over investment decisions
- Participation in any of the clinical trials that were used to receive FDA approval within the last 5 years

If Yes, please specify: _____

Other than salary, have you been compensated for the testimony you plan to provide?

Yes If yes, please answer the following:

Gifts (Value?) _____

Money (Amount?) _____

Expenses

Other (Please explain) _____

No

If you answered yes, who were you compensated by?

_____

Print Name _____

Signature _____ **Date** _____

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

Policy Evaluation: Safety Edit for Attention Deficit Hyperactivity Disorder (ADHD) Medications

Research Goals:

- What proportion of PA requests are for non-preferred drugs and is there opportunity to improve preferred options available on the PDL? Is there opportunity to reduce the number of PA requests?
- Has prescribing according to the best practice standards improved since implementation of the safety edit as measured by the proportion of patients within the age specific dose or prescribed by a psychiatric specialty and the proportion within the drug's labeled indications?
- Has the safety edit interrupted therapy as measured by the proportion of patients who did not receive ADHD therapy within 14 days of index claim denial for PA?
- Is there a difference in harms since implementation of the safety edit as measured by number of patients with ED visits for any cause within 90-days of the index event as well as differences in patients with ED visits specifically for substance abuse or CVD?

Conclusions:

- The majority of denied claims were for non-preferred agents, most commonly amphetamine ER, methylphenidate ER, and guanfacine ER.
- Since implementation of the safety edit, it appears prescribing of ADHD medications according to the best practice standards have improved. There were fewer children under the age of 6 years old with paid claims, and little prescribing outside of the accepted dose range.
- There was an increase in use of ADHD medications in adults age 18 years or older in the study group compared to the control (45% vs. 28%) with 33.4% (458/1373) having a history of substance or alcohol abuse/dependence.
- Similar to what was found in other policy evaluations, the majority of denied claims in both the control group (63.1%) and study group (72.8%) were not followed by a PA request within 14 days of denial. Of the PA requests within 14 days, almost 100% of them were approved.
- No differences were observed between the treatment and study groups in terms of harm from the medications resulting in ED visits and/or hospitalizations within 90 days from the index event.

Recommendations:

- Amend the current safety edit to require that stimulates for adults with a history of alcohol or substance abuse or dependence in the previous 12 months to require a mental health specialist consultation (Appendix 2).
- Approve lisdexamfetamine for binge eating disorder only for adults with an absence of co-morbid mental health illness.
- Recommend the HERC review the funding line for the treatment of ADHD in adults due to the limited evidence of effectiveness and increased utilization.

Background:

Attention-Deficit/Hyperactivity Disorder (ADHD) is neurobehavioral disorder affecting over 11% of school-aged children in 2011[1]. Traditionally, ADHD has been thought of as a childhood disorder, although symptoms may persist into adulthood for many individuals, which may require some to be on lifelong treatment[2]. It is estimated that worldwide ADHD affects approximately 3.4-4.4% of adults[2 3]. Untreated or sub-optimally treated adults may be subjected to executive functioning deficits, which may include inability to complete tasks, prioritize, and reduce overall quality of life[2,3]. Unfortunately, there is very little data on the effectiveness of treatment of ADHD with CNS stimulants in adults and more research is need to understand the potential benefits of the various treatments in adults with ADHD[3]. Comorbid mood, anxiety, substance use, and/or impulse disorders also commonly occur in combination with ADHD in adults.

In addition to the standard non-preferred prior authorization policy, the Oregon state Medicaid fee-for-service (FFS) program implemented a safety edit policy in 10/9/2014 (see Appendix 1) for treatment regimens prescribed by a non-psychiatrist specialist which are: outside of standard age, outside of standard dose, and non-standard polypharmacy. A list of FDA-approved ADHD medications with minimum ages and maximum daily doses can be found in Table A1. Certain medications are deemed "voluntary" if they are designated carve out medications and on the voluntary PDL and hit the PA for nonstandard dosing only. This safety edit was implemented to promote prescribing according to the best practice standards and evaluate use of ADHD medications by non-psychiatrists. The PA safety edit defined "best practices" as ADHD medications prescribed by non-psychiatrists to patients with standard age ranges, receiving standard doses, and proper polypharmacy treatment. [4]

There are no published data evaluating the effects of ADHD specific policies in the Medicaid population; however, many state Medicaid programs across the United States have similar policies in place [4 5 6 7 8]. These medications have a black box warning regarding the high abuse potential[9 10], which is likely the driving factor in states requiring the patient to have at least a year history of no substance-abuse..[4 5] Other states, as well as some of the large health insurance companies, may only necessitate a PA for ADHD medications that are non-preferred or prescribed outside of standard age and dose ranges, or by a non-psychiatrist. [6 7 8 11 12]

The CDC estimates that only 6.1% of children between the ages 4-17 are taking ADHD medications, while they estimated over 11% of children in the US has having an ADHD diagnosis[1]. The safety edits in place are a safeguard to ensure that patients are being prescribed medications appropriately, but it may also potentially serve as a barrier for patients in receiving treatment.[4] Recent data has shown an increased rate of emergency department visits due to dextroamphetamine-amphetamines and methylphenidate use in adults, many of which were due to nonmedical use of these prescription medications.[13] Nonmedical use was evaluated by asking the patient if they had used either a methylphenidate or dextroamphetamine-amphetamine drug that they did not have a prescription for or if it was taken solely for the experience or feeling the drug caused. This study found that nonmedical use of these drugs contributed to 14.1% and 16.4% of adolescent ED visits involving dextroamphetamine-amphetamine or methylphenidate drugs, respectively, and 21.0% and 18.2% of adult ED visits involving dextroamphetamine-amphetamines or methylphenidates, respectively.[13] ADHD stimulants can have severe cardiovascular adverse effects if abused or misused, including but not limited to myocardial infarction, heart arrhythmias, stroke, and sudden cardiac death.[3] A drug class review was completed in 2015, comparing stimulants (methylphenidates, amphetamine-derivatives) and non-stimulants and found no differences in treatment effects, with varying reports of adverse events and harms data between classes.[14]

The goal of this review it to evaluate if the current safety edit in place is meeting those goals of improved safety, while also evaluating how it may be impacting the access to ADHD medications by Medicaid patients, and whether any changes should be implemented.

Methods: Patients were included in this observational cohort study if they had a paid FFS drug claim for any drug in Table A1 or a denied FFS drug claim for any drug in TableA1 with Explanation of Benefit (EOB) code 1056 (i.e. "PA Required"), or 1059 or 3429 ("Non-Preferred Drug) or 0030 or 0148 ("Drug Quantity Per Day Exceeded) or 4268 ("Safety Edit) and simultaneously no EOB of 2017 (i.e. "Patient enrolled in MCO") from 10/8/2013 and through 12/31/2015. To evaluate for prescriptions based on best prescribing standards, a pre- and post- observational cohort was constructed to evaluate the policy. Patients with a paid or denied index claim from July 2013 to June 2014 were defined as the control group; patients with a paid or denied claim from October 2014 through September 2015 were defined as the study group.

Patients were excluded if they had Medicare Part D coverage as indicated by benefit packages of BMM, BMD, MND or MED. Using only FFS claims, the first ADHD medication paid or denied claim per patient during the study period was designated the index event (IE). Patients were excluded if they had a prior claim within 90 days (FFS or CCO) and if they had less than 75% days of combined FFS or coordinated care organization eligibility from 11 months prior to the index month to 3 months after the index month (for a total of 15 months) to ensure the most complete data possible. Modafinil and armodafinil were not included in this analysis and are managed through a separate PA policy.

Total PA requests based on brand name and form for denied index events restricted to the study group will be collected to determine how many PA requests are for non-preferred drugs at the time of the IE.

Baseline characteristics of age, gender, and ethnicity were assessed at the IE. Patients were categorized by whether the index event was a paid or denied claim. Patients were also categorized by the generic drug name, preferred status and dosage form (ER or IR) of index event. Patients with a paid FFS or encounter claim with an International Classification of Diseases (ICD-9) diagnosis code for each of the diagnostic groups from Table 1 were flagged in the year prior to the IE. Patients are categorized in the following mutually exclusive groups: 1) FDA labeled and funded, 2) Unfunded FDA labeled, 3) non-FDA labeled, and 4) None of the above.

Subsequently, contraindications or warnings (Table 1) for ADHD medications as well as patients with a history of substance abuse identified by the presence of any ICD9 code found in Table 2 will be identified.

Table 1: Indications and Contraindications/Precautions for ADHD Medications

ICD-9	**Diagnosis**
FDA Labeled Indications	
314.00-314.9	Attention-deficit hyperactivity disorder (ADHD)/ Attention deficit disorder (ADD)
347.10-347.11	Narcolepsy - symptomatic management
307.5	Binge Eating Disorder*
Unfunded FDA Labeled Indications	
278.01	Exogenous obesity
Unlabeled Indications	

296.3, 296.20-296.22, 296.25-296.26, 296.90-296.99, 298.0, 311, 625.4	Major depressive disorder (MDD) recurrent, unspecified
788.36	Nocturnal enuresis
Chronic Fatigue	
780.71-780.72, 780.79, 140.xx, 209.xx	Fatigue in adult cancer survivors
340.xx	Multiple Sclerosis-related fatigue
780.71	Chronic Fatigue Syndrome
None of the Above	
Contraindications or precautions	
Cardiovascular Disease	
440.9	Advanced atherosclerosis
429.2	Symptomatic cardiovascular disease
429.XX	Severe cardiovascular disease unspecified
428.XX	Heart failure
427.9	Arrhythmia
410.XX	Recent MI
413.XX	Angina
402	Severe HTN
Substance or Alcohol Abuse/Dependence	
29181	Alcohol withdrawal
303.00-303.03	ALCOHOL DEPENDENCE SYNDROME
305.0x	Alcohol Abuse
305.2-305.23	Cannabis abuse
303.90-303.93	OTHER AND UNSPECIFIED ALCOHOL DEPENDENCE
304, 304.0 – 304.03,	Drug Dependence, opioid type dependence, cocaine dependence, cannabis dependence

304.2x 304.3x, 304.4x, 304.9x	
305.5x, 305.6x, 305.7x	Other nondependent drug abuse
29181	Alcohol withdrawal
Other	
242	Hyperthyroidism
300.0X	Anxiety States, Marked anxiety, tension, agitation

*Approved for lisdexamfetamine only

To assess for appropriate age-specific dosing, the dose for a particular prescription was considered standard if the total daily dose was less than or equal to the maximum daily dose listed in Table A1. IF the IE claim exceeded the maximum daily dose, the member was categorized as receiving non-standard dosing. The daily dose was calculated based on the strength x quantity dispensed/day supply. All claims that fall outside of the maximum dosing limit will be categorized by prescriber specialty (Table 2). All claims that fall outside of the recommended age range will also be categorized by prescriber specialty.

There was little (~5%) non-standard polypharmacy prescribing identified in a previous DUE and is not in the scope of this policy evaluation.

Patients whose index event was a denied pharmacy claim were categorized by final PA disposition: No PA Requested, PA requested – Approved and PA Requested – Denied. A further analysis by drug name will be included. Claims will be categorized by generic name, paid or denied, and final disposition of the PA.

The control and study group (both denied and paid index claims) will be categorized and compared as to whether they were hospitalized or had an emergency department encounter for any reason on the day of their index claim or in the 90 days after. All-cause hospitalizations will be captured first, followed by a search for a hospitalization due to any of the precautions or contraindications in Table 2.

Table 2: Provider Specialists

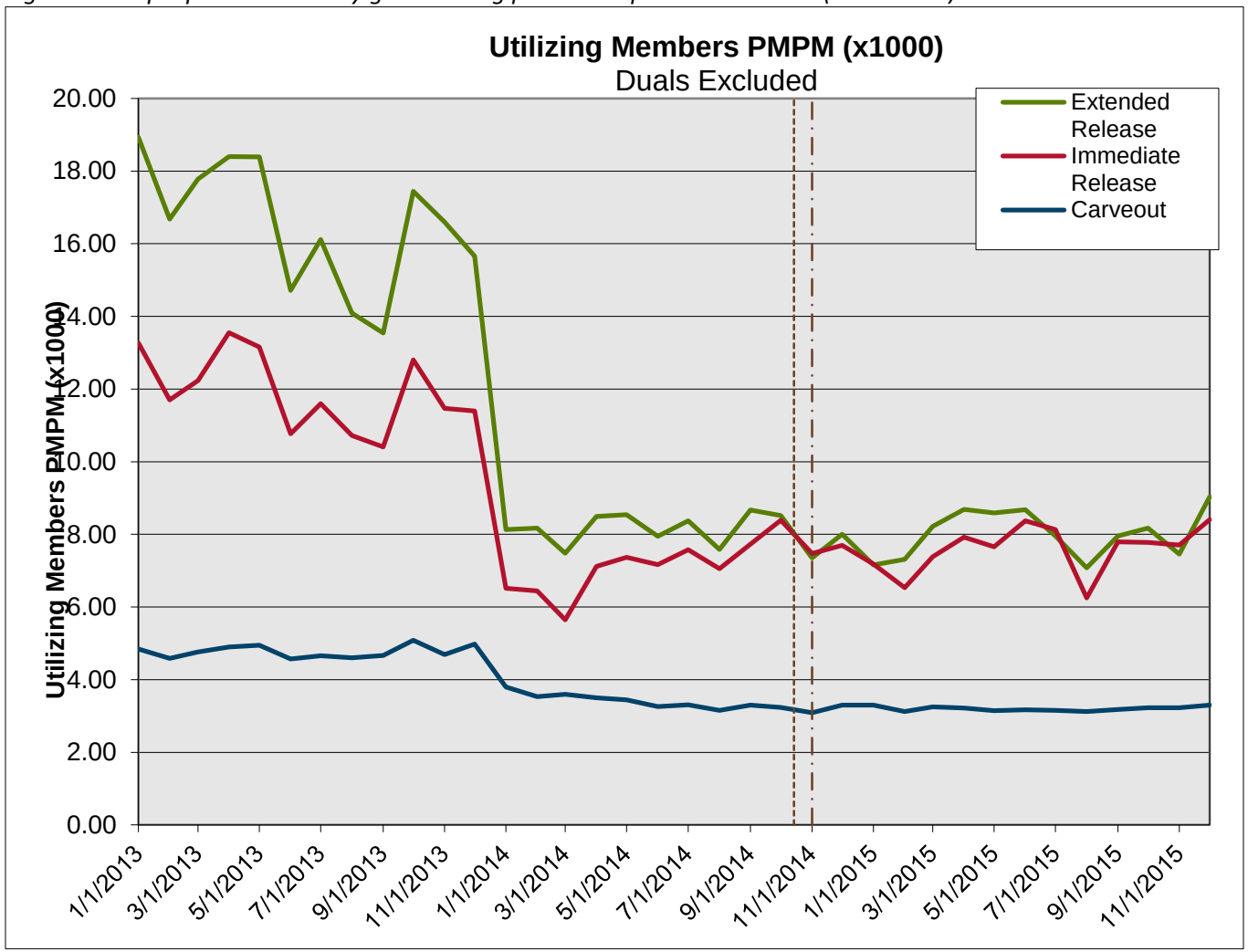
CodeSplProv	**Specialty_Description**
014	Addiction Medicine - Psychiatry
035	Behavioral Rehab Specialist
227	Psychiatrist
312	Psychiatrist
365	Psychiatric Mental Health Nurse Practitioner

Results:

Utilization

Figure 1 shows the utilization of ADHD medications by unique FFS members from January 2013 through November of 2015, categorized as extended release (ER), immediate release (IR) or carve out medications (guanfacine ER, clonidine ER, atomoxetine). The major decrease in January 2014 was due to the expansion population entering FFS. The safety edit was implemented in October of 2014, which did not appear to affect utilization. Extended release and immediate release medications appear to be utilized at similar frequency and are used more than the carveout medications.

Figure 1: unique patient count by generic drug per month per FFS members (2013-2015)



Demographics of Claims Data

Demographics of FFS members and respective claims in both the control and study group are listed in table 3. There were a total of 1,992 index events in the control group, and 3,065 index events in the study group. Mean age increased from 16.4 years in the control group to 21.0 years in the study group. The percentage of FFS members under the age of 6 years decreased from 6.4% to 2.9% from the control to the study group, respectively. The percentage of members above the age of 18 years increased from 27.5% to 44.8%. Index event paid claims for patients outside of normal age ranges decreased from 152 to 9 after implementation of the safety edit. Similarly, index event denied claims for patients outside of the normal age ranges increased from 12 to 197, as a result of the safety edit. There were 12 index event paid claims for patients receiving ADHD medications exceeding the maximum daily dose in the control group, and only 1 in the study group. There were 42 index event paid claims for patients outside of the normal age ranges in the control group, and only 3 in the study group after the PA was implemented.

Table 3: demographics

	Control Group						**Study Group**					
	All Index Events		**Index Event Paid Claim**		**Index Event Denied Claim**		**All Index Events**		**Index Event Paid Claim**		**Index Event Denied Claim**	
N=	**1,992**		1,596	80.1%	396	19.9%	**3,065**		2,074	67.7%	991	32.3%
Mean age (range)	16.4	(2-63)	16.8	(2-63)	14.5	(3-63)	21.0	(1-65)	22.6	(3-65)	17.7	(1-62)
< 6	127	6.4%	113	5.7%	14	0.7%	90	2.9%	19	0.6%	71	2.3%
6-17	1,317	66.1%	1,007	50.6%	310	15.6%	1,602	52.3%	1,017	33.2%	585	19.1%
>= 18	548	27.5%	476	23.9%	72	3.6%	1,373	44.8%	1,038	33.9%	335	10.9%
Female	835	41.9%	666	33.4%	168	8.4%	1,362	44.4%	953	31.1%	409	13.3%
White	1,453	72.9%	1,167	58.6%	286	14.4%	2,182	71.2%	1,471	48.0%	711	23.2%
Patients exceeding max dose per day	24	1.2%	12	0.6%	12	0.6%	46	1.5%	1	0.0%	45	1.5%
- Prescribed by mental health specialist	11	0.6%	4	0.2%	7	0.4%	13	0.4%	0	0.0%	13	0.4%
Patients out of age range	164	8.2%	152	7.6%	12	0.6%	206	6.7%	9	0.3%	197	6.4%
- Prescribed by mental health specialist	44	2.2%	42	2.1%	2	0.1%	61	2.0%	3	0.1%	58	1.9%

Note: Max dose and age range calculations taken on index claim only

Evaluation of PA Requests

To evaluate for opportunities to improve preferred options and decrease the quantity of PA requests, denied claims were broken down by generic drug name (Table 4). The majority of denied claims were for non-preferred agents, most commonly amphetamine ER, methylphenidate ER, and guanfacine ER. The disposition of the PA after a denied claim was also included in Table 3. Only 27.2% of denied claims had a PA requested within 14 days, and 27.1% of those PA requests were approved. Overall, 72.8% of denied claims did not have a PA request sent within 14 days. The number of claims with no PA follow up was particularly high for carve out medications including guanfacine ER (86.5%) and clonidine ER (97.9%). Patients who received a denied claim for carve out drugs and did not have a PA request sent within the 14 days were further evaluated for future pharmacy, including a carve out medication or IR formulation of guanfacine or clonidine in either FFS or CCO claims (Table 4a). The majority of patients (81.3%) with denied claims for carve out medications were switched to a different therapy, whether to the IR formulation or a completely different carve out medication.

Table 4: PA Requests within 14 days of a previously denied claims in the study group

			All Patients with Denied Claim	Patients Requested PA within 14 Days						No PA Request	
				All PA Requests		Approved		Denied			
PDL*	Brand	Form		#	%	#	%	#	%	#	%
			991	**270**	**27.2%**	**269**	**27.1%**	**1**	**0.1%**	**721**	**72.8%**
N	ADDERALL XR	CAP ER 24H	31	17	54.8%	17	54.8%			14	45.2%
N	CONCERTA	TAB ER 24	3	1	33.3%	1	33.3%			2	66.7%
N	DEXMETHYLPHENIDATE HCL	TABLET	16	6	37.5%	6	37.5%			10	62.5%
N	DEXTROAMPHETAMINE SULFATE	TABLET	11	8	72.7%	8	72.7%			3	27.3%
N	DEXTROAMPHETAMINE SULFATE ER	CAPSULE ER	11	4	36.4%	4	36.4%			7	63.6%
N	DEXTROAMPHETAMINE-AMPHET ER	CAP ER 24H	168	66	39.3%	66	39.3%			102	60.7%
N	METADATE ER	TABLET ER	3	1	33.3%	1	33.3%			2	66.7%
N	METHYLIN	TAB CHEW	1							1	100.0%
N	METHYLPHENIDATE ER	CPBP 50-50	1	1	100.0%	1	100.0%			0	0.0%
N	METHYLPHENIDATE ER	TAB ER 24	242	83	34.3%	83	34.3%			159	65.7%
N	METHYLPHENIDATE ER	TABLET ER	38	13	34.2%	13	34.2%			25	65.8%
N	METHYLPHENIDATE HCL	SOLUTION	3	1	33.3%	1	33.3%			2	66.7%
N	METHYLPHENIDATE HCL	TAB CHEW	4	2	50.0%	2	50.0%			2	50.0%
N	METHYLPHENIDATE HCL CD	CPBP 30-70	25	6	24.0%	6	24.0%			19	76.0%
N	METHYLPHENIDATE LA	CPBP 50-50	8	2	25.0%	2	25.0%			6	75.0%
N	METHYLPHENIDATE SR	TABLET ER	2	1	50.0%	1	50.0%			1	50.0%
N	QUILLIVANT XR	SU ER RC24	5	3	60.0%	3	60.0%			2	40.0%
N	RITALIN LA	CPBP 50-50	4	1	25.0%	1	25.0%			3	75.0%
V	CLONIDINE HCL ER	TAB ER 12H	48	1	2.1%	1	2.1%			47	97.9%
V	GUANFACINE HCL ER	TAB ER 24H	251	34	13.5%	33	13.1%	1	0.4%	217	86.5%
V	INTUNIV	TAB ER 24H	48	11	22.9%	11	22.9%			37	77.1%

V	KAPVAY	TAB ER 12H	1						1	100.0%
Y	DEXMETHYLPHENIDATE HCL ER	CPBP 50-50	2						2	100.0%
Y	DEXTROAMPHETAMINE-AMPHETAMINE	TABLET	15	3	20.0%	3	20.0%		12	80.0%
Y	METHYLPHENIDATE HCL	TABLET	9						9	100.0%
Y	STRATTERA	CAPSULE	39	4	10.3%	4	10.3%		35	89.7%
Y	VYVANSE	CAPSULE	2	1	50.0%	1	50.0%		1	50.0%

*PDL status at time of index event

Table 5a: Future Pharmacy for Patients with No PA Request in 14 Days of Denied Claim for Carveout Drug
Future pharmacy includes only another carveout drug as shown below, or clonidine IR or guanfacine IR, from FFS or MCO sources.
Future pharmacy is checked in the 90 days following the date of the denied claim.

Denied Claim for:				Subsequent Pharmacy of type described		No Future Pharmacy of type described	
PDL	Brand	Form		#	%	#	%
V	CLONIDINE HCL ER	TAB ER 12H	47	33	70.2%	14	29.8%
V	GUANFACINE HCL ER	TAB ER 24H	217	186	85.7%	31	14.3%
V	INTUNIV	TAB ER 24H	37	24	64.9%	13	35.1%
V	KAPVAY	TAB ER 12H	1	1	100.0%	0	0.0%
Y	STRATTERA	CAPSULE	35	30	85.7%	5	14.3%

Associated Diagnoses and Contraindications

Sixty-two percent of patients in the control group and 60% in the study group had an FDA labeled and funded indication (ADD/ADHD, binge eating disorder, narcolepsy) for receiving ADHD medications (Table 5). These rates were lower for those 18 years of age and older (49% in the control group and 56% in the study group). There was low overall use for exogenous obesity, which is an unfunded condition. Off-label associated conditions were not significant, and the majority of claims were for major depressive disorder. Over half of patients (54%) over the age of 18 in the study group had a diagnosis that is considered a contraindication or precaution to using these medications. Most notable, 33% of patients 18 years of age or older in the study group had a diagnosis of alcohol or substance abuse or dependence (Table 6).

Table 5: Associated diagnoses in Year Prior to Index Event
Mutually-Exclusive categories

	Control Group				Study Group			
	< 18 Years Old		>= 18 Years Old		< 18 Years Old		>= 18 Years Old	
N=	1,444	72.5%	548	27.5%	1,692	55.2%	1,373	44.8%
FDA Labeled and Funded	963	48.3%	270	13.6%	1,080	63.8%	765	55.7%
ADD/ADHD	963	48.3%	270	13.6%	1,080	63.8%	763	55.6%

Binge Eating Disorder		0.0%		0.0%		0.0%		0.0%
Narcolepsy - symptomatic management		0.0%		0.0%		0.0%	2	0.1%
Unfunded, FDA Labeled	2	0.1%	12	0.6%	2	0.1%	26	1.9%
Exogenous obesity	2	0.1%	12	0.6%	2	0.1%	26	1.9%
Off-Label Indications	91	4.6%	100	5.0%	126	7.4%	218	15.9%
Major Depressive Disorder	77	3.9%	85	4.3%	106	6.3%	182	13.3%
Chronic Fatigue	19	1.0%	36	1.8%	14	0.8%	73	5.3%
Nocturnal enuresis	4	0.2%		0.0%	11	0.7%	2	0.1%
None of the Above	388	19.5%	166	8.3%	484	28.6%	364	26.5%

Table 6: Contraindications in Year Prior to Index Event

	Control Group				**Study Group**			
	< 18 Years Old		**>= 18 Years Old**		**< 18 Years Old**		**>= 18 Years Old**	
N=	1,444	72.5%	548	27.5%	1,692	55.2%	1,373	44.8%
Contraindications/Precautions	323	16.2%	318	16.0%	372	22.0%	748	54.5%
Cardiovascular Disease	7	0.4%	9	0.5%	11	0.7%	29	2.1%
Hyperthyroidism		0.0%		0.0%		0.0%		0.0%
Anxiety States	252	12.7%	225	11.3%	316	18.7%	534	38.9%
Substance or Alcohol Abuse/Dependence	91	4.6%	187	9.4%	74	4.4%	458	33.4%

PA Requests – Control and Study Group

As seen in table 7, the majority of denied claims in both the control group (63.1%) and study group (72.8%) were not followed by a PA request within 14 days of denial. Of the PA requests within 14 days, almost 100% of them were approved.

Table 7: PA Status within 14 days for Patients with Denied Pharmacy Claim as Index Event

PA Requested within 14 days of Denied Claim

	Control Group		**Study Group**	
Patients with Denied Claim =	396		991	
PA Requested	146	36.9%	270	27.2%
Approved	146	36.9%	269	27.1%

Denied	0	0.0%	1	0.1%
No PA Request	250	63.1%	721	72.8%

Emergency Department Visits/Hospitalizations
No differences in all-cause ED visits or hospitalizations were found between the control and study groups (15.1% and 16.9%, respectively [Table 8]). No differences in ED visits or hospitalizations due to contraindications were found between the control and study groups (1.3% and 1.5%, respectively).

Table 8: ED/Hospitalizations within 90 Days of Index Event

	Control Group		**Study Group**	
N=	1,992		3,065	
All Cause ED/Hospitalizations	301	15.1%	517	16.9%
ED/Hospitalizations due to contraindications	25	1.3%	47	1.5%

Discussion:

Implementation of the PA safety edit for dose restrictions in October 2014 and age restrictions in November 2014 did not appear to affect utilization of ADHD medications by FFS members. The large dip in Jan 2014 was due to the ACA expansion population. However, the policy appears to have improved prescribing according to best practice.. There was a decrease in paid claims for patients outside of the standard age range and standard dose range after the PA policy was implemented compared to previously. ces. Additionally, fewer patients under the age of six in the study group received paid claims compared to the control group (0.3% vs. 7.6%, demonstrating an increase in the mean age post-policy and a positive result of PA safety edit. A Further look into these paid claims in the study group revealed that these claims were paid prior to implementation of the new PA policy and no claims outside of best practices were paid after implementation Therefore, the true difference in comparing paid claims between groups for prescriptions outside of best practices is actually larger, giving the PA a larger treatment effect than observed.

Due to the high number of PA requests in this class, drug utilization for denied index events were evaluated and found that of the top 5 prescribed medications, all are non-preferred and 3 are carve out medications. Other than continuing to evaluate cost opportunities, there is no way at this time to reduce the volume of PA requests. Presumably, the reason for the denial is their non-preferred status and not due to clinical inappropriateness. Consistent with previous PA policy evaluations, there is an overall high rate of no PA requests following denied claims. The highest rate comes from the carveout medications (clonidine ER, Strattera, and guanfacine ER). However, the majority of these patients eventually received some type of subsequent pharmacy.

An interesting trend is the increased number of claims for patients over the age of 18 years after the PA safety edit was implemented. This increased utilization by adults is something that should be explored in greater depth, as the evidence is limited for the treatment of ADHD in adults [14 15 16]. Four small short-term trials

provide low-strength evidence of similar effects on ADHD symptoms after 2 to 6 weeks, as well as low-strength evidence of no difference in harms in adults[14]. Currently, the policy does not address the treatment in adults. The exact reason for the increase in utilization in adults is unknown; however, this finding is consistent with recent literature showing an increase of ADHD being diagnosed in adults. There is controversy over the validity of the diagnosis in adults, as the diagnostic criteria are fairly loose and open ended[17].

It is also interesting to note that a high percentage of patients over the age of 18 years 54.5% who were prescribed an ADHD medication had a contraindication or precaution, primarily comorbid anxiety and substance abuse. Roughly one-third of all combined patients included in the data have a documented history of substance or alcohol abuse or dependence. This number parallels the data found from the previous DUE[4], in which 34% of those patients also had a history of substance abuse. ADHD medications have a high abuse potential, and therefore use of these agents should be cautioned in patients with known substance abuse and a higher baseline chance of abuse. The literature consistently demonstrates that adults with ADHD are more likely to have comorbidities than adults without ADHD, including anxiety, bipolar disorder, depression, and drug or alcohol abuse[4 13 16]. Other states (Delaware, Idaho, Texas, Utah, Missouri) have incorporated extensive screening for substance abuse into their PA policies[4], with Idaho and Texas[4 5] automatically excluding patients with a history of substance abuse within the previous 12 months. This criterion should be consideredbecause of the increasing abuse of these medications[1 4 13]. This illustrates the importance of patients having appropriate diagnoses for these medications, especially adults, and having the medications prescribed by a mental health specialist. Otherwise, patients may be receiving medications that are potentially harmful and the risks may outweigh the benefits. There was also a higher rate of off-label use of these medications in adults, primarily those with major depressive disorder.

Current NICE guideline in the treatment and diagnosis of adult ADHD recommends that adult patients presenting with ADHD symptoms, with or without a childhood diagnosis, be referred for assessment by a mental health specialist for proper diagnosis of ADHD.[15] First line therapy recommendations for adult ADHD is methylphenidate. For unresponsive or intolerance to methylphenidate or potential of misuse/abuse, atomoxetine should be considered. However, in patients with a history of substance abuse, the guidelines suggest that if there may be a concern about the potential for drug misuse and diversion, atomoxetine may be considered first line drug treatment. After atomoxetine, controlled-release formulations should be used due to less likelihood of abuse.[15] Survey data suggests that lifetime nonmedical use is more frequent with immediate release methylphenidate or dextroamphetamine compared with mixed amphetamine salts and that amphetamine/dextroamphetamine had the highest rate of diversion.[14] The Center for Disease Control (CDC) also recommends the following criteria are met in adults: 1) several symptoms were present before age 12 years, 2) several symptoms are present in 2 or more settings, 3) clear evidence that the symptoms interfere with, or reduce the quality of work functioning, and 4) the symptoms are not better explained by another mental disorder and do not happen only during the course of another psychotic disorder.

Emergency department visits and hospitalization rates seemed to match what was typically expected, and did not vary between the control and study groups. While it is important to evaluate for major harms such as hospitalizations, especially due to contraindications to the medication, this data does not show that the PA safety edit had any impact on harms within 90 days of an index event.

Limitations:

All of the data collected and analyzed was claims data, which limits the ability to directly connect a patient's diagnosis with the medications being prescribed. Claims data only allows us to make associations and assumptions about why patients are taking certain medications of interest, especially if patients do not have a diagnosis code on file. Data regarding provider types was collected using specialty provider codes, in attempt to compare and contrast prescriptions coming from recognized mental health providers as opposed to non-mental health specialists. However, these codes are also not great at identifying all recognized mental health specialties, and therefore made it difficult to infer how many prescriptions were from mental health specialists. We also only looked at claims data

for index events, and the data could be analyzed more in depth if recurrent patients and utilization was included. Including recurrent claims data would help to support the decision for implementation of an automatic PA approval for a subset of patients meeting pre-defined criteria.

Recommendations for the PA Policy

Overall, the data shows that the goals of the PA safety edit were met. Decreased utilization in inappropriate populations was observed, the majority of claims were for FDA approved and funded conditions, and the PA denied claims for prescriptions were outside of best practices. A potentially beneficial amendment to make to the PA would be to tighten control in adults because the data show that nearly one-third of patients taking these ADHD medications have a prior history of substance abuse. Currently, there is no mechanism to ensure patients with treatment-resistant ADHD symptoms are receiving specialty care nor is there a process to support increased monitoring for members receiving CNS Stimulants with an increased risk of substance misuse. DSM-IV criteria defines substance abuse as a maladaptive pattern of substance use leading to clinically significant impairment or distress, manifested by at least one major criterion in the past 12 months, listed in DSM-IV[18].This amendment would ideally increase safety and decrease abuse of ADHD medications.

Other considerations are to require non-stimulants as first line treatment for adults with a history of substance abuse or misuse or to include appropriate diagnostic criteria in the policy according to DSM-IV for adults.

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Appendix 1:

Table A1: Codes identifying ADHD drugs in fee-for-service or managed care pharmacy or professional claims

GSN	Generic	Strength	mg per Unit	FormDesc	ER	PDL	Min Age (Yrs)	Max Age (Yrs)	Max Daily Units
004999	DEXTROAMPHETAMINE/AMPHETAMINE	5 mg	5	TABLET	0	1	3		12
005000	DEXTROAMPHETAMINE/AMPHETAMINE	10 mg	10	TABLET	0	1	3		6
005001	DEXTROAMPHETAMINE/AMPHETAMINE	20 mg	20	TABLET	0	1	3		3
034359	DEXTROAMPHETAMINE/AMPHETAMINE	30 mg	30	TABLET	0	1	3		2
047131	DEXTROAMPHETAMINE/AMPHETAMINE	7.5 mg	7.5	TABLET	0	1	3		8
047132	DEXTROAMPHETAMINE/AMPHETAMINE	12.5 mg	12.5	TABLET	0	1	3		4.8
047133	DEXTROAMPHETAMINE/AMPHETAMINE	15 mg	15	TABLET	0	1	3		4
048701	DEXTROAMPHETAMINE/AMPHETAMINE	10 mg	10	CAP ER 24H	1	0	6		3
048702	DEXTROAMPHETAMINE/AMPHETAMINE	20 mg	20	CAP ER 24H	1	0	6		1.5
048703	DEXTROAMPHETAMINE/AMPHETAMINE	30 mg	30	CAP ER 24H	1	0	6		1
050428	DEXTROAMPHETAMINE/AMPHETAMINE	5 mg	5	CAP ER 24H	1	0	6		6
050429	DEXTROAMPHETAMINE/AMPHETAMINE	15 mg	15	CAP ER 24H	1	0	6		2
050430	DEXTROAMPHETAMINE/AMPHETAMINE	25 mg	25	CAP ER 24H	1	0	6		1.2
061443	METHYLPHENIDATE HCL	10 mg	10	CSBP 40-60	1	0	6		7.2
061444	METHYLPHENIDATE HCL	15 mg	15	CSBP 40-60	1	0	6		4.8
061445	METHYLPHENIDATE HCL	20 mg	20	CSBP 40-60	1	0	6		3.6
061446	METHYLPHENIDATE HCL	30 mg	30	CSBP 40-60	1	0	6		2.4
061447	METHYLPHENIDATE HCL	40 mg	40	CSBP 40-60	1	0	6		1.8
061448	METHYLPHENIDATE HCL	50 mg	50	CSBP 40-60	1	0	6		1.4
061449	METHYLPHENIDATE HCL	60 mg	60	CSBP 40-60	1	0	6		1.2
060615	METHYLPHENIDATE	10 mg /9 hr	10	PATCH TD24	1	1	6		3
060616	METHYLPHENIDATE	15 mg/ 9 hr	15	PATCH TD24	1	1	6		2
060617	METHYLPHENIDATE	20 mg/ 9 hr	20	PATCH TD24	1	1	6		1.5
060618	METHYLPHENIDATE	30 mg/ 9 hr	30	PATCH TD24	1	1	6		1
005009	DEXTROAMPHETAMINE SULFATE	10 mg	10	TABLET	0	0	6		4
005011	DEXTROAMPHETAMINE SULFATE	5 mg	5	TABLET	0	0	6		8
048982	DEXMETHYLPHENIDATE HCL	2.5 mg	2.5	TABLET	0	0	6		8
048983	DEXMETHYLPHENIDATE HCL	5 mg	5	TABLET	0	0	6		4

048984	DEXMETHYLPHENIDATE HCL	10 mg	10	TABLET	0	0	6		2
064090	DEXTROAMPHETAMINE SULFATE	5 mg/5 mL	1	SOLUTION	0	0	6		40
005005	DEXTROAMPHETAMINE SULFATE	10 mg	10	CAPSULE ER	1	0	6		6
005006	DEXTROAMPHETAMINE SULFATE	15 mg	15	CAPSULE ER	1	0	6		4
005007	DEXTROAMPHETAMINE SULFATE	5 mg	5	CAPSULE ER	1	0	6		12
075025	DEXTROAMPHETAMINE/AMPHETAMINE	2.5 mg/mL	2.5	SUS BP 24H	1	0	6		24
005002	AMPHETAMINE SULFATE	10 mg	10	TABLET	0	0	3		6
005003	AMPHETAMINE SULFATE	5 mg	5	TABLET	0	0	3		12
059190	DEXMETHYLPHENIDATE HCL	5 mg	5	CPBP 50-50	1	1	6		6 if <18 yo 8 if ≥18 yo
059191	DEXMETHYLPHENIDATE HCL	10 mg	10	CPBP 50-50	1	1	6		3 if <18 yo 4 if ≥18 yo
059192	DEXMETHYLPHENIDATE HCL	20 mg	20	CPBP 50-50	1	1	6		1.5 if <18 yo 2 if ≥18 yo
061317	DEXMETHYLPHENIDATE HCL	15 mg	15	CPBP 50-50	1	1	6		2 if <18 yo 2.7 if ≥18 yo
065909	DEXMETHYLPHENIDATE HCL	30 mg	30	CPBP 50-50	1	1	6		1 if <18 yo 1.3 if ≥18 yo
066611	DEXMETHYLPHENIDATE HCL	40 mg	40	CPBP 50-50	1	1	6		0.75 if <18 yo 1 if ≥18 yo
067692	DEXMETHYLPHENIDATE HCL	25 mg	25	CPBP 50-50	1	1	6		1.2 if <18 yo 1.6 if ≥18 yo
067693	DEXMETHYLPHENIDATE HCL	35 mg	35	CPBP 50-50	1	1	6		0.86 if <18 yo 1.1 if ≥18 yo
065570	GUANFACINE HCL	1 mg	1	TAB ER 24H	1	0	6	17	4
065572	GUANFACINE HCL	2 mg	2	TAB ER 24H	1	0	6	17	2
065573	GUANFACINE HCL	3 mg	3	TAB ER 24H	1	0	6	17	1.3
065574	GUANFACINE HCL	4 mg	4	TAB ER 24H	1	0	6	17	1
066895	CLONIDINE HCL	0.1 mg	0.1	TAB ER 12H	1	0	6	17	4
005014	METHAMPHETAMINE HCL	5 mg	5	TABLET	0	0	6		Not established
054676	METHYLPHENIDATE HCL	2.5 mg	2.5	TAB CHEW	0	0	4		24
054677	METHYLPHENIDATE HCL	5 mg	5	TAB CHEW	0	0	4		12
054678	METHYLPHENIDATE HCL	10 mg	10	TAB CHEW	0	0	4		6

054679	METHYLPHENIDATE HCL	5 mg/5 mL	1	SOLUTION	0	0	4		60
054680	METHYLPHENIDATE HCL	10 mg/5 mL	2	SOLUTION	0	0	4		30
004029	METHYLPHENIDATE HCL	20 mg	20	TABLET ER	1	0	6		3.6
044072	METHYLPHENIDATE HCL	10 mg	10	TABLET ER	1	0	6		7.2
045981	METHYLPHENIDATE HCL	18 mg	18	TAB ER 24	1	0	6		4
045982	METHYLPHENIDATE HCL	36 mg	36	TAB ER 24	1	0	6		2
047318	METHYLPHENIDATE HCL	54 mg	54	TAB ER 24	1	0	6		1.3
050172	METHYLPHENIDATE HCL	27 mg	27	TAB ER 24	1	0	6		2.7
004026	METHYLPHENIDATE HCL	10 mg	10	TABLET	0	1	4		10
004027	METHYLPHENIDATE HCL	20 mg	20	TABLET	0	1	4		3
004028	METHYLPHENIDATE HCL	5 mg	5	TABLET	0	1	4		12
053056	METHYLPHENIDATE HCL	10 mg	10	CPBP 30-70	1	0	6		7.2
053057	METHYLPHENIDATE HCL	20 mg	20	CPBP 30-70	1	0	6		3.6
053058	METHYLPHENIDATE HCL	30 mg	30	CPBP 30-70	1	0	6		2.4
060545	METHYLPHENIDATE HCL	40 mg	40	CPBP 30-70	1	0	6		1.8
060546	METHYLPHENIDATE HCL	50 mg	50	CPBP 30-70	1	0	6		1.4
060547	METHYLPHENIDATE HCL	60 mg	60	CPBP 30-70	1	0	6		1.2
075263	METHYLPHENIDATE HCL	20 mg	20	TAB CBP24H	1	0	6		3.6
075264	METHYLPHENIDATE HCL	30 mg	30	TAB CBP24H	1	0	6		2.4
075265	METHYLPHENIDATE HCL	40 mg	40	TAB CBP24H	1	0	6		1.8
070374	METHYLPHENIDATE HCL	5 mg/mL (25 mg/5 mL)	5	SU ER RC24	1	0	6		14.4
053059	METHYLPHENIDATE HCL	20 mg	20	CPBP 50-50	1	0	6		3.6
053060	METHYLPHENIDATE HCL	30 mg	30	CPBP 50-50	1	0	6		2.4
053061	METHYLPHENIDATE HCL	40 mg	40	CPBP 50-50	1	0	6		1.8
053974	METHYLPHENIDATE HCL	10 mg	10	CPBP 50-50	1	0	6		7.2
072092	METHYLPHENIDATE HCL	60 mg	60	CPBP 50-50	1	0	6		1.2
051489	ATOMOXETINE HCL	10 mg	10	CAPSULE	0	1	6		10
051490	ATOMOXETINE HCL	18 mg	18	CAPSULE	0	1	6		5.6
051491	ATOMOXETINE HCL	25 mg	25	CAPSULE	0	1	6		4
051492	ATOMOXETINE HCL	40 mg	40	CAPSULE	0	1	6		2.5
051493	ATOMOXETINE HCL	60 mg	60	CAPSULE	0	1	6		1.7
060390	ATOMOXETINE HCL	80 mg	80	CAPSULE	0	1	6		1.25

060391	ATOMOXETINE HCL	100 mg	100	CAPSULE	0	1	6		1
062283	LISDEXAMFETAMINE DIMESYLATE	30 mg	30	CAPSULE	0	1	6		2.3
062284	LISDEXAMFETAMINE DIMESYLATE	50 mg	50	CAPSULE	0	1	6		1.4
062285	LISDEXAMFETAMINE DIMESYLATE	70 mg	70	CAPSULE	0	1	6		1
063645	LISDEXAMFETAMINE DIMESYLATE	20 mg	20	CAPSULE	0	1	6		3.5
063646	LISDEXAMFETAMINE DIMESYLATE	40 mg	40	CAPSULE	0	1	6		1.75
063647	LISDEXAMFETAMINE DIMESYLATE	60 mg	60	CAPSULE	0	1	6		1.2
073292	LISDEXAMFETAMINE DIMESYLATE	10 mg	10	CAPSULE	0	1	6		7
005009	DEXTROAMPHETAMINE SULFATE	10 mg	10	TABLET	0	0	6		4
005010	DEXTROAMPHETAMINE SULFATE	15 mg	15	TABLET	0	0	6		2.7
005011	DEXTROAMPHETAMINE SULFATE	5 mg	5	TABLET	0	0	6		8
071048	DEXTROAMPHETAMINE SULFATE	2.5 mg	2.5	TABLET	0	0	6		16
071049	DEXTROAMPHETAMINE SULFATE	7.5 mg	7.5	TABLET	0	0	6		5.3
072313	DEXTROAMPHETAMINE SULFATE	20 mg	20	TABLET	0	0	6		2
072314	DEXTROAMPHETAMINE SULFATE	30 mg	30	TABLET	0	0	6		1.3

HSN = hierarchical ingredient code list (HICL) sequence number as reported by First DataBank™

PDL = preferred drug list

0= no; 1=yes

Table A2: Codes Identifying IR clonidine and guanfacine

GSN	Generic	Strength	FormDesc	ER
000364	Guanfacine	1 mg	TABLET	0
011984	Guanfacine	2 mg	TABLET	0
000346	Clonidine	0.1 mg	TABLET	0
000347	Clonidine	0.2 mg	TABLET	0
000348	Clonidine	0.3 mg	TABLET	0

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.
- Stimulants in adults age 18 years and older
- Regimens prescribed outside of standard doses and age range (Tables 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**	**Age ≥18 years lisdexamfetamine only**	**Not approved**	**Not Approved**	**Not approved**

Table 2. Standard Age and Maximum Daily Doses.

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

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

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

Table 3. Standard Combination Therapy for ADHD

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

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

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

Approval Criteria		
4. Will the prescriber consider a change to a preferred agent? Message: • Preferred drugs do not require co-pay and are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred alternatives	**No:** Go to #5
5. Does the patient have a history of drug abuse or drug dependence (e.g. opioids, amphetamines, cocaine, marijuana, hallucinogenic agents) or alcohol abuse in the previous 12 months?	**Yes:** Go to #6	**No:** Go to #7
6. Was the drug prescribed by or in consultation with a psychiatric specialist?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the treated diagnosis Binge Eating Disorder?	**Yes:** Go to #8	**No:** Go to #9
8. Does the patient have significant mental health diagnoses (e.g. major depression, PTSD, social phobia, etc.)?	**Yes:** Pass to RPh: Deny for medical appropriateness	**No:** Go to #9
9. Is the request for an approved FDA indication defined in Table 1?	**Yes:** Go to #10	**No:** Go to #13
10. Are the patient's age and the prescribed dose within the limits defined in Table 2?	**Yes:** Go to #11	**No:** Go to #13
11. 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 #12
12. Is the multi-drug regimen considered a standard combination as defined in Table 3?	**Yes:** Approve for up to 12 months	**No:** Go to #13

Approval Criteria		
13. Was the drug regimen developed by, or in consultation with, a psychiatrist, developmental pediatrician, psychiatric nurse practitioner, sleep specialist or neurologist?	**Yes:** Document name and contact information of consulting provider and approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Doses exceeding defined limits or non-recommended multi-drug regimens of stimulants and/or non-stimulants are only approved when prescribed by a psychiatrist or in consultation with a mental health specialist. May approve continuation of existing therapy once up to 90 days to allow time to consult with a mental health specialist.

P&T Review: *7/16 (MH); 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

Class Update: Tobacco Cessation Products

Date of Review: July 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 high quality evidence that varenicline improves continuous or sustained abstinence compared to placebo (RR 2.24; 95% CI 2.06 to 2.43; NNT 11) and bupropion (RR 1.39; 95% CI 1.25 to 1.54), and moderate quality evidence compared to nicotine patches (RR RR 1.25; 95% CI 1.14 to 1.37).[2] There is also high quality evidence that compared to placebo, patients on varenicline experience more serious adverse events (RR 1.25; 95% CI 1.04 to 1.49).
- 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).[3]
- 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).[4]
- There is insufficient evidence that NRT improves prolonged abstinence rates in pregnant women who continue to smoke.[5,6] 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).[6]

- 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.[7] There is also low quality evidence based on one randomized controlled trial[8] 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).[9]
- 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).[10]
- There is low quality evidence that there is no significant difference in neuropsychiatric adverse events between varenicline, placebo, bupropion or nicotine patches in both patients with and without a history of psychiatric disorders.[11] These results may not be generalizable to those with unstable or untreated psychiatric disorders.

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. [3] It is well confirmed that smoking increases risk of respiratory disease, CVD, diabetes mellitus, autoimmune disorders, reproductive system disorders, and many kinds of cancers.[3] Tobacco addiction is caused by the nicotine, which causes a release of dopamine stimulating a pleasurable effect from smoking.[12] 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.[13] 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.[14]

First-line medications for tobacco dependence include NRT, bupropion SR, and varenicline. [14] 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.[4] 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. [14] 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.[15] 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.[5] 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.[16]

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 2016 Cochrane Systematic Review evaluated the efficacy of nicotine receptor partial agonists, including varenicline for smoking cessation.[2] RCTs comparing varenicline to placebo, bupropion and nicotine patches were included. Thirty-nine varenicline trials were included demonstrating high quality evidence for

improved continuous or sustained abstinence at 6 months or longer of (RR 2.24; 95% CI 2.06 to 2.43) with a number needed to treat (NNT) of 11 (95% CI 9 to 13). [2] There was also high quality evidence from 5 trials that varenicline improved cessation rates compared to bupropion (RR 1.39; 95% CI 1.25 to 1.54) and moderate quality evidence compared to nicotine patches (RR 1.25; 95% CI 1.14 to 1.37; 8 trials). [2] Four trials evaluated varenicline beyond the standard 12-week regimen and found it to be safe and well tolerated. Lastly, limited evidence suggests that varenicline may have a role in relapse prevention (RR 3.64; 95% CI 2.81 to 4.72). There was also high quality evidence that patients on varenicline experienced more serious adverse events than those on placebo (RR 1.25; 95% CI 1.04 to 1.49). This review included the recent EAGLES trial[11] which did not show significant difference in neuropsychiatric adverse events between varenicline and placebo, bupropion, or NRT. A pooled analysis of 4 trials found varenicline to be beneficial in smokers with a psychiatric disorder (RR 2.28; 95% CI 1.82 to 2.87). [2]

A systematic review and meta-analysis of RCTs was conducted to evaluate the efficacy and safety of varenicline combined with NRT to achieve abstinence.[3] 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.[10] 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.[5] 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. [17] 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.[18] 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.[18] 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.[11]

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.[4] 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	12-week continued abstinence 1. 23 (23%) 2. 26 (26%) OR 1.19; 95% CI 0.62-2.28); p=0.61 Nausea 1. 18 (18%) 2. 80 (80%) RR 4.4 (2.99-6.7); P<0.001 Vomiting 1. 3 (3%) 2. 36 (36%) RR 12 (95% CI 3.8-48.3); p<0.001
Schnoll, et al.[19] 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	24 week abstinence: Standard: 21.7% Extended/Maintenance: 27.2% P=0.17 Multivariate model controlled for covariates; abstinence rates Extended/Maintenance versus standard: OR 1.70; 95% CI 1.02-2.81 52 week abstinence: Standard/extended: 23.8%

				Maintenance: 20.3% P=0.44; OR 1.17; 95% CI 0.69-1.90
Baker, et al.[20] 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.[8] 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.[21] 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[6] 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.[9] 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.[22] 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.[23] 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[24] 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.[25] 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.[7] 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	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

		week 12 after 12 weeks' open-label varenicline and behavioral therapy			
EAGLES trial[11] 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

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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.

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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.

13. Anthenelli RM, Benowitz, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomized, placebo-controlled clinical trial. *Lancet*. 2016 Apr 22.

BACKGROUND: Substantial concerns have been raised about the neuropsychiatric safety of the smoking cessation medications varenicline and bupropion. Their efficacy relative to nicotine patch largely relies on indirect comparisons, and there is limited information on safety and efficacy in smokers with psychiatric disorders. We compared the relative neuropsychiatric safety risk and efficacy of varenicline and bupropion with nicotine patch and placebo in smokers with and without psychiatric disorders.

METHODS: We did a randomised, double-blind, triple-dummy, placebo-controlled and active-controlled (nicotine patch; 21 mg per day with taper) trial of varenicline (1 mg twice a day) and bupropion (150 mg twice a day) for 12 weeks with 12-week non-treatment follow-up done at 140 centres (clinical trial centres, academic centres, and outpatient clinics) in 16 countries between Nov 30, 2011, and Jan 13, 2015. Participants were motivated-to-quit smokers with and without psychiatric disorders who received brief cessation counselling at each visit. Randomisation was computer generated (1:1:1:1 ratio). Participants, investigators, and research personnel were masked to treatment assignments. The primary endpoint was the incidence of a composite measure of moderate and severe neuropsychiatric adverse events. The main efficacy endpoint was biochemically confirmed continuous abstinence for weeks 9-12. All participants randomly assigned were included in the efficacy analysis and those who received treatment were included in the safety analysis. The trial is registered at ClinicalTrials.gov (number NCT01456936) and is now closed.

FINDINGS: 8144 participants were randomly assigned, 4116 to the psychiatric cohort (4074 included in the safety analysis) and 4028 to the non-psychiatric cohort (3984 included in the safety analysis). In the non-psychiatric cohort, 13 (1·3%) of 990 participants reported moderate and severe neuropsychiatric adverse events in the varenicline group, 22 (2·2%) of 989 in the bupropion group, 25 (2·5%) of 1006 in the nicotine patch group, and 24 (2·4%) of 999 in the placebo group. The varenicline-placebo and bupropion-placebo risk differences (RDs) for moderate and severe neuropsychiatric adverse events were -1·28 (95% CI -2·40 to -0·15) and -0·08 (-1·37 to 1·21), respectively; the RDs for comparisons with nicotine patch were -1·07 (-2·21 to 0·08) and 0·13 (-1·19 to 1·45), respectively. In the psychiatric cohort, moderate and severe neuropsychiatric adverse events were reported in 67 (6·5%) of 1026 participants in the varenicline

group, 68 (6·7%) of 1017 in the bupropion group, 53 (5·2%) of 1016 in the nicotine patch group, and 50 (4·9%) of 1015 in the placebo group. The varenicline-placebo and bupropion-placebo RDs were 1·59 (95% CI -0·42 to 3·59) and 1·78 (-0·24 to 3·81), respectively; the RDs versus nicotine patch were 1·22 (-0·81 to 3·25) and 1·42 (-0·63 to 3·46), respectively. Varenicline-treated participants achieved higher abstinence rates than those on placebo (odds ratio [OR] 3·61, 95% CI 3·07 to 4·24), nicotine patch (1·68, 1·46 to 1·93), and bupropion (1·75, 1·52 to 2·01). Those on bupropion and nicotine patch achieved higher abstinence rates than those on placebo (OR 2·07 [1·75 to 2·45] and 2·15 [1·82 to 2·54], respectively). Across cohorts, the most frequent adverse events by treatment group were nausea (varenicline, 25% [511 of 2016 participants]), insomnia (bupropion, 12% [245 of 2006 participants]), abnormal dreams (nicotine patch, 12% [251 of 2022 participants]), and headache (placebo, 10% [199 of 2014 participants]). Efficacy treatment comparison did not differ by cohort.

INTERPRETATION: The study did not show a significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch or placebo. Varenicline was more effective than placebo, nicotine patch, and bupropion in helping smokers achieve abstinence, whereas bupropion and nicotine patch were more effective than placebo.

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

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: *7/16 (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

Literature Scan: Antidepressants

Date of Review: July 2016

Date of Last Review: September 2014
Literature Search: October 2014 – June 2016

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

Conclusions:

- A Cochrane review published in 2014 compared the efficacy and tolerability profile of paroxetine to tricyclic antidepressants (TCAs), other selective serotonin reuptake inhibitors (SSRIs) and newer antidepressants. Most of the studies included in the analysis were at unclear or high risk of bias due to poor reporting of study characteristics or incomplete outcome reporting. Although some possibly meaningful differences between paroxetine and other antidepressants (ADs) were noted, no definitive conclusions can be drawn regarding the preference of one AD over another. There is no new comparative evidence between antidepressants that changes the previous conclusions.
- The Agency for Healthcare Research and Quality (AHRQ) funded a systematic review to evaluate the benefits and harms of second generation antidepressants (SGAs) compared to non-pharmacologic interventions such as cognitive behavioral therapy (CBT) or herbal supplements such as St. John's wort. The authors found low quality evidence with a high risk of bias and concluded both CBT and SGAs are reasonable choices for first line treatment of adults with depression.
- Several systematic reviews evaluated the safety and efficacy of antidepressants in specific populations such as post-partum women and patients with cancer, epilepsy or end stage renal disease. In the absence of robust and reliable evidence the authors were unable to draw effective conclusions regarding the impact of antidepressants in managing depression in these unique populations. More studies in each of these populations is needed to guide clinical practice.
- Two systematic evaluations focused on antidepressant therapy in pediatric patients concluded that selective serotonin reuptake inhibitors (SSRIs) are better tolerated with superior efficacy compared to TCA therapy. One systematic review concluded fluoxetine was best tolerated and the most effective for treating depression in children and adolescents. However, the quality of the studies ranged from low to moderate quality with unclear to high risk of bias.
- A retrospective cohort study conducted in children enrolled in the Tennessee Medicaid program found no evidence of increased suicide risk for sertraline, paroxetine, citalopram, escitalopram or venlafaxine compared with fluoxetine in children and adolescents.
- Vilazodone received an expanded indication from the Food and Drug Administration (FDA) in March 2015 for a lower 20 mg dose to treat major depressive disorder. An additional Phase III trial demonstrated the efficacy of the 20mg dose in treating major depressive disorder.
- New safety warnings were issued by the FDA after reports of orthostatic hypotension, falls and syncope were reported with therapeutic doses of duloxetine. An analysis of patients from all placebo controlled trials revealed that patients treated with duloxetine reported a higher rate of falls compared to patients treated with placebo.

Recommendations:

- There is no evidence of a difference in safety or efficacy between antidepressants and preference can be established on cost and patient specific factors. Evaluate comparative antidepressant costs in Executive Session.

Previous Conclusions:

- There is low quality evidence that shows there are minimal differences in efficacy between first and second generation antidepressants. While some meta-analyses show a trend towards greater improvement with tricyclic antidepressants (TCAs) compared to selective serotonin receptor inhibitors (SSRIs), TCAs are no longer favored when only higher quality studies are considered.
- The safety profiles of antidepressants vary by class, and there is no comprehensive analysis that directly compares the rate and type of adverse events between first and second generation antidepressants. There is low quality evidence to show that SSRIs are more tolerable than TCAs, as a larger proportion of patients treated with TCAs withdrew treatment due to adverse events compared to those treated with SSRIs. MAOIs are associated with more drug-drug and food-drug interactions than any other class of antidepressants.

Previous Recommendations:

- The selection of the appropriate medication for a patient should be chosen based on the properties of an individual drug, as opposed to a drug group.
- In alignment with treatment guidelines, first and second generation antidepressants should be accessible to patients, with the selection of the individual agent dependent on severity of condition, comorbidities, medication history, and tolerability of side effects for the individual patient.
- Recommend including first generation antidepressants to the voluntary PDL and evaluate costs in executive session. Consider a non-preferred status for MAOIs, given the known safety concerns including high risks of drug-drug and drug-food interactions. Also maintain nefazodone as non-preferred due to hepatic safety concerns.

Methods:

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

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will not be identified and reviewed if there is ample evidence from high-quality systematic reviews.

New Systematic Reviews:

Comparative Assessments

Paroxetine Compared To Other Antidepressants

A 2014 Cochrane review compared the SSRI paroxetine with other antidepressants (ADs) to evaluate efficacy, safety, and tolerability in adults with depression.[1] One hundred fifteen RCTs involving 26,134 patients were included in the meta-analysis. Ninety nine (86%) of the 115 RCTs were double blinded. In 54 studies paroxetine was compared with TCAs including: dothiepin, nortriptyline, amitriptyline, imipramine, desipramine, maprotiline, mianserin, clomipramine, lofepramine, and doxepin.[1] Twenty-one trials compared paroxetine with other SSRIs including: sertraline, escitalopram, fluoxetine and fluvoxamine.[1] Forty studies evaluated paroxetine with other ADs including: trazodone, milnacipran, venlafaxine, nefazodone, reboxetine, bupropion, hypericum, tianeptine, mirtazapine, duloxetine, amisulpride, and agomelatine. The authors assessed the study methodology as poor with substantial unclear risk of bias. The evidence the reviewers found in terms of efficacy, acceptability and tolerability of paroxetine compared with certain antidepressants (ADs), was of low to moderate quality.[1] No statistically significant difference was noted in efficacy between paroxetine and TCAs as a class (OR: 1.04, 95% CI 0.92 to 1.17).[1] When number of people who responded to treatment with paroxetine was compared to SSRIs, a difference in favor of citalopram over paroxetine (OR: 1.54, 95% CI 1.04 to 2.28) was noted.[1] For the other ADs in the efficacy assessment, there was a trend in favor of paroxetine over reboxetine (OR: 0.82, 95% CI 0.66 to 1.02).[1] In head-to-head comparisons with TCAs, paroxetine was better tolerated than clomipramine (OR: 0.67, 95% CI 0.52) and imipramine (OR: 0.65, 95% CI 0.50 to 0.85).[1] The analysis of dropouts due to side effects revealed that amitriptyline (OR: 0.74, 95% CI 0.56 to 0.98), clomipramine (OR: 0.59, 95% CI 0.41 to 0.84), and imipramine (OR: 0.58, 95% CI 0.43 to 0.77) were significantly less well tolerated than paroxetine.[1] For the SRRI comparison, paroxetine was less well tolerated than fluoxetine (OR: 1.34, 95% CI 1.06 to 1.70).[1] No differences were found between paroxetine and the other SSRI's in terms of number of patients who experienced side effects (OR: 1.12, 95% CI 0.42-2.97).[1] For the assessment of other ADs and patient drop out due to side effects, a difference between paroxetine and reboxetine (OR: 0.38, 95% CI 0.17 to 0.86) was noted in favor of paroxetine; and a difference between paroxetine and tianeptine (OR: 3.38, 95% CI 1.31 to 8.71) was noted in favor of tianeptine.[1] Data from this review suggest some possible differences between paroxetine and other ADs, but the clinical meaning of these differences is uncertain, and no definitive implications for clinical practice can be drawn.[1] Although this Cochrane review included numerous studies, it is difficult to draw conclusions as to which antidepressant may be preferred over another agent. Patient tolerance and improvement in symptoms must be evaluated on a case by case basis when antidepressant therapy is warranted.

<u>Second Generation Antidepressants Compared To Psychological and Complementary Treatments</u>

A systematic review funded by the Agency for Healthcare Research and Quality (AHRQ) focused on comparing second generation antidepressant (SGA) pharmacotherapy to alternative interventions such as cognitive behavioral therapy (CBT), herbal therapy such as St. John's wort, or exercise.[2] Forty three trials which compared the benefits and harms of SGAs with other treatments were included in the evidence synthesis. The authors rated 37% of the trials as having a high risk of bias.[2] When CBT was compared to SGAs, similar response rates were noted (44% vs. 46%; relative risk [RR], 0.90 [95% CI, 0.76 to 1.07]).[2] Remission rates were similar between CBT and SGA treatment groups (41% vs. 48%; RR, 0.98 [CI, 0.73 to 1.32]).[2] In both treatment groups, 16% of patients discontinued treatment (RR, 1.00 [CI, 0.55 to 1.81]).[2] Treatment discontinuations because of adverse events were numerically higher for patients on SGAs but did not reach statistical significance (8% vs. 3%; RR, 2.51 [CI, 0.40 to 15.46]) when compared to CBT.[2] Similar response rates for patients treated with SGAs or St. John's wort (52% vs. 54%; RR, 0.96 [CI, 0.83 to 1.11) were noted.[2] No statistically significant difference in remission rates (30% vs. 36%; RR, 0.85 [CI, 0.70 to 1.04]) was observed between SGAs and St. John's wort treatment groups.[2] Patients treated with antidepressants had a significantly higher risk for treatment discontinuation (16% vs. 12%; RR, 1.28 [CI, 1.01 to 1.62]) and discontinuation because of adverse events (7% vs. 4%; RR, 1.70 [CI, 1.12 to 2.60]) than those on St. John's wort.[2] No significant differences in remission rates were noticed with exercise. Based on the limited, weak evidence the authors concluded both CBT and SGAs are reasonable choices as first line therapy for patients with depression.[2]

Antidepressants in Specific Populations

<u>Epilepsy</u>

Symptoms of depression such as low mood, tiredness, or apathy occur in approximately one third of patients with epilepsy.[3–5] Many prescribers are concerned that antidepressant therapy may exacerbate underlying seizures in their epileptic patients.[6] A Cochrane review reviewed the safety of antidepressants in treating depression and their effect on seizure recurrence.[7] The authors identified 8 studies for their review. Three RCTs and 5 non-randomized prospective cohort studies met the inclusion criteria. The five cohort studies were rated as low quality evidence with high risk of bias.[7] All the RCTs had unclear risk of bias.[7] When the data were combined into a meta-analysis to assess improvement in depression, the authors rated the quality of evidence as low.[7] Paroxetine was compared to doxepin in 67 patients.[7] The risk ratio for the proportion of patients with 50% improvement in depression scores for paroxetine versus doxepin was 1.16 (95% CI 0.88-1.52).[7] Venlafaxine was compared to no treatment in 64 patients.[7] The risk ratio for the proportion with a 50% or more improvement in depression scores for venlafaxine versus no treatment was 3.25 (95% CI 1.19 to 8.90).[7] The authors were unable to pool the data for a meta-analysis regarding seizure frequency due to either unreported data or substantial heterogeneity.[7] The authors concluded that robust evidence to evaluate the effectiveness of antidepressants in patients with epilepsy is currently unavailable. [7]

Cancer

Major depression among patients with cancer is estimated to occur in 15% of this population.[8] A 2015 Cochrane review sought to assess the effects and acceptability of antidepressants for treating depression in adults with cancer.[9] The authors identified 9 RCTs including 861 participants in their assessment. Fluoxetine, mianserin, amitriptyline, and desipramine were the antidepressants studied in the trials.[9] Overall the studies were rated as low quality with unclear to high risk of bias.[9] No statistically significant differences were noted between antidepressants as a class and placebo (standard mean difference (SMD) = -0.45 96% CI -1.01 to 0.11) or when SSRIs were compared to TCAs (SMD = -0.08 95% CI -0.34 to 0.18).[9] The authors found limited, reliable evidence to derive any effective conclusions regarding efficacy of antidepressants in cancer patients.[9]

End-Stage Renal Disease

Approximately 25% of adults with end-stage renal disease (ESRD) have some symptoms of depression.[10] Clearance of certain antidepressants (selegiline, amitriptyline, venlafaxine, desvenlafaxine, milnacipran, and bupropion) can be reduced by impaired renal function.[11] A 2016 Cochrane review updated a 2005 summary in order to evaluate the benefit and harms of antidepressants for treating depression in adults with ESRD treated with dialysis.[12] Adults aged 18 years and older with ESRD were included in the assessment. Depression was identified via interview or depression scale; patients with bipolar affective disorder were excluded. The following medications were studied: citalopram, escitalopram, fluoxetine and sertraline. The authors identified 4 studies in their update which involved 170 subjects. The authors rated the quality of the studies as low to medium quality with unclear to high risk of bias.[12] Most of the studies were placebo controlled and short term, limited to 12 weeks or shorter. Estimated effects on efficacy and safety outcomes were imprecise and difficult to generalize and the small number of studies limited the power of statistical testing.[12] The authors concluded there is insufficient evidence to identify effective treatments for depression in ESRD patients.[12]

Children and Adolescents

The prevalence of depression is estimated to be approximately 3 % for children (6-12 years old) and approximately 6 % for adolescents (13-18 years old).[13] Which antidepressants are safe and effective to use in children and adolescents is controversial. A meta-analysis was performed to compare the efficacy and acceptability of SSRIs versus TCAs in depressed children, adolescents, and young adults.[14] A literature search was conducted from 1970 to December, 2013. Five trials of moderate quality with a total of 422 patients were included in the review. The mean age of the patients was 15 years (range: 7-24 years).[14] The primary efficacy outcome was the standardized mean difference (SMD) for change scores in depression rating scales. A negative value indicated more relief from depression.[14] The secondary measure was proportion of patients that responded to treatment. SSRIs were more effective than TCAs in primary efficacy (SMD = −0.52; 95% CI, −0.81 to −0.24; P = 0.0003). [14] Patients taking SSRIs had a significantly greater response to depressive symptoms than patients taking TCAs (RR =

1.55; 95% CI, 1.04 to 2.29; P = 0.03).[14] More patients taking TCAs discontinued treatment than patients taking SSRIs (35.8% vs 25.1%; RR = 0.70; 95% CI, 0.52 to 0.93; P = 0.02).[14] The authors concluded SSRI therapy had superior efficacy and was better tolerated compared with TCA therapy in young patients.[14]

Another systematic review searched published literature through May, 2015 to identify RCTs that studied antidepressant therapy in children and adolescents.[15] Mean overall change in depression symptoms and the proportion of patients who discontinued treatment due to any adverse events were the 2 outcomes evaluated by the reviewers. Thirty four trials including 5260 participants were included in the meta-analysis.[15] The following 14 antidepressants were studied: amitriptyline, citalopram, clomipramine, desipramine, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline, and venlafaxine. The authors rated the evidence as low quality as most of the studies as had moderate to high risk of bias.[15] Only 4 studies had low risk of bias.[16] Standardized mean difference (SMD) was calculated to evaluate effect size and odds ratio was calculated for tolerability. In terms of efficacy, only fluoxetine was better than placebo (SMD −0.51, 95% CI −0.99 to −0.03).[15] Nortriptyline was significantly less effective than seven other antidepressants and placebo (SMDs ranging between −1.65 and −1.14).[15] In terms of tolerability, fluoxetine was significantly better tolerated than duloxetine (OR 0.31, 95% CI 0.13 to 0.95) and imipramine (OR 0.23, 95% CI 0.04 to 0.78), and citalopram and paroxetine were significantly better tolerated than imipramine alone (OR 0.27, 95% CI 0.04 to 0.96 and OR 0.22,95% CI 0.08 to 0.87, respectively).[15] Imipramine was significantly less well tolerated than placebo (OR 5.49, 95% CI 1.96 to 20.86) as was venlafaxine (OR 3.19, 95% CI 1.01 to 18.70) and duloxetine (OR 2.80, 95% CI 1.20 to 9.42).[15] The authors concluded that fluoxetine was the best tolerated and most effective agent for treating depression in children and adolescents.[15] However, the evidence they based their conclusions upon was of low quality due to poor study methodology, risk of bias, and possible selective reporting.

Postnatal Depression

A 2001 Cochrane review focused on identifying evidence for treatment of postnatal depression. At that time, the authors found insufficient evidence to draw substantial conclusions to guide antidepressant therapy in postnatal depression.[17] A 2014 update aimed to address the effects of antidepressants in comparison with other treatments, placebo or usual treatment for postnatal depression. [18]The authors identified 6 RCTs to include in their qualitative synthesis. Three trials that compared SSRIs to placebo were robust enough for a pooled analysis.[18] Sertraline was evaluated in 3 studies; fluoxetine, paroxetine and nortriptyline were evaluated in 1 study each. Studies were rated as low quality with unclear to high risk of bias.[18] The meta-analysis that compared SSRI to placebo showed a 43% (RR 1.43, 95% CI 1.01-2.03) greater chance of response for the SSRI treated patients compared to those who received placebo.[18] The authors were unable to draw conclusions regarding the effectiveness of one antidepressant over another because most of the studies were underpowered to detect differences in efficacy.[18]

In 2014, the AHRQ sponsored a systematic review to evaluate antidepressant treatment of depression during pregnancy and the postpartum period.[19] The authors identified 15 observational studies that provided evidence on the safety and efficacy of antidepressants for depression in pregnancy.[19] The studies compared antidepressant treatment with no treatment in pregnant women. In postpartum women, antidepressants were compared alone to a combination of medication and non-pharmacologic therapy.[19] There was not enough evidence to draw conclusions on the comparative benefits or harms of antidepressants for improving depression symptoms, functional capacity, breast feeding, mother-infant interactions, or infant development.[19] The authors concluded that evidence regarding comparative benefits and harms of pharmacologic therapy for depression in pregnancy and post- partum women is largely inadequate and that studies focused on treating women with postnatal depression is essential.[19]

Safety

Risk of Suicide

A retrospective cohort study including 36,842 children enrolled in Tennessee Medicaid between 1995 and 2006 compared the risk for medically treated suicide attempts among new users of sertraline, paroxetine, citalopram, escitalopram and venlafaxine to new users of fluoxetine.[20] The mean age of new users of the antidepressants included in the study was 14.0 years.[20] Diagnosis of record included major depressive disorder (47.4%), attention deficit disorder, conduct disorder and anxiety.[20] The rate of confirmed suicide attempts for current users of the study drugs ranged from 24.0 per 1000 person-years (paroxetine) to 29.1 Per 1000 person-years (citalopram).[20] For users of sertraline, paroxetine, citalopram, escitalopram, and venlafaxine, the adjusted rate of suicide attempts did not differ significantly from that for users of fluoxetine (24.8 per 1000 person years).[20] The authors found no evidence of increased suicide risk for sertraline, paroxetine, citalopram, escitalopram or venlafaxine compared with fluoxetine in children and adolescents.[20]

Sexual Dysfunction

An AHRQ funded systematic review evaluated the risk of treatment-emergent sexual dysfunction (TESD) in patients that were taking SGAs.[21] Sixty three studies (58 RCTs and five observational studies) with low to moderate risk of bias were included in the assessment.[21] Based on network meta-analyses of 66 pairwise comparisons from 37 RCTs, most comparisons showed a similar risk of SD among included SGAs.[21] However, credible intervals were wide and included differences that would be considered clinically relevant.[21] The authors observed three main patterns: bupropion had a statistically significantly lower risk of TESD than some other SGADs, and both escitalopram and paroxetine showed a statistically significantly higher risk of TESD.[21]

New Guidelines:

In 2005, the National Institute for Clinical Excellence (NICE) and National Collaborating Centre for Mental Health (NCCMH) initially published guidelines focused on caring for children and young people aged 5 to 18 years with depression.[22] The guidelines were updated as of March, 2015 to reflect new evidence in two areas:

- The psychological therapies for the treatment of depression in children and young people.
- The use of antidepressant treatment and psychological therapy, either alone or together for the treatment of depression in children and young people.

The updated guidelines recommend CBT for all children and young adults with mild depression. For initial treatment of moderate to severe depression, CBT in combination with fluoxetine is recommended for young people 12-18 years of age. At the time of publication, fluoxetine did have UK marketing authorization for use in patients aged 12-18 years without a previous trial of psychological therapy that was ineffective.[22] In addition, in the UK fluoxetine was only approved to use in children aged 8 years and older.[22]

AHRQ supports the 2014 revisions to the 2008 Working Group of the Clinical Practice Guideline on the Management of Depression on Adults published by the Galician Health Technology Assessment Agency and Spanish Ministry of Health.[23, 24] Significant recommendations include:

- Patients with chronic and/or recurrent depression are recommended a combination of drug therapy and cognitive behavioral therapy.[23]
- The initial selection of drug therapy should be based mainly on the side effect profile and tolerability, safety and pharmacological properties, as well as other factors such as previous response to treatment, cost and patient preferences.[23]
- SSRIs are antidepressants with the most evidence and better risk/benefit ratio, and should be considered as the first choice of treatment.[23]
- Although there is evidence of the efficacy of St. John's Wort in the treatment of mild to moderate depression, its use is not recommended for the following reasons:
  –Lack of knowledge about of the active ingredients, mechanisms of action and persistence of the antidepressant effect.
  –A lack of standardization of the dose.
  –The variability of different commercial preparations, which may have different amounts and proportions of its components and may not be therapeutically equivalent.[23]

The American College of Physicians (ACP) developed guidelines to provide evidence on the comparative effectiveness of depression treatment with SGAs versus nonpharmacological therapy.[25] Based on moderate quality evidence, ACP recommends that clinicians select between either cognitive behavioral therapy or second-generation antidepressants to treat patients with major depressive disorder after discussing treatment effects, adverse effect profiles, cost, accessibility, and preferences with the patient.[25]

New Formulations/Indications:
Viibryd® (vilazodone) received an expanded indication from FDA in March 2015 for a lower 20 mg dose to treat adults with major depressive disorder.[26] When Viibryd was initially FDA approved in 2013, the recommended dose was 40mg once a day with food based on 3 Phase III studies. An additional Phase III trial demonstrated the efficacy of the 20mg dose in treating major depressive disorder. No dose related adverse reactions were reported with either 20 or 40mg doses of Viibryd.[26]

New FDA Safety Alerts:
Cymbalta® (Duloxetine): November 2014: New warnings and precautions describe that orthostatic hypotension, falls, and syncope have been reported with therapeutic doses of Cymbalta.[27]
Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during Cymbalta treatment, particularly after dose increases. The risk of falling appears to be related to the degree of orthostatic decrease in blood pressure as well as other factors that may increase the underlying risk of falls. In an analysis of patients from all placebo-controlled trials, patients treated with Cymbalta reported a higher rate of falls compared to patients treated with placebo. Risk appears to be related to the presence of orthostatic decrease in blood pressure. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors and in patients taking Cymbalta at doses above 60 mg daily.[27]
Consideration should be given to dose reduction or discontinuation of Cymbalta in patients who experience symptomatic orthostatic hypotension, falls and/or syncope during Cymbalta therapy. Risk of falling also appeared to be proportional to a patient's underlying risk for falls and appeared to increase steadily with age. As elderly patients tend to have a higher underlying risk for falls due to a higher prevalence of risk factors such as use of multiple medications, medical comorbidities and gait disturbances, the impact of increasing age by itself is unclear. Falls with serious consequences including bone fractures and hospitalizations have been reported.[27]

Brintellix® (vortioxetine): July 2015: Drug Safety Communication - Brand Name Change to Trintellix®, to Avoid Confusion with Antiplatelet Drug Brilinta (ticagrelor).[28] In a Med Watch Alert, FDA warned that name confusion between Brintellix and Brilinta had resulted in prescribing and dispensing errors since Brintellix was approved in September 2013. Due to continued reports of name confusion between the two medicines used for very different purposes, FDA worked with Brintellix manufacturer Takeda Pharmaceuticals to change the drug's brand name.[28]

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	GENERIC	BRAND	PDL	CARVED OUT
ORAL	TABLET	AMITRIPTYLINE HCL	AMITRIPTYLINE HCL	Y	Y
ORAL	TABLET	WELLBUTRIN	BUPROPION HCL	Y	Y
ORAL	TABLET ER	BUPROPION HCL SR	BUPROPION HCL	Y	Y
ORAL	TABLET	BUPROPION HCL	BUPROPION HCL	Y	Y
ORAL	TABLET ER	WELLBUTRIN SR	BUPROPION HCL	Y	Y
ORAL	TABLET	CELEXA	CITALOPRAM HYDROBROMIDE	Y	Y
ORAL	TABLET	CITALOPRAM HBR	CITALOPRAM HYDROBROMIDE	Y	Y
ORAL	SOLUTION	CITALOPRAM HBR	CITALOPRAM HYDROBROMIDE	Y	Y
ORAL	TABLET	DESIPRAMINE HCL	DESIPRAMINE HCL	Y	Y
ORAL	TABLET	NORPRAMIN	DESIPRAMINE HCL	Y	Y
ORAL	ORAL CONC	DOXEPIN HCL	DOXEPIN HCL	Y	Y
ORAL	TABLET	ESCITALOPRAM OXALATE	ESCITALOPRAM OXALATE	Y	Y
ORAL	TABLET	LEXAPRO	ESCITALOPRAM OXALATE	Y	Y
ORAL	SOLUTION	LEXAPRO	ESCITALOPRAM OXALATE	Y	Y
ORAL	TABLET	LEXAPRO	ESCITALOPRAM OXALATE	Y	Y
ORAL	SOLUTION	FLUOXETINE HCL	FLUOXETINE HCL	Y	Y
ORAL	TABLET	FLUOXETINE HCL	FLUOXETINE HCL	Y	Y
ORAL	TABLET	SARAFEM	FLUOXETINE HCL	Y	Y
ORAL	TABLET	FLUVOXAMINE MALEATE	FLUVOXAMINE MALEATE	Y	Y
ORAL	TABLET	IMIPRAMINE HCL	IMIPRAMINE HCL	Y	Y
ORAL	TABLET	TOFRANIL	IMIPRAMINE HCL	Y	Y
ORAL	TABLET	MAPROTILINE HCL	MAPROTILINE HCL	Y	Y
ORAL	TAB RAPDIS	MIRTAZAPINE	MIRTAZAPINE	Y	Y
ORAL	TAB RAPDIS	REMERON	MIRTAZAPINE	Y	Y

ORAL	TABLET	MIRTAZAPINE	MIRTAZAPINE	Y	Y
ORAL	TABLET	REMERON	MIRTAZAPINE	Y	Y
ORAL	SOLUTION	NORTRIPTYLINE HCL	NORTRIPTYLINE HCL	Y	Y
ORAL	TABLET	PAROXETINE HCL	PAROXETINE HCL	Y	Y
ORAL	TABLET	PAXIL	PAROXETINE HCL	Y	Y
ORAL	TABLET	PROTRIPTYLINE HCL	PROTRIPTYLINE HCL	Y	Y
ORAL	ORAL CONC	SERTRALINE HCL	SERTRALINE HCL	Y	Y
ORAL	ORAL CONC	ZOLOFT	SERTRALINE HCL	Y	Y
ORAL	TABLET	SERTRALINE HCL	SERTRALINE HCL	Y	Y
ORAL	TABLET	ZOLOFT	SERTRALINE HCL	Y	Y
ORAL	CAPSULE	SURMONTIL	TRIMIPRAMINE MALEATE	Y	Y
ORAL	TABLET	VENLAFAXINE HCL	VENLAFAXINE HCL	Y	Y
ORAL	TAB ER 24H	APLENZIN	BUPROPION HBR	V	Y
ORAL	TAB ER 24H	BUPROPION XL	BUPROPION HCL	V	Y
ORAL	TAB ER 24H	FORFIVO XL	BUPROPION HCL	V	Y
ORAL	TAB ER 24H	WELLBUTRIN XL	BUPROPION HCL	V	Y
ORAL	CAPSULE	CLOMIPRAMINE HCL	CLOMIPRAMINE HCL	V	Y
ORAL	TAB ER 24H	DESVENLAFAXINE ER	DESVENLAFAXINE	V	Y
ORAL	TAB ER 24H	PRISTIQ ER	DESVENLAFAXINE SUCCINATE	V	Y
ORAL	CAPSULE DR	CYMBALTA	DULOXETINE HCL	V	Y
ORAL	TAB ER 24	DESVENLAFAXINE FUMARATE ER	DESVENLAFAXINE FUMARATE	V	Y
ORAL	TAB ER 24	KHEDEZLA	DESVENLAFAXINE	V	Y
ORAL	CAPSULE DR	DULOXETINE HCL	DULOXETINE HCL	V	Y
ORAL	CAPSULE DR	IRENKA	DULOXETINE HCL	V	Y
ORAL	SOLUTION	ESCITALOPRAM OXALATE	ESCITALOPRAM OXALATE	V	Y
ORAL	SOLUTION	LEXAPRO	ESCITALOPRAM OXALATE	V	Y
ORAL	CAPSULE DR	FLUOXETINE DR	FLUOXETINE HCL	V	Y
ORAL	CAPSULE DR	PROZAC WEEKLY	FLUOXETINE HCL	V	Y
ORAL	CAP ER 24H	FLUVOXAMINE MALEATE ER	FLUVOXAMINE MALEATE	V	Y
ORAL	CAPSULE	IMIPRAMINE PAMOATE	IMIPRAMINE PAMOATE	V	Y
ORAL	TABLET	MARPLAN	ISOCARBOXAZID	V	Y
ORAL	CAP SA 24H	FETZIMA	LEVOMILNACIPRAN HCL	V	Y
ORAL	CAP24HDSPK	FETZIMA	LEVOMILNACIPRAN HCL	V	Y
ORAL	TABLET	NEFAZODONE HCL	NEFAZODONE HCL	V	Y
ORAL	CAPSULE	BRISDELLE	PAROXETINE MESYLATE	V	Y
ORAL	ORAL SUSP	PAXIL	PAROXETINE HCL	V	Y
ORAL	TAB ER 24H	PAROXETINE HCL	PAROXETINE HCL	V	Y
ORAL	TAB ER 24H	PAXIL CR	PAROXETINE HCL	V	Y
ORAL	TABLET	PEXEVA	PAROXETINE MESYLATE	V	Y

ORAL	TABLET	NARDIL	PHENELZINE SULFATE	V	Y
ORAL	TABLET	PHENELZINE SULFATE	PHENELZINE SULFATE	V	Y
TRANSDERM	PATCH TD24	EMSAM	SELEGILINE	V	Y
ORAL	TABLET	PARNATE	TRANYLCYPROMINE SULFATE	V	Y
ORAL	TABLET	TRANYLCYPROMINE SULFATE	TRANYLCYPROMINE SULFATE	V	Y
ORAL	TAB ER 24	VENLAFAXINE HCL ER	VENLAFAXINE HCL	V	Y
ORAL	TAB DS PK	VIIBRYD	VILAZODONE HCL	V	Y
ORAL	TABLET	VIIBRYD	VILAZODONE HCL	V	Y
ORAL	TABLET	AMOXAPINE	AMOXAPINE		Y
ORAL	TAB DS PK	SAVELLA	MILNACIPRAN HCL		
ORAL	TABLET	SAVELLA	MILNACIPRAN HCL		
ORAL	TAB ER 24H	OLEPTRO ER	TRAZODONE HCL		Y
ORAL	TABLET	TRAZODONE HCL	TRAZODONE HCL		Y

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 4 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations June 6, 2016

1. *exp Depressive Disorder, Major/dt [Drug Therapy] 6533*
2. *Depression/ or Long-Term Synaptic Depression/ or Depression, Postpartum/*
3. *exp Anxiety/dt [Drug Therapy] 3037*
4. *exp Premenstrual Dysphoric Disorder/dt [Drug Therapy] 5*
5. *Citalopram/ 3647*
6. *escitalopram.mp. 1424*
7. *Fluoxetine/ 5913*
8. *Fluvoxamine/ 1311*
9. *Paroxetine/ 3085*
10. *Sertraline/ 2294*
11. *Duloxetine Hydrochloride/ 1231*
12. *Desvenlafaxine Succinate/ 216*
13. *levomilnacipran.mp. 26*
14. *Bupropion/ 2287*
15. *mirtazapine.mp. 1564*
16. *nefazodone.mp. 626*
17. *vortioxetine.mp. 105*
18. *Vilazodone Hydrochloride/ 70*
19. *Venlafaxine Hydrochloride/ 2095*
20. *Amitriptyline/ 1898* *21*
21. *Imipramine/ 1972*
22. *Desipramine/ 1356*
23. *Doxepin/ 270*
24. *Maprotiline/ 151*
25. *Nortriptyline/ 724*
26. *Protriptyline/ 17*

27. Trimipramine/ 73
28. Clomipramine/ 1035
29. Isocarboxazid/ 9
30. Phenelzine/ 184
31. Selegiline/ 1190
32. Tranylcypromine/ 269
33. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 24873
34. limit 33 to (humans and yr="2014 -Current") 1354
35. 1 or 2 or 3 or 4 75231
36. limit 35 to (humans and yr="2014 -Current") 11698
37. 33 and 36 387
38. limit 37 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or meta analysis or pragmatic clinical trial or randomized controlled trial or systematic reviews) 194

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: *7/16 (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: July 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 (RR 1.08; 05% CI, 0.62 to 1.87).[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 with the minor modification in Appendix 2. Costs should be evaluated in executive session.

Previous Conclusions/Recommendations:

- Evidence does not support a difference in effectiveness or harms outcomes between antiviral agents for HSV. 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:
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 (RR 0.26; 95% CI 0.13 to 0.51).[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 a 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 also decreased occurrence of HSV to 0.09 episodes/month. Short-term (≤ 1 month) use of topical agents did not 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]

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 assessed in 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 decreased 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 with 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 alone 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:

None identified.

New Formulations/Indications:

None identified.

New FDA Safety Alerts:
None identified.

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

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

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 for Herpes Simplex Virus

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

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the diagnosis uncomplicated herpes simplex virus infection (B002; B0089; B001; B009)?	**Yes:** Go to #4	**No:** Go to #7

<table>
<tr><th colspan="3">Approval Criteria</th></tr>
<tr><td>4. Pass to RPh: Is the patient immunocompromised (document ICD10 code).
Examples:
• Diagnosis of cancer AND currently undergoing chemotherapy or radiation. Document therapy and length of treatment.
• Solid organ transplant
• HIV/AIDS</td><td>Yes: Approve for up to 12 months</td><td>No: Go to #5</td></tr>
<tr><td>5. Is the patient currently taking an immunosuppressive drug?

Document name of drug. If is drug not in the list below, pass to RPh for evaluation. Immunosuppressive drugs include, but are not limited to:
<table>
<tr><th colspan="2">Immunosuppressants</th></tr>
<tr><td>Abatacept</td><td>Infliximab</td></tr>
<tr><td>Adalimumab</td><td>Leflunomide</td></tr>
<tr><td>Anakinra</td><td>Methotrexate</td></tr>
<tr><td>Apremilast</td><td>Natalizumab</td></tr>
<tr><td>Azathioprine</td><td>Rituximab</td></tr>
<tr><td>Basiliximab</td><td>Secukinumab</td></tr>
<tr><td>Certolizumab pegol</td><td>Sirolimus</td></tr>
<tr><td>Cyclosporine</td><td>Tacrolimus</td></tr>
<tr><td>Cyclosporine</td><td>Tocilizumab</td></tr>
<tr><td>Etanercept</td><td>Tofacitinib</td></tr>
<tr><td>Golimumab</td><td>Ustekinumab</td></tr>
<tr><td>Hydroxychloroquine</td><td>Vedolizumab</td></tr>
</table></td><td>Yes: Approve for up to 90 days</td><td>No: Pass to RPh. GIf patient has diabetes mellitus or sickle cell disease, go to #6. All others go to #7.</td></tr>
<tr><td>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.</td><td>Yes: Pass to RPh. Deny; not funded by the OHP.</td><td>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.</td></tr>
</table>

Approval Criteria		
~~7.~~6. RPh only: All other indications need to be evaluated as to whether they are an OHP-funded condition.	If funded and clinic provides supporting literature, approve for length of treatment. If length of treatment is not provided, approve for 3 months. Note: deny non-viral diagnoses (medical appropriateness)	If non-funded, deny (not funded by the OHP). Note: Deny viral ICD-10 codes that do not appear on the OHP funding list pending a more specific diagnosis code (not funded by the OHP).

P&T Review: *7/16 (KS); 1/14; 1/12; 9/10 (KS)*
Implementation: *1/1/11*

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: Drugs for BPH

Date of Review: July 2016

Date of Last Review: May 2014
Literature Search: May 2016

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

Conclusions:
- One new guideline, 3 systematic reviews and one Food and Drug Administration (FDA) safety alert have been published for benign prostatic hypertrophy (BPH) therapies since the last review.[1-5]
- There is evidence that therapies for BPH all significantly improve the International Prostate Symptom Score (IPSS) compared to placebo by -3.69 to -7.06 points. Doxazocin and terazosin were associated with the most improved IPSS scores of -7.06 and -6.76, respectively.[1] The IPSS is a validated tool comprised of up to 35 points based on 8 questions. A minimally important difference is a decrease of 3 or more points; a moderate improvement is a decrease of 5 or more points; and marked improvement in symptoms is a decrease of 8 or more points.[2]
- Evidence from the Agency for Healthcare Research and Quality (AHRQ) found alpha-1 blockers to have similar or superior outcomes to newer therapies, or combination of therapies, for BPH. Alpha-1 blockers silodosin and tamsulosin changed IPSS scores by -7.8 and -7.2, respectively (weighted mean difference [WMD] -0.63; 95% CI, -1.62 to 0.36).[3] Other evidence showed tadalafil and tamsulosin resulted in -5.6 and -5.9 IPSS point reduction, respectively (WMD 0.07; 95% CI, -2.12 to 2.23). The addition of an alpha-1 blocker (tamsulosin or alfuzosin) to tadalafil provided an additional 1.6 point IPSS decrease over alpha-1 blocker monotherapy (-10.4 vs. -8.6; WMD -2.01; 95% CI, -4.03 to -0.00). Similar differences were seen with the combination of tadalafil and finasteride compared to finasteride alone (-5.5 vs. -4.5 points (CI not provided).
- Adverse events were more common with silodosin compared to placebo and tamsulosin. Tadalafil was associated with higher risk of adverse events compared to tamsulosin.[3]
- Guideline recommendations from the National Institute for Health and Care Excellence (NICE) support current preferred drug list (PDL) placement for drugs used in the treatment of BPH.[4]

Recommendations:
- No changes are recommended to the PDL or prior authorization criteria for BPH treatments.
- Consider costs in executive session.

Previous Conclusions/Conclusions:
- There is no new evidence for comparative effectiveness or harms outcomes between drugs used for BPH. 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:
A systematic review evaluated the comparative effectiveness of monotherapies for the treatment of BPH. Drugs included in the review were the following: terazosin, doxazosin, tamsulosin, alfuzosin, silodosin, naftopidil, finasteride, dustasteride, tolterodine, fesoterodine, and solifenacin.[1] The primary outcome was change in IPSS. One hundred twenty-four trials were included with two-thirds having a treatment duration longer than one year. The median age of patients was 65 years with a median baseline IPSS score of 17.85 with moderate to severe symptoms.[1] The evidence was rated as moderate in quality. In placebo comparisons, a network meta-analysis found BPH therapies to decrease IPSS scores by -3.69 to -7.06 points. The largest decreases were found with doxazosin (absolute effect [AE] -7.06; 95% CI, -10.41 to -3.71) and terazosin (AE -6.76; 95% CI, -10.16 to -3.35). Significant IPSS changes were seen for all treatments except tolterodine and solifenacin. Most changes in IPSS were comparable to each other except for doxazocin and terazosin which were found to be significantly more effective than tamsulosin, alfuzosin, tadalafil, naftopidil, dutasteride, finasteride, tolterodine and solifenacin.[1] A significantly higher incidence of adverse effects (RR 1.33 to 2.10) was found with doxazosin, terazosin, silodosin, fesoterodine and tadalafil. Therapies that were associated with the highest incidence of withdrawals due to adverse events were: alfuzosin, terazosin, dutasteride, tolterodine, tadalafil, sildenafil and vardenafil.[1]

A systematic review by AHRQ evaluated medications for symptom management associated with BPH.[3] Evidence was analyzed from 57 RCTs and 5 observational studies which included the following medications: silodosin, tolterodine, solifenacin, festoterodine, mirabegron, tadalafil and sildenafil.[3] In a review of alpha-1 blockers, 4 12-week trials found silodosin to be more effective than placebo in improving lower urinary tract symptoms (LUTS) caused by BPH with a weighted mean difference (WMD) in IPSS score of -2.7.[3] Silodosin was compared to tamsulosin in trials lasting 4 to 12 weeks and was found to reduce IPSS scores similar to tamsulosin (-7.8 vs. -7.2) but with a degree of heterogeneity (I^2 = 76%). More adverse events were associated with silodosin compared to tamsulosin, however, withdrawal rates were similar.[3] For anticholinergics, combination therapy of tolterodine, solifenacin and fesoterodine combined with alpha-1 blockers were similar in efficacy to alpha-1 blocker monotherapy. There was insufficient evidence to compare the adverse events of combination versus monotherapy.[3] For phosphodiesterase-5 (PDE-5) inhibitors, tadalafil improved IPSS scores more than placebo in a pooled analysis of 10 12-week trials (n=3516) of mostly white participants (-5.5 vs. -3.4, respectively). Four small trials found tadalafil combined with an alpha-1 blocker to be more effective in symptom improvement than alpha-1 blocker monotherapy (-10.4 and -8.6) respectively.[3] A one-point improvement in IPSS scores was found with tadalafil/finasteride combination over finasteride monotherapy. Tadalafil was similar to tamsulosin in improving IPSS scores, -5.6 vs. -5.9, in men studied for 3 months. Evidence for sildenafil comparisons were deemed insufficient. Adverse events with tadalafil are similar to alpha-1 blockers but withdrawals related to adverse events are higher.[3] For

beta-3 adrenergic agonist, there was insufficient evidence on mirabegron to draw efficacy conclusions.[3] Limitations to the evidence were risk of performance and detection bias, limited applicability to patients over 70 years of age and high percentage of patients in PDE-5 inhibitor trials having erectile dysfunction. Long term effects on blood pressure, drug interactions and maintenance of symptom improvement has not been studied.

A systematic review and meta-analysis analyzed the efficacy and safety of dutasteride compared to placebo in men with symptomatic BPH.[5] Seven RCTs, 2 open-label extension trials and 2 finasteride comparison trials were included (n=12,129). The primary outcome was the change in urinary symptoms assessed by changes in IPSS. Dutasteride was more effective in decreasing IPSS compared to placebo (weighted mean difference [WMD] -1.78, 95% CI, -3.01 to -0.55) but with significant heterogeneity (I^2 = 69%).[3] Symptom improvement was similar in dutasteride and finasteride comparisons. Dustasteride was associated with adverse events more commonly than placebo (RR 1.04; 95% CI, 1.00 to 1.07). Withdrawal rates were similar between groups.[5]

New Guidelines:

National Institute for Health and Care Excellence (NICE)

In 2015 a guideline on the assessment and management of the lower urinary tract in men was released.[4] Recommendations as they pertain to drug treatment are: men with symptomatic lower urinary tract symptoms (LUTS) unresponsive to conservative management should be offered drug therapy with an alpha-1 blocker; men with enlarged prostates (estimated at ≥30 gms or PSA >1.4 ng/ml) and at risk of progression should be offered an 5-alpha reductase inhibitor; and combination therapy with an 5-alpha reductase inhibitor and an alpha-1 blocker should be offered to men with moderate to severe LUTS and enlarged prostate. Men with LUTS should not be offered a PDE-5 inhibitor for the sole treatment of LUTS.[4]

New FDA Drug Approvals:

None identified.

New Formulations/Indications:

None identified.

New FDA Safety Alerts:

In July of 2014 the FDA warned of the possibility of intraoperative floppy iris syndrome (IFIS) during cataract and glaucoma surgery in some patients on or previously treated with alpha-1 blockers, including tamsulosin.[6]

References:

1. Yuan JQ, Mao C, Wong S, et al. Comparative effectiveness and safety of monodrug therapies for lower urinary tract symptoms associated with benign prostatic hyperplasia. *Medicine*; 94:e974. Doi: 10.1097/MD0000000000000974.
2. Barry MJ, Williford WO, Chang Y et al. Benign prostatic hyperplasia specific health 30 status measures in clinical research: how much change in the American Urological 31 Association symptom index and the benign prostatic hyperplasia impact index is 32 perceptible to patients? J Urol 1995; 154: 1770–4 3.
3. Brasure M, MacDonald R, Dahm P, et al. Newer medications for lower urinary tract symptoms attributed to benign prostatic hyperplasia: a review. Comparative Effectiveness Review No. 178. AHRQ Publication No. 16-EHC024-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed June 2, 2016.
4. National Clinical Guideline Centre for Acute and Chronic Conditions. Lower urinary tract symptoms in men: assessment and management. London (UK): *National Institute for Health and Care Excellence (NICE)*, 2015. June: no: 97.
5. Park T, Choi JY. Efficacy and safety of dutasteride for the treatment of symptomatic benign prostatic hyperplasia (BPH): a systematic review and meta-analysis. *World J Urol* 2014: 32:1093-1105. DOI: 10.1007/s00345-014-1258-9.
6. Food and Drug Administration. Flomax (tamsulosin) hydrochloride capsules safety warning. July 2014 Drug Safety Labeling Changes. Available at: http://www.fda.gov/safety/medwatch/safetyinformation/ucm197087.htm. Accessed April 30, 2016.
7. Roehrborn C, Perez I, Roos E, et al. Efficacy and safety of a fixed-dose combination of dutasteride and tamsulosin treatment (Duodart®) compared with watchful waiting with initiation of tamsulosin therapy if symptoms do not improve, both provided with lifestyle advice, in the management of treatment-naïve men with moderately symptomatic benign prostatic hyperplasia: 2-year CONDUCT study results. *BJU Int* 2015;116:450-459.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAP ER 24H	FLOMAX	TAMSULOSIN HCL	Y
ORAL	CAP ER 24H	TAMSULOSIN HCL	TAMSULOSIN HCL	Y
ORAL	CAPSULE	TERAZOSIN HCL	TERAZOSIN HCL	Y
ORAL	TABLET	CARDURA	DOXAZOSIN MESYLATE	Y
ORAL	TABLET	DOXAZOSIN MESYLATE	DOXAZOSIN MESYLATE	Y
ORAL	TABLET	FINASTERIDE	FINASTERIDE	Y
ORAL	TABLET	PROSCAR	FINASTERIDE	Y
ORAL	CAPSULE	AVODART	DUTASTERIDE	N
ORAL	CAPSULE	DUTASTERIDE	DUTASTERIDE	N
ORAL	CAPSULE	RAPAFLO	SILODOSIN	N
ORAL	TAB ER 24	CARDURA XL	DOXAZOSIN MESYLATE	N
ORAL	TAB ER 24H	ALFUZOSIN HCL ER	ALFUZOSIN HCL	N
ORAL	TAB ER 24H	UROXATRAL	ALFUZOSIN HCL	N
ORAL	CAPSULE	JALYN	DUTASTERIDE/TAMSULOSIN	N

Appendix 2: New Clinical Trials

A total of 347 citations were manually reviewed from the literature search. After further review, 346 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining trial is briefly described in the table below. The full abstract is included in Appendix 3.

Table 1: Description of Clinical Trial

Study	Comparison	Population	Primary Outcome	Results
Roehrborn, et al[7] OL, PG, RCT	Dutasteride 0.5 mg and tamsulosin 0.4 mg vs. (D/T) Watchful waiting ± tamsulosin if no symptom improvement (WW)	Treatment naïve men with moderately symptomatic BPH (IPSS score of 8-19) at risk of progression n = 742	Symptomatic improvement from baseline to 24 months, measured by IPSS	D/T: -5.4 points WW: -3.6 points (ETD 1.8; 95 % CI -2.5 to -1.2; P < 0.001)
Abbreviations: IPSS = International Prostate Symptom Score (IPSS); OL = open label; PG = parallel group; RCT = randomized controlled trial				

Appendix 3: Abstracts of Clinical Trials

Roehrborn C, Perez I, Roos E, et al. Efficacy and safety of a fixed-dose combination of dutasteride and tamsulosin treatment (Duodart®) compared with watchful waiting with initiation of tamsulosin therapy if symptoms do not improve, both provided with lifestyle advice, in the management of treatment-naïve men with moderately symptomatic benign prostatic hyperplasia: 2-year CONDUCT study results. *BJU Int* 2015;116:450-459.

Objective: To investigate whether a fixed-dose combination (FDC) of 0.5 mg dutasteride and 0.4 mg tamsulosin is more effective than watchful waiting with protocol-defined initiation of tamsulosin therapy if symptoms did not improve (WW-All) in treatment-naïve men with moderately symptomatic benign prostatic hyperplasia (BPH) at risk of progression. **Methods**: This was a multicentre, randomised, open-label, parallel-group study (NCT01294592) in 742 men with an International Prostate Symptom Score (IPSS) of 8–19, prostate volume ≥30 mL and total serum PSA level of ≥1.5 ng/mL. Patients were randomised to FDC (369 patients) or WW-All (373) and followed for 24 months. All patients were given lifestyle advice. The primary endpoint was symptomatic improvement from baseline to 24 months, measured by the IPSS. Secondary outcomes included BPH clinical progression, impact on quality of life (QoL), and safety. **Results**: The change in IPSS at 24 months was significantly greater for FDC than WW-All (–5.4 vs −3.6 points, $P < 0.001$). With FDC, the risk of BPH progression was reduced by 43.1% ($P < 0.001$); 29% and 18% of men in the WW-All and FDC groups had clinical progression, respectively, comprising symptomatic progression in most patients. Improvements in QoL (BPH Impact Index and question 8 of the IPSS) were seen in both groups but were significantly greater with FDC ($P < 0.001$). The safety profile of FDC was consistent with established profiles of dutasteride and tamsulosin. **Conclusion**: FDC therapy with dutasteride and tamsulosin, plus lifestyle advice, resulted in rapid and sustained improvements in men with moderate BPH symptoms at risk of progression with significantly greater symptom and QoL improvements and a significantly reduced risk of BPH progression compared with WW plus initiation of tamsulosin as per protocol.

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to April Week 3 2016

Search Strategy:

#	Searches	Results	Annotations
1	Doxazosin/	841	
2	Finasteride/	1646	
3	Dutasteride/	442	
4	silodosin.mp.	214	
5	alfuzosin.mp.	401	
6	tamsulosin.mp.	1256	
7	1 or 2 or 3 or 4 or 5 or 6	4129	
8	limit 7 to (english language and humans and yr="2014 -Current")	301	
9	limit 8 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or randomized controlled trial or systematic reviews)	143	

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to April Week 3 2016

Search Strategy:

#	Searches	Results	Annotations
1	benign prostatic hypertrophy.mp. or Prostatic Hyperplasia/	11249	
2	limit 1 to (english language and humans)	8840	
3	limit 2 to yr="2014 -Current"	879	
4	limit 3 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial or controlled clinical trial or meta-analysis or practice guideline or randomized controlled trial or systematic reviews)	204	

Benign Prostatic Hypertrophy (BPH) Medications

Goal(s):

- BPH with urinary obstruction is an OHP-funded treatment only when post-void residuals are 150 mL or more.
- Restrict use for male pattern baldness and erectile dysfunction, which are not OHP-funded conditions.

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. Will the prescriber consider switching 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 request for renewal of current therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request for an alpha-1 blocker, and does the patient have a diagnosis related to functional and mechanical disorders of the genitourinary system including bladder outlet obstruction?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Has the patient tried and failed a 2-month trial of a preferred alpha-1 blocker?	**Yes:** Approve an alpha-1 blocker for up to 12 months	**No:** Pass to RPh. Deny until patient has tried and failed a covered alternative
6. Does the patient have a diagnosis of benign prostatic hypertrophy (BPH) or enlarged prostate with obstruction?	**Yes:** Approve for up to 12 months	**No:** Go to #7
7. Does the patient have a diagnosis of unspecified urinary obstruction or BPH without obstruction?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #8
8. RPh Only: All other conditions need to be evaluated to see if diagnosis is funded: **Funded:** covered diagnoses related to prostate may be approved for 1 year. **Not Funded:** unfunded diagnoses (e.g., hair growth, erectile dysfunction) should be denied (not funded by the OHP). • Alpha-1 blockers and 5-alpha reductase inhibitors may be used concurrently for BPH up to 1 year. Alpha-1 blockers may be discontinued once prostate is reduced to normal size. • If urine retention (obstructive), ask for more specific diagnosis.		

Renewal Criteria		
1. Is the request for an alpha-1 blocker and does the patient have a diagnosis related to functional and mechanical disorders of the genitourinary system including bladder outlet obstruction?	**Yes:** Go to #2	**No:** Go to #3
2. Has the patient also been taking a 5-alpha reductase inhibitor for the last year?	**Yes:** Recommend against combination therapy exceeding 1 year.	**No:** Approve for the shorter of 12 months or length of the prescription
3. Does the patient have a diagnosis of BPH or enlarged prostate with obstruction?	**Yes:** Approve for up to 12 months	**No:** Go to #4
4. Does the patient have a diagnosis of unspecified urinary obstruction or benign prostatic hyperplasia without obstruction?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #5

5. RPh only: All other indications need to be evaluated as to whether they are a funded condition: • Alpha Blockers and 5-alpha reductase inhibitors may be used concurrently for BPH up to 1 year. Alpha-blockers may be discontinued once prostate is reduced to normal size. • If urine retention, obstructive, ask for more specific diagnosis.	If funded and clinic provides supporting literature, approve for up to 12 months.	If non-funded, deny (not funded by the OHP).

P&T Review: *7/16 (KS); 11/12; 9/10; 3/10; 5/08; 2/06*
Implementation: *2/21/13; 1/1/11; 4/20/10; 5/22/08; 7/1/06; 9/30/05*

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

Literature Scan: Anti-Parkinson's Agents

Date of Review: July 2016

Date of Last Review: September 2014
Literature Search: August 2014 – May 2016

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

Conclusions:
- Since the previous Parkinson's disease drug class scan, there is limited new comparative evidence from one systematic review with meta-analysis and three randomized controlled trials. There are also two new levodopa and carbidopa formulations approved by the U.S. Food and Drug Administration (FDA) for the treatment of Parkinson's disease and one new FDA safety alert.
- There is low quality evidence that levodopa monotherapy is more effective than levodopa-sparing therapy for improving activities of daily living and motor symptoms as measured by the unified Parkinson's disease rating scale (UPDRS)[Scale 0-176, 0 = no disability, 176 = worst disability; mean difference 0.95 (52 point scale), 95% CI, 0.51 to 1.39; p<0.0001 and 2.89 (108 point scale), 95% CI, 1.56 to 4.21; p<0.0001, respectively] but less effective than levodopa-sparing therapy for improvement of mental functioning [mean change from baseline -0.30 (16 point scale), 95% CI, -0.51 to -0.09; p=0.0005]. The clinical significance of these differences remain unclear.
- There is low quality evidence that levodopa monotherapy results in a worsening of motor complications compared to levodopa-sparing treatment (33.7% vs. 24.4%, respectively; p<0.0001), has increased risk of dyskinesia (RR 1.88, 95% CI, 1.37 to 2.59; p<0.0001), and higher incidence of wearing-off phenomenon (41.2% vs. 29.6%; p<0.00001). There is insufficient evidence of no difference in self-reported quality of life measurement scores between levodopa and levodopa-sparing therapy in the treatment of PKD.

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

Previous Conclusions and Recommendations:
- Evidence does not support a difference in efficacy or effectiveness between agents for PD.
- Make tolcapone non-preferred due to reported liver toxicity.
- Make carbidopa/levodopa ER preferred on PDL.
- There is insufficient evidence that rotigotine is more efficacious or safer than other oral dopamine agonists in the treatment of PD. It may be a reasonable option for patients with difficulty swallowing that may be addressed by use of the patch. Make rotigotine transdermal (Neupro) non-preferred on the PDL.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

New Systematic Reviews:
A meta-analysis by Xie, et al. evaluated the use of levodopa monotherapy versus levodopa sparing therapy for initial treatment of Parkinson's disease (PKD).[1] The American Academy of Neurology (AAN) and European Federation of Neurological Societies/Movement Disorder Society-European Section (EFNS/MDS-ES) have recommended either levodopa or dopamine agonists as first-line agents for symptomatic treatment of early PKD, with the initial choice dependent upon patient age, disease stage, symptoms, and preferences.[2,3] Treatment of PKD with levodopa monotherapy has been widely used to ameliorate symptoms, however, it has also been associated with motor fluctuations and dyskinesias with prolonged use. Eleven RCTs (n=3584) were identified and included in the meta-analysis with 35 to 1406 subjects in each study. Follow-up ranged from 1 year to 10 years. Of the eleven levodopa-sparing groups, five trials used the dopamine agonist pramipexole, cabergoline was used in three trials, ropinirole in two trials, and bromocriptine was used in one trial.[1] The outcomes measured included the Unified Parkinson's disease Rating Scale (UPDRS, parts 1-3), motor complications (dyskinesia, wearing off phenomenon and on-off fluctuation), and health-related quality of life measures through the Parkinson's disease questionnaire (PDQ-39), and EuroQol (EQ-5D).

The UPDRS effects were assessed through tests of mental functioning (part 1), activities of daily living [ADL] (part 2), and motor symptoms (part 3). The total UPDRS scoring scale ranged from zero to 176 (0 = no disability, 176 = worst disability). Pooled data for three of the trials compared mental functioning (UPDRS part 1: score 0 to 16 points) and showed a slight but statistically significant difference and worsening of overall symptoms with levodopa monotherapy versus levodopa-sparing treatment (mean change from baseline: -0.30, 95% CI, -0.51 to -0.09; p=0.0005).[1] However, pooled data of six trials comparing activities of daily living (UPDRS part 2: score 0 to 52 points) showed that levodopa monotherapy resulted in significant improvements over the levodopa-sparing group (mean difference: 0.95, 95% CI, 0.51 to 1.39; p<0.0001). Motor symptoms (UPDRS part 3: score 0 to 108 points) and UPDRS total scores were improved with levodopa monotherapy (mean change 2.89, 95% CI, 1.56 to 4.21; p<0.0001, and 3.33, 95%CI, 1.04 to 5.61; p=0.004, respectively).

Eight trials reported motor complication outcomes (n=3269) which were found to be higher in the levodopa monotherapy groups than levodopa-sparing therapy (33.7% vs. 24.4%, respectively; risk ratio (RR) 1.53, 95% CI, 1.25-1.87; p<0.0001).[1] Dyskinesia incidence was higher with levodopa monotherapy (RR 1.88; 95% CI, 1.37 to 2.59; p<0.0001). Incidence of wearing-off phenomenon was higher with levodopa monotherapy (41.2% vs. 29.6%; RR 1.36, 95% CI, 1.20 to 1.55; p<0.00001) but there was no statistically significant difference detected in on-off fluctuations (6.5% vs 3.1%; RR 2.07, 95% CI, 0.70 to 6.16; p=0.19).[1]

The PDQ-39 (39 questions, each scored 0 to 4) or EQ-5D (5 questions, 3 response types plus 0 – 100 point visual analog scale) were quality of life assessment tools utilized in 5 of the 11 studies. PDQ-39 scores from the individual trials revealed no significant difference between levodopa monotherapy and levodopa-sparing therapy in three of the five trials, while the remaining two trials showed statistically significant average score improvement of 1.8 ($p<0.05$) for levodopa monotherapy. The clinical significance of this difference is unclear. EQ-5D results were only available for four of the eleven trials, and all but one of the studies assessed did not show a statistically significant difference between treatment groups ($p>0.05$).

New Guidelines:
None identified**.**

New Formulations/Indications:
Rytary® (carbidopa and levodopa) extended release capsules for oral use was approved by the FDA in January 2015 based on pharmacokinetic studies.[4] The new formulation of carbidopa/levodopa joins the carbidopa/levodopa formulation already marketed under various product names. Rytary® is indicated for the treatment of PKD, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.

Duopa® (carbidopa and levodopa) enteral suspension was approved by the FDA in January 2015.[5] The new formulation of carbidopa/levodopa has the same active ingredient but is supplied as a solution for administration via percutaneous endoscopic gastrostomy with jejunal tube (PEG-J). Duopa® is indicated for the treatment of motor fluctuations in patients with advanced Parkinson's disease.

There is insufficient comparative data that these new formulations provide any improved efficacy or safety over other agents available in the class.

New FDA Safety Alerts:
In February 2015, the FDA Center for Drug Evaluation and Research (CDER) issued a safety labeling change warning about increased risk of adverse events in patients using Neupro® (rotigotine) Transdermal System.[6] For patients with advanced PKD on maximum doses of Neupro®, incidence of orthostasis was higher for Neupro® than placebo (32% vs 27%, respectively), resulted in more weight gain and fluid retention (Neupro 9% vs. placebo 1%), had a higher incidence of dyskinesia (Neupro 14% vs. placebo 7%), and more application site reactions (36% Neupro vs. 13% placebo). Notable increases in systolic blood pressure (>20 mmHg) and diastolic blood pressure (>10 mmHg) was at least 5% higher in all patients taking Neupro® versus placebo. Patients with early-stage PKD on Neupro® therapy had an increased risk for low hemoglobin (Neupro 8% vs placebo 5%) and low serum glucose (Neupro 15% vs. placebo 6%) at levels below normal reference range. Specific reference ranges and interpretive details were unavailable.

References:

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4. Rytary (carbidopa and levodopa) extended-release capsules [Prescribing Information]. Hayward, CA: Impax Pharmaceticals, a division of Impax Laboatories, Inc., January 2015.

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7. Olanow CW, Kieburtz K, Odin P, et al. “Continuous Intrajejunal Infusion of Levodopa-Carbidopa Intestinal Gel for Patients with Advanced Parkinson’s Disease: A Randomised, Controlled, Double-Blind, Double-Dummy Study.” *The Lancet Neurology* 2014;13:141–49. doi:10.1016/S1474-4422(13)70293-X.

8. Stocchi F, Hsu A, Khanna S, et al. “Comparison of IPX066 with Carbidopa–levodopa plus Entacapone in Advanced PD Patients.” *Parkinsonism & Related Disorders* 2014;20:1335–40. doi:10.1016/j.parkreldis.2014.08.004.

9. Mizuno Y, Masahiro N, Kazuko H, et al. “Rotigotine vs Ropinirole in Advanced Stage Parkinson’s Disease: A Double-Blind Study.” *Parkinsonism & Related Disorders* 2014;20:1388–93. doi:10.1016/j.parkreldis.2014.10.005.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	BENZTROPINE MESYLATE	BENZTROPINE MESYLATE	Y
ORAL	TABLET	CARBIDOPA-LEVODOPA	CARBIDOPA/LEVODOPA	Y
ORAL	TABLET	SINEMET 10-100	CARBIDOPA/LEVODOPA	Y
ORAL	TABLET	SINEMET 25-100	CARBIDOPA/LEVODOPA	Y
ORAL	TABLET	SINEMET 25-250	CARBIDOPA/LEVODOPA	Y
ORAL	TABLET ER	CARBIDOPA-LEVODOPA ER	CARBIDOPA/LEVODOPA	Y
ORAL	TABLET ER	SINEMET CR	CARBIDOPA/LEVODOPA	Y
ORAL	TABLET	CARBIDOPA-LEVODOPA-ENTACAPONE	CARBIDOPA/LEVODOPA/ENTACAPONE	Y
ORAL	TABLET	STALEVO 100	CARBIDOPA/LEVODOPA/ENTACAPONE	Y
ORAL	TABLET	STALEVO 125	CARBIDOPA/LEVODOPA/ENTACAPONE	Y
ORAL	TABLET	STALEVO 150	CARBIDOPA/LEVODOPA/ENTACAPONE	Y
ORAL	TABLET	STALEVO 200	CARBIDOPA/LEVODOPA/ENTACAPONE	Y
ORAL	TABLET	STALEVO 50	CARBIDOPA/LEVODOPA/ENTACAPONE	Y
ORAL	TABLET	STALEVO 75	CARBIDOPA/LEVODOPA/ENTACAPONE	Y
ORAL	TABLET	COMTAN	ENTACAPONE	Y
ORAL	TABLET	ENTACAPONE	ENTACAPONE	Y
ORAL	TABLET	MIRAPEX	PRAMIPEXOLE DI-HCL	Y
ORAL	TABLET	PRAMIPEXOLE DIHYDROCHLORIDE	PRAMIPEXOLE DI-HCL	Y
ORAL	CAPSULE	SELEGILINE HCL	SELEGILINE HCL	Y
ORAL	ELIXIR	TRIHEXYPHENIDYL HCL	TRIHEXYPHENIDYL HCL	Y
ORAL	TABLET	TRIHEXYPHENIDYL HCL	TRIHEXYPHENIDYL HCL	Y
ORAL	CAPSULE	AMANTADINE HCL	AMANTADINE HCL	N
ORAL	SYRUP	AMANTADINE HCL	AMANTADINE HCL	N
ORAL	TABLET	AMANTADINE HCL	AMANTADINE HCL	N
ORAL	CAPSULE	BROMOCRIPTINE MESYLATE	BROMOCRIPTINE MESYLATE	N
ORAL	CAPSULE	PARLODEL	BROMOCRIPTINE MESYLATE	N
ORAL	TABLET	PARLODEL	BROMOCRIPTINE MESYLATE	N
ORAL	TABLET	BROMOCRIPTINE MESYLATE	BROMOCRIPTINE MESYLATE	N
ORAL	TABLET	CARBIDOPA	CARBIDOPA	N
ORAL	TABLET	LODOSYN	CARBIDOPA	N
ORAL	CAPSULE ER	RYTARY	CARBIDOPA/LEVODOPA	N
ORAL	TAB RAPDIS	CARBIDOPA-LEVODOPA	CARBIDOPA/LEVODOPA	N
ORAL	TAB ER 24H	MIRAPEX ER	PRAMIPEXOLE DI-HCL	N
ORAL	TAB ER 24H	PRAMIPEXOLE ER	PRAMIPEXOLE DI-HCL	N
ORAL	TABLET	AZILECT	RASAGILINE MESYLATE	N

ORAL	TABLET	REQUIP	ROPINIROLE HCL	N
ORAL	TABLET	ROPINIROLE HCL	ROPINIROLE HCL	N
ORAL	TAB ER 24H	REQUIP XL	ROPINIROLE HCL	N
ORAL	TAB ER 24H	ROPINIROLE ER	ROPINIROLE HCL	N
TRANSDERM	PATCH TD24	NEUPRO	ROTIGOTINE	N
ORAL	TABLET	SELEGILINE HCL	SELEGILINE HCL	N
ORAL	TAB RAPDIS	ZELAPAR	SELEGILINE HCL	N
ORAL	TABLET	TASMAR	TOLCAPONE	N
ORAL	TABLET	TOLCAPONE	TOLCAPONE	N

Anticholinergics: *benztropine; trihexyphenidyl*
COMT* Inhibitors: *entacapone; tolcapone*
Dopaminergic Agents: *carbidopa/levodopa*
Dopamine Agonists: *amantadine; bromocriptine; pramipexole; ropinirole; rotigotine*
MAO- B** Inhibitors: *selegiline; rasagaline*

*COMT = Catechol-O-methyl transferase; **MAO-B = Monoamine oxidase B

Appendix 2: New Clinical Trials

A total of 120 citations were manually reviewed from the literature search. After manual review, 117 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 3 trials are briefly described in the table below. The full abstracts are included in **Appendix 3**.

Table 1. Description of Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Olanow CW et al., 2014[7] RCT, DB, DD, PC	Levodopa-carbidopa intestinal gel (LCIG) vs levodopa-carbidopa Immediate-release oral (LCIRO)	≥30 y/o w/ PKD dx ≥ 10 years Mean age 64 y/o 65% male 93% white (n=71)	Change in mean number of off-time hours 3 days prior to both baseline and 12-week final visit normalized to a 16 hour waking day	Treatment Difference: LCIG vs LCIRO -1.91(95% CI, -3.05 to -0.76) P=0.0015
Stocchi F et al., 2014[8] RCT, DB, DD, CS	IPX066 (ER Carbidopa-levodopa) plus entacapone vs Carbidopa-levodopa IR plus entacapone (CL+E)	≥30 y/o w/ advanced idiopathic PKD dx ≥ 10 years Mean age 64 75% male 98% white (n=91)	Mean percent "off-time" during waking hours during last 3 days of each treatment period	Mean percent "off-time": IPX066: 24.0% (95% CI, 7.8% to 40.2%) CL+E: 32.5% (95% CI, 10.6% to 54.4%) P<0.0001
Mizuno Y et al., 2014[9] RCT, DB, DD, PC, PG	Rotigotine (RTG) vs ropinirole (ROP)	Japanese subjects with diagnosis of PKD Mean age 66 y/o 61% female (n=414)	Change in UPDRS Part III "ON" state sum score from baseline to week 16	Treatment Difference: ROT vs PBO -6.4(95% CI, -8.6 to -4.2); p<0.001 ROP vs PBO -5.1(95% CI, -7.4 to -2.8); p<0.001 ROT vs ROP -1.4(95% CI, -3.2 to 0.4); p=0.137 (NS)

Abbreviations: CS = crossover study; DB = double blind; DD = double dummy; dx = diagnosis; PKD = Parkinson's disease; PC = placebo controlled; PG = parallel group; RCT=randomized controlled trial; UPDRS = Unified Parkinson's disease Rating Scale; y/o = years old

Appendix 3: Abstracts of Clinical Trials

1. Olanow, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. *Lancet Neurol.* 2014 Feb;13(2):141-149.

BACKGROUND: Levodopa is the most effective therapy for Parkinson's disease, but chronic treatment is associated with the development of potentially disabling motor complications. Experimental studies suggest that motor complications are due to non-physiological, intermittent administration of the drug, and can be reduced with continuous delivery. We aimed to assess efficacy and safety of levodopa-carbidopa intestinal gel delivered continuously through an intrajejunal percutaneous tube.

METHODS: In our 12-week, randomised, double-blind, double-dummy, double-titration trial, we enrolled adults (aged ≥ 30 years) with advanced Parkinson's disease and motor complications at 26 centres in Germany, New Zealand, and the USA. Eligible participants had jejunal placement of a percutaneous gastrojejunostomy tube, and were then randomly allocated (1:1) to treatment with immediate-release oral levodopa-carbidopa plus placebo intestinal gel infusion or levodopa-carbidopa intestinal gel infusion plus oral placebo. Randomisation was stratified by site, with a mixed block size of 2 or 4. The primary endpoint was change from baseline to final visit in motor off-time. We assessed change in motor on-time without troublesome dyskinesia as a prespecified key secondary outcome. We assessed efficacy in a full-analysis set of participants with data for baseline and at least one post-baseline assessment, and imputed missing data with the last observation carried forward approach. We assessed safety in randomly allocated patients who underwent the percutaneous gastrojejunostomy procedure. This study is registered with ClinicalTrials.gov, numbers NCT00660387 and NCT0357994.

FINDINGS: From baseline to 12 weeks in the full-analysis set, mean off-time decreased by 4.04 h (SE 0.65) for 35 patients allocated to the levodopa-carbidopa intestinal gel group compared with a decrease of 2.14 h (0.66) for 31 patients allocated to immediate-release oral levodopa-carbidopa (difference -1.91 h [95% CI -3.05 to -0.76]; p=0.0015). Mean on-time without troublesome dyskinesia increased by 4.11 h (SE 0.75) in the intestinal gel group and 2.24 h (0.76) in the immediate-release oral group (difference 1.86 [95% CI 0.56 to 3.17]; p=0.0059). In the safety analyses 35 (95%) of 37 patients allocated to the levodopa-carbidopa intestinal gel group had adverse events (five [14%] serious), as did 34 (100%) of 34 patients allocated to the immediate-release oral levodopa-carbidopa group (seven [21%] serious), mainly associated with the percutaneous gastrojejunostomy tube.

INTERPRETATION: Continuous delivery of levodopa-carbidopa with an intestinal gel offers a promising option for control of advanced Parkinson's disease with motor complications. Benefits noted with intestinal gel delivery were of a greater magnitude than were those obtained with medical therapies to date, and our study is, to our knowledge, the first demonstration of the benefit of continuous levodopa delivery in a double-blind controlled study.

2. Stocchi, et al. Comparison of IPX066 with carbidopa-levodopa plus entacapone in advanced PD patients. *Parkinsonism & Related Disorders.* 20(12):1335-40, 2014 Dec.

BACKGROUND: IPX066, an investigational extended-release carbidopa-levodopa (CD-LD) preparation, has demonstrated a rapid attainment and prolonged maintenance of therapeutic LD plasma concentrations in advanced Parkinson's disease (PD). This phase-3 crossover study assessed its efficacy and safety vs. CD-LD plus entacapone (CL + E).

METHODS: At baseline, all patients had motor fluctuations despite a stable regimen of CL + E or CD-LD-entacapone combination tablets (CLE). The study included a 6-week conversion from CL + E or CLE to IPX066, followed by two 2-week, double-blind crossover treatment periods in randomized order, one on IPX066 (and placebo CL + E), the other on CL + E (and placebo IPX066), separated by 1-week open-label IPX066 treatment. The primary efficacy measure was mean percent daily "off" time during waking hours (from patient diaries).

RESULTS: Of 91 randomized patients, 84 completed the study. Their median daily LD dosage was 1495 mg from IPX066 and 600 mg from CL + E, corresponding, after correction for bioavailability, to an approximately 22% higher LD exposure on IPX066. Compared with CL + E, IPX066 demonstrated a lower percent "off" time (24.0% vs. 32.5%; $p < 0.0001$), lower "off" time (3.8 vs. 5.2 h/day; $p < 0.0001$), and higher "on" time without troublesome dyskinesia (11.4 vs. 10.0 h/day; $p < 0.0001$). Other endpoints, including patient-reported treatment preference, also favored IPX066 ($p < 0.05$). During double-blind treatment, 20.2% and 13.6% of patients reported adverse events on IPX066 and CL + E, respectively. The most common were dyskinesia (4 patients), insomnia (3), and confusional state (3) for IPX066, and fall (2) for CL + E.

CONCLUSIONS: In advanced PD, IPX066 showed improved efficacy, compared with CL + E, and appeared to be well tolerated.

3. Mizuno et al. Rotigotine vs ropinirole in advanced stage Parkinson's disease: a double-blind study. *Parkinsonism & Related Disorders*. 20(12):1388-93, 2014 Dec.

OBJECTIVE: To confirm the superiority of transdermal rotigotine up to 16 mg/24 h over placebo, and non-inferiority to ropinirole, in Japanese Parkinson's disease (PD) patients on concomitant levodopa therapy.

METHODS: This trial was a randomized, double-blind, double-dummy, three-arm parallel group placebo- and ropinirole-controlled trial. Four-hundred and twenty PD patients whose motor symptoms were not well controlled by levodopa treatment were randomized 2:2:1 to receive rotigotine, ropinirole (up to 15 mg/day) or placebo during a 16-week treatment period followed by a 4-week taper period. The primary variable was change in the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (ON state) sum score from baseline to the end of the treatment period.

RESULTS: The difference in the change in the UPDRS Part III (ON state) sum score from baseline to the end of treatment between rotigotine and placebo groups was -6.4 +/- 1.2 (95% CI: -8.7 to -4.1; $p < 0.001$), indicating superiority of rotigotine over placebo. The difference between rotigotine and ropinirole groups was -1.4 +/- 1.0 (95% CI: -3.2 to 0.5), below the non-inferiority margin, indicating the non-inferiority of rotigotine to ropinirole. Application site reaction was seen in 57.7% of the patients in the rotigotine group and in 18.6% in the ropinirole group ($P < 0.001$). No other safety issue was noted.

CONCLUSIONS: Rotigotine was well tolerated at doses up to 16 mg/24 h and showed similar efficacy to ropinirole except that the application site reaction was much higher in the rotigotine group.

Appendix 4: Medline Search Strategy

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

1. *benztropine.mp. or Benztropine/290*
2. *carbidopa.mp. or Carbidopa/1212*
3. *levodopa.mp. or Levodopa/10053*
4. *entacapone.mp./489*
5. *pramipexole.mp./1062*
6. *selegiline.mp. or Selegiline/1494*
7. *trihexyphenidyl.mp. or Trihexyphenidyl/292*
8. *amantidine.mp./19*
9. *bromocriptine.mp. or Bromocriptine/2305*
10. *rasagiline.mp./444*
11. *ropinirole.mp./682*
12. *rotigotine.mp./266*
13. *tolcapone.mp./331*
14. *Dopamine Agonists/ or Antiparkinson Agents/ or antiparkinson.mp./15147*
15. *1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13/15356*
16. *14 and 15/7249*
17. *limit 16 to (yr="2014 -Current" and english and humans and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))/120*

Anti-Parkinson's Agents

Goals:

- Promote preferred drugs for Parkinson's disease.
- Restrict use for non-funded conditions like restless leg syndrome.

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. Is the diagnosis Parkinson's disease or another chronic neurological condition?	**Yes:** Go to #5	**No:** Go to #3
3. Is the diagnosis Restless Leg Syndrome?	**Yes:** Pass to RPh. Deny; not funded by the OHP.	**No:** Go to #4
4. RPh only: All other indications need to be evaluated to determine if treatment is for a funded condition.	**Funded:** Go to #5	**Not Funded:** Deny; not funded by the OHP.

Approval Criteria		
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for the shorter of 1 year or length of prescription.

P&T Review: *7/16 (DE); 9/14; 9/13; 09/10*
Implementation: *1/1/14, 1/1/11*

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: Bone Resorption Inhibitors and Related 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:

Efficacy

- The Endocrine Society recommends IV zoledronic acid 5 mg in a single dose for most patients with active Paget's disease who are at risk for complications unless contraindications exist.[1]
- One systematic review and meta-analysis found no statistically significant and consistent difference in vertebral and nonvertebral fracture risk reduction between bisphosphonates, denosumab, or teriparatide.[2]
- Denosumab had lower rates of nonvertebral fracture compared to other bisphosphonates or placebo in one systematic review and meta-analysis.[3] On the contrary, two systematic reviews and meta-analyses found that denosumab had an increased risk for infections.[2,3]
- A systematic review and meta-analysis found no benefit in terms of vertebral or nonvertebral fracture risk with bisphosphonate use at 12 months in patients with cystic fibrosis, though a significant increase in percent change in bone mineral density (BMD) of the lumbar spine, hip and femur.[4]
- In patients with osteogenesis imperfecta, oral alendronate and IV pamidronate showed no difference in fracture incidence.[5] A significant increase was seen in Z score BMD between patients dosed 0.2 mg/kg versus 2 mg/kg of IV risedronate.[5] No difference was seen in patients treated with zoledronic acid versus pamidronate in change in number of fractures.[5]
- Bisphosphonate-treated patients with inflammatory bowel disease had improvements in BMD at the lumbar spine and total hip and lower rates of vertebral and nonvertebral fractures when compared to active controls.[6]
- Early breast cancer patients scheduled to receive aromatase inhibitors had a greater increase in BMD in the lumbar spine in terms of percent change and absolute change in bisphosphonate treated groups compared to groups treated with oral calcium, oral vitamin D or cholecalciferol with or without placebo.[7]
- Patients with Parkinson disease and previous stroke had reduced rates of hip fractures when treated with bisphosphonates compared to controls.[8]

Safety

- Raloxifene was not found to prevent nonvertebral fractures and is associated with a significant rate of severe side effects including thromboembolic events, pulmonary embolism, and fatal strokes.[2]
- Cases of osteonecrosis of the jaw have been reported with bisphosphonate use but are associate much more significantly with IV bisphosphonates versus oral formulations and in patients being treated for malignant conditions.[2]

- No statistically significant difference among any bisphosphonates in terms of gastrointestinal safety outcomes were found in one systematic review.[2] In addition, no significant relationship was discovered between oral alendronate and risedronate for risk of upper GI harms.[2] Another systematic review found that zoledronic acid had the highest probability of GI-related adverse events (91%) followed by etidronate (8%) and alendronate (1%).[9] Etidronate (56%) had the highest rate of upper GI adverse events followed by alendronate (40%) and risedronate (1%).[9] The incidence of nausea was highest with zoledronic acid (70%) followed by alendronate (29%), placebo (1%), and risedronate (0%).[9]
- Absolute rates of cardiovascular (CV) events were slightly higher in bisphosphonate treated patients (6.5%) versus controls (6.2%) over 25-36 months.[10] The absolute risk of atrial fibrillation conversely was minimally lower in bisphosphonate treated patients (1.4%) versus control (1.5%) over 25-36 months though the risk associated with zoledronic acid was somewhat elevated compared to controls (OR 1.24; 95% CI: 0.96 to 1.61).[10] Rates of MI, stroke, and CV death were similar at between patients treated with bisphosphonates versus controls.[10]

Recommendations:

- Consider inclusion of zoledronic acid due to the Endocrine Society's recommendation for use as first-line for Paget's disease.
- Consider inclusion of bazedoxifene on preferred list due to superiority over other bisphosphonates in patients at high risk for fractures (FRAX score ≥20%).

Previous Conclusions and Recommendations:

- There is no new comparative evidence that suggests changes to previous recommendations are needed:
    - Consider inclusion of denosumab, zoledronic acid, risedronate, alendronate in various routes and dosing schedules for osteoporosis treatment based upon cost.
    - Include at least one nitrogen-containing bisphosphonate for Paget 's disease (zoledronic acid, pamidronate, risedronate, alendronate or ibandronate).
    - Make calcitonin, raloxifene and teriparatide non-preferred due to limited evidence to reduce non-vertebral and hip fracture risk in post-menopausal women. Calcitonin has limited evidence for Paget 's disease.
    - Make tiludronate non-preferred as it is only indicated for Paget's, is not a nitrogen containing bisphosphonate and it has insufficient evidence for osteoporosis treatment.
- 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:

Efficacy:

Crandall C, et al. *Ann Intern Med.* (2014)[2]

The purpose of this systematic review was to update a review about the benefits and harms of pharmacologic treatments used to prevent fractures in at risk adults.[2] Three-hundred and fifteen RCTs and systematic reviews were included.[2] Five network meta-analysis of placebo-controlled or head-to-head trials found that differences in vertebral and nonvertebral fracture risk reduction among any of the bisphosphonates, denosumab, or teriparatide were not consistent or statistically significant.[2] There was also agreement amongst the meta-analyses that raloxifene does not prevent nonvertebral fractures, and there is less evidence supporting nonvertebral fracture reduction efficacy for ibandronate than for the other bisphosphonates, denosumab, or teriparatide.[2]

An increase rate of atypical subtrochanteric fractures is seen in those treated with bisphosphonates but the association has only been established in observational studies, case studies, and case series.[2] A meta-analysis of 5 case-control studies and 6 cohort studies found an overall pooled risk ratio (RR) of 1.70 (95% CI: 1.22 to 2.37).[2] Data are sufficient to conclude that bisphosphonate use increases the risk for atypical femoral fractures though the strength of evidence is low.[2] The risk of atypical femoral fracture is lower (30-100 fold) than the risk of hip fracture among untreated persons with osteoporosis. Use of denosumab has also been linked to occurrences of atypical femoral fractures.[2]

An increased risk of esophageal cancer was seen in 2 observational studies but was not seen in 2 others.[2] Several observational studies have found no increased risk or statistically significant decreases in risk for all types of cancer in general.[2] A meta-analysis of 4 studies found no statistically significant risks (OR 1.74; 95% CI: not reported) for esophageal cancer in patients with bisphosphonate treatment.[2] An evaluation of teriparatide found no association with osteosarcoma after 7 years of follow-up.[2] Five studies (2 observational studies, 2 meta-analyses, and 1 systematic review) did not find an increased risk of atrial fibrillation and 1 meta-analysis found an increased risk of atrial fibrillation with bisphosphonate use.[2]

The previous review showed an increased risk for mild upper gastrointestinal side effects with use of alendronate (OR 1.07; 95% CI: 1.01 to 1.14), teriparatide (OR 3.26; 95% CI: 2.82 o 3.78), and denosumab (OR 1.74; 95% CI: 1.29 to 2.38).[2] A network meta-analysis did not find any statistically significant differences among any bisphosphonates in terms of gastrointestinal safety outcomes.[2] A case-control study found no significant relationship between oral alendronate or risedronate for the risk of subsequent hospitalizations for serious upper gastrointestinal harms (e.g., perforations, ulcers, and bleeding).[2] Pooled data from 4 trials of denosumab showed an increased risk for infection (RR 1.28; 95% CI: 1.02 to 1.60).[2]

Twenty-three publications and 2408 cases of osteonecrosis of the jaw showed that 88% of cases were associated with intravenous bisphosphonates (OR 2.32; 95% CI: 1.30 to 3.91; I^2=41%) and 89% of patients were being treated for a malignant condition.[2] Cases of osteonecrosis of the jaw have also been reported with denosumab use.[2]

Teriparatide was associated with increased risk for hypercalcemia (OR 12.90; 95% CI: 10.49 to 16.00). Zoledronic acid was associated with increased risk for hypocalcemia (OR 7.22; 95% CI: 1.81 to 42.70).[2] Raloxifene use was associated with hot flashes (OR 1.58; 95% CI: 1.35 to 1.84), thromboembolic events (OR 1.63; 95% CI: 1.36 to 1.98), pulmonary embolism (OR 1.82; 95% CI: 1.16 to 2.92), and fatal strokes (OR 1.56; 95% CI: 1.04 to 2.39).[2] Teriparatide was associated with headaches (OR 1.46; 95% CI: 1.27 to 1.69).[2] Zoledronic acid infusion was associated with myalgia, arthralgia, pyrexia, chills, and influenza-like symptoms with a composited odds ratio of 6.39 (95% CI: 5.76 to 7.09).[2]

Conwell L, et al. *Cochrane Database of Systematic Reviews*. (2014)[4]
Trials were examined that compared bisphosphonates to controls (other bisphosphonates, placebo, or usual treatment of oral calcium and/or vitamin D) in patients with cystic fibrosis for the prevention or treatment of osteoporosis.[4] The primary outcome examined was fractures and secondary outcomes examined BMD via dual-energy X-ray absorptiometry (DXA) and survival.[4] Six RCTs (12-24 months) and one abstract of an RCT met the inclusion criteria to be included within the systematic review.[4] No included trials reported sample size or power calculations.[4] Four trials assessed bisphosphonates with oral calcium and oral vitamin D versus oral calcium and vitamin D supplementation alone.[4] Bisphosphonates used as the intervention in these trials were intravenous pamidronate in one trial, oral alendronate in one trial and intravenous zoledronate in two trials.[4] One trial assessed intravenous pamidronate with oral calcium versus oral calcium alone.[4] Two trials compared bisphosphonates (oral risedronate in one trial and oral alendronate in one trial) to placebo.[4]

A statistically significant difference between bisphosphonates and controls in new non-vertebral was not found at 12 months (OR 0.19; 95% CI: 0.01 to 4.21) and at 24 months (OR 2.11; 95% CI: 0.18 to 25.35).[4] Similarly, there was no significant difference between groups at 12 months for both vertebral and non-vertebral fractures (OR 0.72; 95% CI: 0.13 to 3.80).[4] Pooled results showed significant increases in percent change in BMD in the bisphosphonate group at the lumbar spine (MD 5.67%; 95% CI: 4.81 to 6.53; I^2=0%) and at the hip or femur (MD 4.29%; 95% CI: 2.45 to 6.13; I^2=74%).[4] No significant difference in survival was observed in pooled data of oral risedronate or intravenous pamidronate.[4] Other trials reported no deaths in either treatment or control groups.[4] No specific comparisons between bisphosphonates or other active comparators were found.[4]

Data from the one trial of participants who received lung transplants was analyzed separately in the systematic review.[4] No statistically significant difference was found in the number of participants with new vertebral fractures (OR 3.92; 95% CI: 0.36 to 42.20) or new non-vertebral fractures (OR 0.46; 95% CI: 0.09 to 2.27).[4] Change in percent BMD was significantly higher in the bisphosphonate group at the lumbar spine (MD 6.20%; 95% CI: 4.28 to 8.12) and at the hip or femur (MD 7.90%; 95% CI: 5.78 to 10.02).[4]

Dwan K, et al. *Cochrane Database of Systematic Reviews.* (2014)[5]
The systematic review was performed as there currently exists no consensus on the effectiveness and safety of bisphosphonates in the treatment of osteogenesis imperfecta (OI).[5] Trials were selected that examined bisphosphonates to improve BMD in OI compared to placebo, no treatment control, or comparator interventions (sodium fluoride, testosterone, vitamin D, etc) and different formulations of bisphosphonates.[5] Fourteen randomized controlled trials were included of which six trials compared oral bisphosphonates to placebo, three trials compared an IV bisphosphonate to placebo, one trial compared different doses of oral bisphosphonates, one trial compared oral to IV bisphosphonates and two trials compared different IV bisphosphonates.[5]

Oral versus IV Bisphosphonates
Oral alendronate and IV pamidronate treatment groups showed no difference in fracture incidence (MD 0.50; 95% CI: -0.64 to 1.64) or BMD at 12 months (MD 0.30; 95% CI: -1.11 to 1.71) or 24 months (MD 0.20; 95% CI: -1.32 to 1.72).[5]

Different Doses of Oral or IV Bisposphonates
No difference in the number of crush-fractured vertebrae was seen when comparing each of the three dose groups of risedronate including 0.2, 1, 2 mg/kg/week).[5] Pamidronate 6 mg/kg versus 12 mg/kg showed no difference in BMD of the lumbar spine at 12 month (MD 45.00; 95% CI: -30.15 to 120.15) or the number of crush-fractured vertebrae with rate ratio of 1.28 (95% CI: 0.67 to 2.45).[5] A statistically significant difference was seen between risedronate 0.2 mg/kg versus 2 mg/kg in terms of z score BMD adjusting for the baseline value of each outcome and age (MD -1.18; 95% CI: -1.97 to -0.39).[5] No difference in

BMD at the lumbar spine was seen between risedronate 0.2 mg/kg/week versus 1 mg/kg/week (MD -0.50; 95% CI: -1.29 to 0.29) or 1 mg/kg/week versus 2 mg/kg/week (MD -0.68; 95% CI: -1.46 to 0.10).[5]

Comparison of IV Bisphosphonates
No difference was reported between zoledronic acid and pamidronate in change in number of fractures per patient from baseline (MD -0.41; 95% CI: -1.45 to 0.63).[5] One trial showed a statistically significant change in lumbar spine BMD that favored zoledronic acid over pamidronate (MD 8.06; 95% CI: 0.48 to 15.64) while another favored pamidronate over zoledronic acid (MD -1.50; 95% CI: -2.86 to -0.14).[5]

Melek J, et al. *Clin Gastroenterol Hepatol.* (2014)[6]
The objective of this systematic review was to compare improvement in BMD at the lumbar spine and total hip, risk of fractures, tolerability, and safety between medical therapies used for low BMD in patients with inflammatory bowel disease.[6] Nineteen RCTs were included of which 2 used calcium and vitamin D as therapies, 13 used bisphosphonates, 4 used fluoride, 1 used calcium, and 1 used low-impact exercise.[6] Thirteen studies evaluated bisphosphonates including alendronate, pamidronate, ibandronate, risedronate, etidronate, clodrate, and zoledronate that ranged in length from 8 weeks to 42 months.[6] Comparators to bisphosphonates included placebo, no treatment, vitamin D, and fluoride.[6] Pooled data showed a positive effect of bisphosphates on BMD at the lumbar spine (standard difference in means (SDm) of 0.51; 95% CI: 0.29 to 0.72; p<0.01; I^2=84.7%) and total hip (SDm 0.26; 95% CI: 0.04 to 0.49; p=0.02; I^2=16.7%).[6] Bisphosphonates were found to reduce the risk of vertebral fractures.[6] Bisphosphonate treatment was superior to controls at reducing vertebral and nonvertebral fractures with pooled ORs of 0.35 (95% CI: 0.06-1.95; p=0.23) and 0.38 (95% CI: 0.15 to 0.96; p=0.04).[6] Adverse events were not significant for use with bisphosphonates (OR 1.24; 95% CI: 0.83-1.85; p=0.29).[6] No specific comparisons between bisphosphonates were found.[6]

Su G, et al. *Archives of Medical Research*. (2014)[7]
The objective of this systematic review was to compare changes in percentage and absolute change in lumbar spine BMD in with treatment with bisphosphonates in postmenopausal, early breast cancer patients scheduled to receive aromatase inhibitors.[7] Eleven articles were included.[7] Ibandronate and alendronate were utilized each in 1 study, zoledronic acid in 4 studies, and risedronate in 5 studies.[7] All except for one study used calcium and vitamin D supplementation in both treatment and control groups during the studies.[7] Comparators were oral calcium and oral vitamin D or cholecalciferol with or without placebo.[7] Pooled data showed that BMD in the lumbar spine was higher in the bisphosphonate group in terms of percentage change (WMD 5.42; 95% CI: 4.37 to6.48; I^2=74.6%) and the absolute change (0.21 g/cm^2 (95% CI: 0.13 to 0.28; I^2=0%).[7] Percent change and absolute change of BMD at the total hip were significantly increased in the bisphosphate group (WMD 3.01; 95% CI: 2.01 to 4.01; I^2=80%) and (0.07 g/cm^2; 95% CI: 0.02 to 0.12; I^2=0%).[7] No specific comparisons between bisphosphonates were found.[7]

Zhang W, et al. *J Stroke Cerebrovasc Dis.* (2014)[8]
The purpose of this systematic review was to compare the efficacy of different bisphosphonates against hip fracture in elderly patients with stroke and Parkinson disease.[8] Eight RCTs were included with 5 RCTs for stroke and 3 RCTs for Parkinson disease.[8] Bisphosphonates studied included etidronate in 2 studies, risedronate in 4 studies, and alendronate in 2 studies.[8] Comparators included placebo in 7 studies and alphacalcidol in 1 study.[8] The relative risk of hip fractures with bisphosphate treatment compared to control treatment was significantly reduced for patient with stroke (RR 0.20; CI: 0.07 to 0.54) and patients with Parkinson disease (RR 0.26; CI: 0.13 to 0.52).[8]

Safety:
Kim DH, et al. PLoS ONE. (2015)[10]

This systematic review was to determine the effects of bisphosphonates on total adverse cardiovascular (CV) events, atrial fibrillation, myocardial infarction (MI), stroke, and CV deaths in adults with osteoporosis or at risk for low bone mass.[10] Fifty-eight RCTs that reported at least 1 CV outcome were included in the systematic review.[10] Total adverse CV event data was available in 14 trials that showed an absolute risk of 6.5% in bisphosphate-treated patients versus 6.2% in control patient over 25-36 months (OR 0.98; 95% CI: 0.84 to 1.14; I^2=0%).[10] Forty-one trials provided data on atrial fibrillation showing an absolute risk of 1.4% in bisphosphonate-treated patients and 1.5% in control patients over 25-36 months (OR 1.08; 95% CI: 0.92 to 1.25; I^2=0%).[10] The risk of atrial fibrillation seemed somewhat elevated for patients treated with zoledronic acid (OR 1.24; 95% CI: 0.96 to 1.61).[10] Bisphosphonate-treated patients and control patients showed low and similar rates of MI (1.0% versus 1.2%), stroke (1.6% versus 1.9%), and CV death (1.5% versus 1.4%).[10] A major limitation to the results is that trials excluded due to lack of CV data probably had few or no CV events and therefore the absolute risk of CV events is potentially overestimated.[10] Most trials included generally healthy patients and therefore the generalizability of the results may not be applicable to those with a higher risk of CV events.[10]

Tadrous M, et al. *Osteoporos Int.* (2014)[9]

This systematic review compared gastrointestinal safety between different bisphosphonates.[9] Fifty RCTs were included in the analysis which utilized alendronate in 29 trials, risedronate in 10 trials, zoledronate in 7 trials, etidronate in 3 trials, and 1 trial utilized alendronate and risedronate in multiple treatment arms.[9] Comparators were placebo, alendronate, risedronate, and etidronate served as comparators.[9] Study lengths varied from 3 to 45 months with an average length of 18 months.[9]

Forty-six studies were used to analyze occurrence of any GI-related adverse event which showed that zolendronic acid had the highest probability (91%) followed by etidronate (8%), alendronate (1%).[9] Some bisphosphonates showed lower odds of causing any GI adverse events than zoledronic acid including alendronate (OR 0.62; 95% CI: 0.39 to 0.96), risedronate (OR 0.57; 95% CI: 0.36 to 0.88), and placebo (OR 0.55; 95% CI: 0.35 to 0.84).[9] Thirty-eight studies were used to analyze differences in upper GI adverse events which showed the highest risk in patients treated with etidronate (56%) followed by alendronate (40%) and risedronate (1%).[9] Eighteen studies were utilized to compare the incidence of nausea in bisphosphonate-treated patients.[9] The incidence of nausea was shown to be highest in patients treated with zoledronic acid (70%) followed by alendronate (29%), placebo (1%), and risedronate (0%).[9]

Zhou Z, et al. *Int J Clin Exp Pathol.* (2014)[3]

The purpose of this systematic review and meta-analysis was to compare the safety of denosumab versus bisphosphonates or placebo in postmenopausal women with osteoporosis or low bone mineral density.[3] Eleven RCTs were that compared denosumab to placebo in 7 trials, alendronate in 4 trials, and ibandronate and risedronate in 1 trial, respectively (2 trials included 2 arms of comparison for active control and placebo comparison).[3]

Pooled data found no significant difference between denosumab and bisphosphonates or placebo for any adverse events (RR=0.99; 95% CI: 0.98 to 1.01; p=0.29), serious adverse events (RR=1.05; 95% CI: 0.98 to 1.13; p=0.18), neoplasm or cancer (RR=1.14; 95% CI: 0.95 to 1.37; p=0.16), or death (RR=0.77; 95% CI: 0.57 to 1.04; p=0.09).[3] Denosumab had a significantly increased rate of serious adverse events related to infections when compared to bisphosphonates or placebo (RR=1.23; 95% CI: 1.00 to 1.52; p=0.05) and a lower rate of non-vertebral fractures (RR=0.86; 95% CI=0.74 to 1.00; p=0.05).[3] No significant heterogeneity was found (p>0.05, I^2<50%) among all included studies.[3]

New Guidelines:

Endocrine Society Clinical Practice Guideline (2014)[1]

Bisphosphonate therapy is strongly recommended for most patients with active Paget's disease who are at risk for future complications based on moderate quality evidence.[1] Low quality evidence supports the weak recommendation for use of a potent bisphosphonates in patients with Paget's disease to prevent

worsening hearing loss, before undergoing elective total joint replacement or osteotomy to prevent intraoperative hemorrhaging and postoperative loosening of prosthesis, before surgery for treatment of osteosarcoma or giant cell tumor, in cases of paraplegia, and for patients with congestive heart failure.[1] The Endocrine Society makes a weak recommendation based on moderate quality evidence for use of a single dose of 5-mg IV zoledronate unless patients have contraindications such as CrCl <35 mL/min.[1] The recommendation for the use of zoledronate is based on evidence of superiority of disease control seen in long term follow-up studies due to its more rapid, more frequent, and much more sustained disease control after a single IV infusion.[1] Treatment based on oral bisphosphonates or less potent IV bisphosphonates has shown biochemical remission from Paget's disease lasting 1-3 years while zoledronate has produced disease remission lasting more than 6 years.[1] Zoledronate is therefore more cost-effective and convenient to treat most patients with active disease without contraindications.[1] Patients with Paget's disease and contraindication to zoledronate should be treated if symptomatic or at risk of severe complications from Paget's disease.[1] In patients with contraindications for IV zoledronate due to renal impairment, oral bisphosphonates are considered a safer alternative due to lower peak serum concentrations.[1]

New Formulations/Indications:

Xgeva (denosumab)[11]

New Indication (December 2014): treatment of hypercalcemia of malignancy refractory to bisphosphate therapy.[11]

New FDA Safety Alerts:

No new FDA Safety Alerts.

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	ACTONEL	RISEDRONATE SODIUM	Y
ORAL	TABLET	ALENDRONATE SODIUM	ALENDRONATE SODIUM	Y
ORAL	TABLET	BONIVA	IBANDRONATE SODIUM	Y
ORAL	TABLET	FOSAMAX	ALENDRONATE SODIUM	Y
ORAL	TABLET	IBANDRONATE SODIUM	IBANDRONATE SODIUM	Y
ORAL	TABLET	RISEDRONATE SODIUM	RISEDRONATE SODIUM	Y
INJECTION	VIAL	MIACALCIN	CALCITONIN,SALMON,SYNTHETIC	N
INTRAVEN	SYRINGE	BONIVA	IBANDRONATE SODIUM	N
INTRAVEN	SYRINGE	IBANDRONATE SODIUM	IBANDRONATE SODIUM	N
NASAL	SPRAY/PUMP	CALCITONIN-SALMON	CALCITONIN,SALMON,SYNTHETIC	N
NASAL	SPRAY/PUMP	FORTICAL	CALCITONIN,SALMON,SYNTHETIC	N
NASAL	SPRAY/PUMP	MIACALCIN	CALCITONIN,SALMON,SYNTHETIC	N
ORAL	SOLUTION	ALENDRONATE SODIUM	ALENDRONATE SODIUM	N
ORAL	TABLET	ETIDRONATE DISODIUM	ETIDRONATE DISODIUM	N
ORAL	TABLET	EVISTA	RALOXIFENE HCL	N
ORAL	TABLET	FOSAMAX PLUS D	ALENDRONATE SODIUM/VITAMIN D3	N
ORAL	TABLET	RALOXIFENE HCL	RALOXIFENE HCL	N
ORAL	TABLET DR	ATELVIA	RISEDRONATE SODIUM	N
ORAL	TABLET DR	RISEDRONATE SODIUM DR	RISEDRONATE SODIUM	N
ORAL	TABLET EFF	BINOSTO	ALENDRONATE SODIUM	N
SUB-Q	PEN INJCTR	FORTEO	TERIPARATIDE	N
SUB-Q	SYRINGE	PROLIA	DENOSUMAB	N
INTRAVEN	INFUS. BTL	RECLAST	ZOLEDRONIC ACID/MANNITOL&WATER	
INTRAVEN	INFUS. BTL	ZOLEDRONIC ACID	ZOLEDRONIC ACID/MANNITOL&WATER	
INTRAVEN	INFUS. BTL	ZOMETA	ZOLEDRONIC ACID/MANNITOL&WATER	
INTRAVEN	PIGGYBACK	ZOLEDRONIC ACID	ZOLEDRONIC ACID/MANNITOL&WATER	
INTRAVEN	VIAL	IBANDRONATE SODIUM	IBANDRONATE SODIUM	
INTRAVEN	VIAL	PAMIDRONATE DISODIUM	PAMIDRONATE DISODIUM	
INTRAVEN	VIAL	ZOLEDRONIC ACID	ZOLEDRONIC ACID	
INTRAVEN	VIAL	ZOMETA	ZOLEDRONIC ACID	
SUB-Q	VIAL	XGEVA	DENOSUMAB	

Appendix 2: New Clinical Trials

A total of 251 citations were manually reviewed from the literature search. After further review, 251 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical or surrogate outcome such as BMD).

Table 1: Description of Clinical Trials
No clinical trials met search criteria.

Appendix 3: Medline Search Strategy

[Example]
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 Risedronate Sodium/ 1001
2 exp Alendronate/ 3023
3 ibandronate.mp. 773 Advanced
4 exp Etidronic Acid/ 1665
5 exp Teriparatide/ 1033
6 exp Denosumab/ 808
7 zoledronic acid.mp. 3082
8 pamidronate.mp. 2144
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10544
10 limit 9 to (yr="2014 -Current" and humans and (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews) 230

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 Calcitonin/ 5722
2 exp Paget Disease, Extramammary/ 841
3 exp Hypercalcemia/ 4059
4 exp Osteoporosis, Postmenopausal/ or exp Osteoporosis/ 34503
5 2 or 3 or 4 39255
6 1 and 5 781
7 limit 6 to (yr="2014 - 2016" and humans and (clinical study 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 randomized controlled trial or systematic reviews) 11

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 Raloxifene Hydrochloride/ 2307
2 exp Osteoporosis/ 34503
3 1 and 2 822
4 limit 3 to (yr="2014 - 2016" and humans and (clinical study 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 randomized controlled trial or systematic reviews) 10

Bone Resorption Inhibitors and Related Agents

Goal(s):

- To ensure appropriate drug use and safety of bone resorption suppression agents by authorizing utilization in specified patient populations.

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. Is this an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Will the prescriber consider a change to a preferred product? Note: • 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 #4
4. Is the request for raloxifene?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Is the patient pregnant and/or at increased risk for thromboembolism or stroke?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: inform prescriber of pregnancy category X and boxed warning for venous thromboembolism and stroke.	**No:** Approve for up to 12 months
6. Is the request for teriparatide and is the patient at high risk for fractures? Examples include: • Postmenopausal women with osteoporosis • Men with primary or hypogonadal osteoporosis • Osteoporosis associated with sustained glucocorticoid therapy	**Yes:** Go to #7	**No:** Pass to RPh. Go to #8
7. Does the patient meet one of the following conditions: • Concomitant bisphosphonate; or • Pediatric or young adult with open epiphyses; or • History of osteosarcoma or skeletal malignancies; or • Metabolic bone disease; or • Underlying hypercalcemic disorders; or • Unexplained elevated alkaline phosphatase levels?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 12 months
8. RPh only: All other indications need to be evaluated as to whether they are funded by the OHP or not.	If funded and clinic provides supporting literature, approve for up to 12 months	If non-funded, deny; not funded by the OHP

P&T Review: *7/16; 9/10*
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: 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: Yes

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)

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Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use 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: Oral Antiepileptic Drugs

Date of Review: July 2016

Date of Last Review: March 2015
Literature Search: March 2015 – April 2016

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

Conclusions:

- There were no new comparative systematic reviews or evidence-based guidelines of antiepileptic drugs (AEDs) identified on which to recommend changes to the PDL class.
- Two AED medications received expanded indications in 2015. Esclicarbazepine is now approved to use as adjunctive therapy in the treatment of partial-onset seizures. Previously, it was only approved for use as monotherapy. The indications for perampanel were expanded to include treatment of primary generalized tonic-clonic seizures in patients 12 years of age and older. Perampanel was initially approved by the U.S. Food and Drug Administration (FDA) in 2012 for the treatment of partial onset seizures among epilepsy patients.
- The FDA approved a new oral suspension formulation of perampanel which provides an additional option for patients who have difficulty swallowing tablets.
- The American Academy of Neurology and the American Epilepsy Society published evidence-based guidelines for starting AEDs in adults after a first seizure. The authors found moderate evidence that immediate AED therapy as compared with no treatment is likely to reduce absolute risk by about 35% for a seizure recurrence within the subsequent 2 years.
- There is moderate quality evidence lacosamide is effective and well tolerated in the short term when used as add-on treatment for drug-resistant partial epilepsy in adults.
- There are insufficient data to address the risk-benefit balance of vigabatrin versus carbamazepine monotherapy for epilepsy in adults and children.
- There is moderate quality evidence that describes common adverse effects with lamotrigine therapy in pediatric patients. The most commonly reported adverse events include: rash, headache, fever, somnolence, vomiting, seizure aggravation, dizziness, cough, aggression, ataxia and insomnia. Children on lamotrigine monotherapy had lower incidences of adverse events compared to multiple AEDs.
- There is low quality evidence that levetiracetam is effective in reducing neuropathic pain but it is associated with an increase in adverse events and premature discontinuation due to side effects.
- There is moderate quality evidence that discontinuing an AED in children prior to at least 2 seizure-free years is associated with a higher recurrence rate than waiting 2 or more seizure-free years. The optimal time of withdrawal is not clear due to insufficient evidence. There is no evidence to guide AED discontinuation in adults.
- For all the currently marketed AEDs, there is no evidence to support the use of any of them in treating migraines. Topiramate, sodium valproate and divalproex are effective prophylactic treatments for episodic migraine in adults. There is insufficient evidence to further support the use of gabapentin in migraine prophylaxis.
- There is low quality evidence that topiramate may be effective in reducing the frequency of binge eating in patients with binge-eating disorder.

Recommendations:

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

Previous Conclusions:

- There were no new comparative systematic reviews or evidence-based guidelines of antiepileptic drugs (AEDs) identified on which to recommend changes to the PDL class.
- FDA expanded the black-boxed warnings on valproate products to include possible fetal neural tube defects and other structural abnormalities (e.g., craniofacial defects, cardiovascular malformations, hypospadias, limb malformations) when used during pregnancy.
- There is insufficient evidence that controlled-release carbamazepine is more effective than the immediate-release formulations; however, low quality evidence suggests the controlled-release formulations may be more tolerable.
- There is insufficient evidence that felbamate is effective as add-on therapy for refractory partial-onset epilepsy.
- There is moderate quality evidence that tiagabine is effective at reducing seizure frequency but is associated with more dizziness, fatigue, nervousness and tremor when used as add-on therapy in patients with localization-related seizures who have failed at least two AEDs as monotherapy.
- There is moderate quality evidence that in the short term, adding pregabalin at doses ranging from 150-600 mg per day to AED therapy can significantly reduce seizure rates and cease seizures altogether in patients with drug-resistant partial epilepsy. There is insufficient evidence, however, for longer treatment duration and insufficient evidence comparing pregabalin against other adjunctive treatments.
- There is moderate quality evidence that in the short term, adding topiramate at doses no greater than 300 mg per day to AED therapy can significantly reduce rates and cease seizures altogether in patient with drug-resistant partial epilepsy. There is insufficient evidence, however, for longer treatment duration and insufficient evidence comparing topiramate against other adjunctive treatments.

Previous Recommendations:

- Retire current PA criteria for pregabalin which will be replaced with the PA criteria “Drugs Used for Non-funded Pain Conditions”.
- Remove PA criteria for preferred topiramate products due to cost effectiveness.
- 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:

Lacosamide Add-on Therapy for Partial Epilepsy in Adults

A Cochrane review by Weston, et al. evaluated the efficacy and tolerability of lacosamide (LCM) when used as an add-on treatment for patients with drug-resistant partial epilepsy.[1] Eligible studies were randomized, placebo, controlled trials (RCTs) in which lacosamide doses ranged from 200 to 600 mg per day.[1] Three RCTs involving 1311 subjects were included in the analysis. The participants were experiencing seizures despite taking a minimum of 2 AEDs.[1] The reviewers rated the quality of the studies as moderate to high with low risk of bias. The following outcomes were assessed: 50% or greater reduction in seizure frequency, seizure freedom, treatment withdrawal for any reason, and adverse events. Trial duration ranged from 24 to 26 weeks. The overall risk ratio (RR) for a 50% or greater reduction in seizure frequency for LCM compared with placebo was 1.70 (95% confidence interval (CI) 1.38 to 2.10); for seizure freedom for LCM compared with placebo was 2.50 (95% CI 0.85 to 7.34); and for treatment withdrawal for LCM compared with placebo was 1.88 (95% CI 1.40 to 2.52).[1] Adverse effects associated with LCM administration included abnormal coordination (RR 6.12, 99% CI 1.35 to 27.77), diplopia (RR 5.29, 99% CI 1.97 to 14.23), dizziness (RR 3.53, 99% CI 2.20 to 5.68), nausea (RR 2.37, 99% CI 1.23 to 4.58) and vomiting (RR 3.49, 99% CI 1.43 to 8.54).[1] LCM doses at 200 mg per day were well tolerated with no significant differences in withdrawal rate. [1] However, as the LCM dose was titrated up to 400 mg per day participants were almost twice as likely to withdraw due to side effects.[1] At the 600 mg dose, patients were 3-times more likely to withdraw due to side effects.[1] The authors concluded LCM is effective in the short term when used as add-on treatment for drug-resistant partial epilepsy in adults. [1] The authors noted that adverse effects with LCM were common and more likely to occur at higher doses.[1]

Vigabatrin Versus Carbamazepine Monotherapy for Epilepsy

Xiao, et al. updated their 2012 Cochrane review to investigate the efficacy and safety of vigabatrin (VGB) versus carbamazepine (CBZ) monotherapy for epilepsy in children and adults.[2] Five RCTs including a total of 734 participants compared VGB to CBZ in patients newly diagnosed with epilepsy. Subject age ranged from 6 months to 65 years.[2] The authors assessed only one study as good quality and the other 4 studies as poor quality with unclear to high risk of bias.[2] The primary outcome was time to treatment withdrawal. Secondary outcomes were time to achieve 6-month and 12-month remission after randomization, time to first seizure after randomization and adverse events. Not all studies reported the same outcomes as those identified for the review, so the authors were unable to extract aggregate data for synthesis of a meta-analysis.[2] No significant differences favored one drug over the other in terms of time to treatment withdrawal or time to achieve 6-month remission after dose stabilization.[2] Compared with CBZ, VGB was associated with more occurrences of weight gain and fewer occurrences of skin rash and drowsiness.[2] No differences in visual field defects and visual disturbances were noted.[2] The authors concluded there is insufficient data to address the risk-benefit balance of VGB versus CBZ monotherapy for epilepsy.[2]

Safety of Lamotrigine in Pediatrics

Equnsula, et al. completed a systematic review to identify adverse drug reactions associated with lamotrigine in children.[3] All studies involving pediatric patients aged 18 years or younger who had received at least one dose of lamotrigine were included.[3] The primary outcome measure was to compare the safety of lamotrigine AEDs. A secondary outcome was any adverse event observed with when lamotrigine was administered in combination with other AEDs secondary to a drug interaction.[3] A total of 78 articles involving 3783 pediatric patients were identified. The most common types of articles were case reports (n=50) followed by 12 prospective cohort trials and 9 RCTs.[3] All RCTs and cohort studies were evaluated as good quality and eligible for inclusion in the final data aggregation.[3] There were 2222 adverse events reported.[3] Rash was the most commonly reported adverse event, occurring in 7.3% of the patients, and was the most common reason for treatment discontinuation.[3] Stevens-Johnson syndrome was rarely reported, with a risk of 0.09 per 100 patients.[3] Discontinuation due to an adverse drug reaction (ADR) was noted in 72 children (1.9% of all treated patients).[3] Fifty-eight percent of treatment discontinuations were attributed to different forms of rash and 21% due to increased seizures.[3] There were significantly higher risks of dizziness (RR 4.57, 95% CI 1.88 to 11.12, $p<0.001$), abdominal pain (RR 2.53,

95% CI 1.12 to 5.70, p=0.03) and nausea (RR 5.94, 95% CI 1.59 to 22.13, p=0.008) with lamotrigine than placebo.[3] Headache (5.3% with monotherapy and 8.3% with polytherapy, p=0.02), somnolence (1.5% with monotherapy and 18.6% with polytherapy , p<0.001), nausea (0.9% with monotherapy and 4.3% with polytherapy, p=0.01), vomiting (0% with monotherapy and 8.7% with polytherapy, p<0.001), dizziness (1.2% with monotherapy and 10.7% with polytherapy, p<0.001) and abdominal pain (1.5% with monotherapy and 5.1% with polytherapy, p=0.01) were significantly lower among children on monotherapy.[3] Rash was the most common adverse effect that resulted in lamotrigine treatment discontinuation. [3]The authors concluded children on lamotrigine monotherapy had lower incidences of adverse events compared with the patients receiving multiple AEDs.[3]

Early Versus Late Antiepileptic Drug Withdrawal For People With Epilepsy In Remission

Strozzi, et al. updated a 2001 Cochrane review to evaluate optimal timing of AED discontinuation to reduce adverse effects associated with long-term use of AEDs.[4] The primary outcome was difference in seizure relapse rates between early and late withdrawal of AEDs in epileptic patients in remission.[4] Five randomized trials including 924 children were included in the analysis.[4] Due to the difficulties of simulating withdrawal of medication, none of the studies were blinded.[4] All of the study participants were pediatric epileptic patients 16 years and younger at randomization.[4] The pooled risk ratio for seizure relapse after AED withdrawal after two years of therapy was 1.34 (95% CI 1.13 to 1.59, p=0.0007).[4] Early discontinuation was associated with greater relapse rates in children with partial seizures (RR 1.51; 95% CI 0.97 to 2.35, p=0.07).[4] Variables associated with higher risk of seizure relapse were abnormal EEG findings (RR 1.44, 95% CI 1.13 to 1.83, p=0.003), especially epileptiform activity (RR 2.58, 95% CI 2.03 to 3.28, p<0.0001); epilepsy onset before 2 years or after 10 years of age; history of status epilepticus; intellectual disability (IQ < 70); and high seizure frequency before and during treatment.[4] The authors concluded that discontinuing AED medication in children prior to at least 2 seizure-free years is associated with a higher recurrence rate than waiting 2 or more seizure-free years.[4] The optimal time of withdrawal is not clear due to insufficient evidence.[4] There is no evidence to guide AED discontinuation in adults who have been seizure-free.[4]

Levetiracetam For Neuropathic Pain in Adults

A Cochrane review completed by Wiffen, et al. assessed the analgesic efficacy and adverse events of levetiracetam use in adults with chronic neuropathic pain conditions.[5] Primary outcomes included: participant-reported pain relief ≥30%, participant-reported pain relief ≥50%, and Patient Global Impression of Change (PGIC) improvement (moderate to substantial). The authors included 6 studies: 5 small, cross-over studies with 174 participants, and one parallel group study with 170 participants.[5] Participants were treated with levetiracetam (2000 mg to 3000 mg daily) or placebo between 4 and 14 weeks.[5] Each study included participants with a different type of neuropathic pain; central pain due to multiple sclerosis, pain following spinal cord injury, painful polyneuropathy, central post-stroke pain, postherpetic neuralgia, and post-mastectomy pain. The evidence was very low quality, downgraded because of the small size of the treatment arms, and because studies reported results using last observation carried forward (LOCF) imputation for withdrawals or using only participants who completed the study according to the protocol, where there were greater than 10% withdrawals.[5] There were insufficient data for a pooled efficacy analysis in particular neuropathic pain conditions, but individual studies did not show any analgesic effect of levetiracetam compared with placebo.[5] The authors pooled results for any outcome considered substantial pain relief (≥50% pain intensity reduction or “complete” or “good” responses on the verbal rating scale) for 4 studies with dichotomous data; response rates across different types of neuropathic pain was similar with levetiracetam (10%) and placebo (12%), with no statistical difference (RR 0.9; 95% CI 0.4 to1.7).[5] Data were pooled across different conditions for adverse events and withdrawals.[5] Based on very limited data, significantly more participants experienced an adverse event with levetiracetam than with placebo (number needed to treat for an additional harmful event (NNH) 8.0 (95% CI 4.6 to 32)).[5] There were significantly more adverse event withdrawals with levetiracetam (NNH 9.7 (6.7 to 18)).[5] The amount of evidence for levetiracetam in neuropathic pain conditions was very small and potentially biased because of the methods of analysis used in the studies.[5] There was no indication that levetiracetam was effective in reducing neuropathic pain, but it was associated with an increase in adverse events and withdrawal from therapy due to adverse events.[5]

Anticonvulsants in Migraine Prophylaxis

Mulleners, et al. updated their 2013 Cochrane review evaluating the efficacy and tolerability of several AEDs in preventative treatment of episodic migraine headaches in adults.[6] Prospective, controlled trials of AEDs taken regularly to prevent the occurrence of migraine attacks, to improve migraine-related quality of life, or both, were included in the review.[6] Thirty-seven published and 3 unpublished studies were evaluated.[6] The specific AEDs studied included: topiramate, valproate, gabapentin, pregabalin, lamotrigine, carbamazepine, clonazepam, levetiracetam, oxcarbazepine, vigabatrin and zonisamide.[6] Outcomes measured in the analysis included headache frequency, quality of life and adverse events.[6] The studies were rated as low to moderate quality evidence with moderate to high risk of bias. Mean headache frequency was reduced by 4 days with valproate and by 1 day with topiramate when compared to placebo.[6] There was no evidence of efficacy in preventing migraine headaches for any of the other AEDs.[6] The reviewers found insufficient evidence to further support the use of gabapentin in migraine prophylaxis.[6]

Anticonvulsants in Binge-Eating Disorder

Binge-eating disorder (BED) involves the recurrent consumption of an amount of food that is larger than most people would consume under similar circumstances.[7] McElroy and colleagues have evaluated the short- and long-term effects of topiramate in treating BED associated with obesity.[9,10] In a double blinded, 14-week trial, 61 outpatients with BED and a body mass index (BMI) ≥30 kg/m^2 were randomly assigned to receive topiramate (n=30) or placebo (n=31).[9] A total of 26 patients (42%) did not complete the 14 weeks of treatment. Nine patients withdrew from the study because of adverse events (TPM: n=6; PBO: n=3), 3 because of lack of efficacy (TPM: N=1; PBO: N=2), 13 because of nonadherence with the study protocol (TPM: n=6; PBO: n=7) and one participant withdrew because of an exacerbation of a previous medical condition.[9] Patients in the topiramate arm were more likely to withdraw from the study due to adverse effects than patients in the placebo arm. The authors noted a greater reduction from baseline in binge frequency with the TPM group (94%) relative to PBO (46%) in the intent-to-treat group (p=0.02). Thirty-one patients entered an open label, 42-week extension period: 15 patients received TPM and 16 patients continued on PBO. Twenty-one (67%) patients discontinued the extension trial due to nonadherence (TPM n=5, PBO n = 6), adverse events (TPM n=1, PBO = 7), or lack of efficacy (TPM n=2).[10] Ten patients completed 56 weeks of TPM therapy. Mean binge frequency was statistically significantly decreased from baseline in the 10 patient completer group (mean change = -5 binges/week, p=0.002).[10] The authors concluded long term (56 weeks) treatment with TPM was associated with sustained reductions in binge-eating frequency.[10] The extension trial was in a small population, open label, nonrandomized, and not controlled which contribute to significant weaknesses of the study. Furthermore, the study had a high attrition rate in both the short term and extension phases. Finally, patients with bipolar disorder, active substance abuse, psychosis or severe personality disorders were excluded from the study, which limits the ability to generalize these findings to all patients with BED.[10] Further long term studies that evaluate the safety and efficacy of topiramate in treating BED are warranted.

New Guidelines:

The American Academy of Neurology and the American Epilepsy Society published evidence-based guidelines for starting AEDs in adults after a first seizure. Based on data from studies including mixed cohorts of both AED-treated and untreated subjects, an adult with an unprovoked first seizure is at greatest risk of a recurrence relatively early, within the first 2 years (21%–45%), and especially in the first year, and this risk appears to be lower for patients treated with AEDs.[11] Immediate AED therapy as compared with no treatment is likely to reduce absolute risk by about 35% for a seizure recurrence within the subsequent 2 years.[11] However, immediate AED treatment as compared with treatment delayed until a second seizure occurs is unlikely to improve the chance of attaining sustained seizure remission over the longer term (>3 years). [11] Studies of the nature and incidence of adverse events indicate a wide range of predominantly mild and

reversible adverse events that occur in approximately 7% to 31% of patients.[11] General consensus remains that initiating AED therapy should be individualized based upon patient characteristics after an in depth risk-benefit analysis.

New Formulations/Indications:

Perampanel (Fycompa) was initially approved by the FDA in 2012 for the treatment of partial onset seizures among epilepsy patients aged 12 and older.[8] In 2015 the indications were expanded to include treatment of primary generalized tonic-clonic (PGTC) seizures in patients 12 years of age and older. The efficacy of perampanel as adjunctive therapy in patients with idiopathic generalized epilepsy experiencing PGTC seizures was established in one multicenter RCT conducted at 78 sites in 16 countries.[12] Eligible patients on a stable dose of 1 to 3 AEDs experiencing at least 3 PGTC seizures during the 8-week baseline period were randomized to either perampanel or placebo. Efficacy was analyzed in 162 patients (perampanel n=81, placebo n=81) who received medication and at least one post-treatment seizure assessment. Compared with placebo, perampanel showed a greater median percent change in PGTC seizure frequency per 28 days (−38.4% vs. −76.5%; $p < 0.0001$) and greater 50% PGTC seizure responder rate (39.5% vs. 64.2%; $p = 0.0019$).[12] During maintenance, 12.3% of placebo-treated patients and 30.9% of perampanel-treated patients achieved PGTC seizure freedom. For the safety analysis, the most frequent treatment-emergent adverse events with perampanel were dizziness (32.1%) and fatigue (14.8%).[12]

The FDA approved a new oral suspension formulation of perampanel which provides an additional option for patients who have difficulty swallowing tablets. The liquid formulation has been designated as bioequivalent to the tablet formulation by the FDA. Perampanel can be abused or lead to drug dependence so it has been designated by the US Drug Enforcement Administration (DEA) as a federally controlled substance (CIII). The oral suspension is available in a concentration of 0.5 mg/mL.

Eslicarbazepine (Aptiom) was approved in 2013 by the FDA as monotherapy for treatment of partial-onset seizures.[13] In 2015 the indications were expanded to include the use of esclicarbazepine as adjunctive therapy in the treatment of partial-onset seizures based on results of 3 RCTs.[14–16] In 3 trials that assessed this indication, patients had a median duration of epilepsy of 19 years and a median baseline seizure frequency of 8 seizures per 28 days. Two-thirds (69%) of subjects used 2 concomitant AEDs and 28% used 1 concomitant AED. The most commonly used AEDs were carbamazepine (50%), lamotrigine (24%), valproic acid (21%), and levetiracetam (18%). Patients were started on a daily dose of 400 mg or 800 mg and subsequently increased by 400 mg per day after 1 or 2 weeks, until the final daily target dose was achieved. The primary efficacy endpoint in all 3 trials was change in seizure frequency during the maintenance dosing phase. Compared to placebo, seizure reduction with esclicarbazepine was statistically significant at treatment at doses of 1200 mg per day in all 3 studies (least square (LS) Mean =5.35, 95% CI =4.63-6.12, p=0.0003; LS Mean =5.5, 95% CI =4.6-6.5, p=0.021; LS Mean =6.0, 95% CI =5.26-6.84, p=0.004).[14–16] The most common adverse effects were dizziness, somnolence, nausea, headache, and diplopia.[12]

New FDA Safety Alerts:

Ezogabine [FDA Drug Safety Communication]: FDA determines that risk of retinal abnormalities, potential vision loss, and skin discoloration associated with ezogabine requires additional study. Based on reviews of additional safety reports from patients treated with ezogabine, the FDA determined that potential risks of vision loss due to pigment changes in the retina and of skin discoloration can be adequately managed by following the current recommendations in the official Potiga labeling. To further explore any potential long-term consequences of these pigment changes, the FDA has required the Potiga manufacturer, GlaxoSmithKline, to conduct a long-term observational study.[17]

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL	CARVEOUT
ORAL	CAP SPRINK	DEPAKOTE SPRINKLE	DIVALPROEX SODIUM	Y	Y
ORAL	CAP SPRINK	DIVALPROEX SODIUM	DIVALPROEX SODIUM	Y	Y
ORAL	CAPSULE	CELONTIN	METHSUXIMIDE	Y	
ORAL	CAPSULE	DEPAKENE	VALPROIC ACID	Y	Y
ORAL	CAPSULE	DILANTIN	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	CAPSULE	ETHOSUXIMIDE	ETHOSUXIMIDE	Y	
ORAL	CAPSULE	GABAPENTIN	GABAPENTIN	Y	
ORAL	CAPSULE	NEURONTIN	GABAPENTIN	Y	
ORAL	CAPSULE	PHENYTEK	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	CAPSULE	PHENYTOIN SODIUM EXTENDED	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	CAPSULE	VALPROIC ACID	VALPROIC ACID	Y	Y
ORAL	CAPSULE	ZARONTIN	ETHOSUXIMIDE	Y	
ORAL	CAPSULE	ZONEGRAN	ZONISAMIDE	Y	
ORAL	CAPSULE	ZONISAMIDE	ZONISAMIDE	Y	
ORAL	ORAL SUSP	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	ORAL SUSP	DILANTIN-125	PHENYTOIN	Y	
ORAL	ORAL SUSP	OXCARBAZEPINE	OXCARBAZEPINE	Y	
ORAL	ORAL SUSP	PHENYTOIN	PHENYTOIN	Y	
ORAL	ORAL SUSP	TEGRETOL	CARBAMAZEPINE	Y	
ORAL	ORAL SUSP	TRILEPTAL	OXCARBAZEPINE	Y	
ORAL	SOLUTION	DEPAKENE	VALPROIC ACID (AS SODIUM SALT)	Y	Y
ORAL	SOLUTION	ETHOSUXIMIDE	ETHOSUXIMIDE	Y	
ORAL	SOLUTION	KEPPRA	LEVETIRACETAM	Y	
ORAL	SOLUTION	LEVETIRACETAM	LEVETIRACETAM	Y	
ORAL	SOLUTION	VALPROIC ACID	VALPROIC ACID (AS SODIUM SALT)	Y	Y
ORAL	SOLUTION	ZARONTIN	ETHOSUXIMIDE	Y	
ORAL	TAB CHEW	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	TAB CHEW	DILANTIN	PHENYTOIN	Y	
ORAL	TAB CHEW	PHENYTOIN	PHENYTOIN	Y	
ORAL	TAB ER 12H	CARBAMAZEPINE ER	CARBAMAZEPINE	Y	
ORAL	TAB ER 12H	TEGRETOL XR	CARBAMAZEPINE	Y	
ORAL	TAB ER 24H	DEPAKOTE ER	DIVALPROEX SODIUM	Y	Y
ORAL	TAB ER 24H	DIVALPROEX SODIUM ER	DIVALPROEX SODIUM	Y	Y
ORAL	TABLET	BANZEL	RUFINAMIDE	Y	

ORAL	TABLET	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	TABLET	EPITOL	CARBAMAZEPINE	Y	
ORAL	TABLET	GABITRIL	TIAGABINE HCL	Y	
ORAL	TABLET	KEPPRA	LEVETIRACETAM	Y	
ORAL	TABLET	LAMICTAL	LAMOTRIGINE	Y	Y
ORAL	TABLET	LAMOTRIGINE	LAMOTRIGINE	Y	Y
ORAL	TABLET	LEVETIRACETAM	LEVETIRACETAM	Y	
ORAL	TABLET	MYSOLINE	PRIMIDONE	Y	
ORAL	TABLET	OXCARBAZEPINE	OXCARBAZEPINE	Y	
ORAL	TABLET	PEGANONE	ETHOTOIN	Y	
ORAL	TABLET	PRIMIDONE	PRIMIDONE	Y	
ORAL	TABLET	TEGRETOL	CARBAMAZEPINE	Y	
ORAL	TABLET	TIAGABINE HCL	TIAGABINE HCL	Y	
ORAL	TABLET	TOPAMAX	TOPIRAMATE	Y	
ORAL	TABLET	TOPIRAMATE	TOPIRAMATE	Y	
ORAL	TABLET	TRILEPTAL	OXCARBAZEPINE	Y	
ORAL	TABLET	VIMPAT	LCM	Y	
ORAL	TABLET DR	DEPAKOTE	DIVALPROEX SODIUM	Y	Y
ORAL	TABLET DR	DIVALPROEX SODIUM	DIVALPROEX SODIUM	Y	Y
RECTAL	KIT	DIASTAT	DIAZEPAM	Y	
RECTAL	KIT	DIASTAT ACUDIAL	DIAZEPAM	Y	
ORAL	ELIXIR	PHENOBARBITAL	PHENOBARBITAL	Y	
ORAL	TABLET	PHENOBARBITAL	PHENOBARBITAL	Y	
ORAL	TAB DS PK	LAMICTAL (BLUE)	LAMOTRIGINE	V	Y
ORAL	TAB DS PK	LAMICTAL (GREEN)	LAMOTRIGINE	V	Y
ORAL	TAB DS PK	LAMICTAL (ORANGE)	LAMOTRIGINE	V	Y
ORAL	TAB DS PK	LAMOTRIGINE	LAMOTRIGINE	V	Y
ORAL	TAB ER 24	LAMICTAL XR	LAMOTRIGINE	V	Y
ORAL	TAB ER 24	LAMOTRIGINE ER	LAMOTRIGINE	V	Y
ORAL	TAB RAPDIS	LAMICTAL ODT	LAMOTRIGINE	V	Y
ORAL	TAB RAPDIS	LAMOTRIGINE ODT	LAMOTRIGINE	V	Y
ORAL	TB CHW DSP	LAMICTAL	LAMOTRIGINE	V	Y
ORAL	TB CHW DSP	LAMOTRIGINE	LAMOTRIGINE	V	Y
ORAL	TB ER DSPK	LAMICTAL XR (BLUE)	LAMOTRIGINE	V	Y
ORAL	TB ER DSPK	LAMICTAL XR (GREEN)	LAMOTRIGINE	V	Y
ORAL	TB ER DSPK	LAMICTAL XR (ORANGE)	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMICTAL ODT (BLUE)	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMICTAL ODT (GREEN)	LAMOTRIGINE	V	Y

ORAL	TB RD DSPK	LAMICTAL ODT (ORANGE)	LAMOTRIGINE	V	Y
ORAL	CAP ER 24H	TROKENDI XR	TOPIRAMATE	N	
ORAL	CAP SPR 24	QUDEXY XR	TOPIRAMATE	N	
ORAL	CAP SPR 24	TOPIRAMATE ER	TOPIRAMATE	N	
ORAL	CAP SPRINK	TOPAMAX	TOPIRAMATE	N	
ORAL	CAP SPRINK	TOPIRAMATE	TOPIRAMATE	N	
ORAL	CAPSULE	LYRICA	PREGABALIN	N	
ORAL	CPMP 12HR	CARBAMAZEPINE ER	CARBAMAZEPINE	N	
ORAL	CPMP 12HR	CARBATROL	CARBAMAZEPINE	N	
ORAL	ORAL SUSP	BANZEL	RUFINAMIDE	N	
ORAL	ORAL SUSP	FELBAMATE	FELBAMATE	N	
ORAL	ORAL SUSP	FELBATOL	FELBAMATE	N	
ORAL	ORAL SUSP	ONFI	CLOBAZAM	N	
ORAL	POWD PACK	SABRIL	VIGABATRIN	N	
ORAL	SOLUTION	GABAPENTIN	GABAPENTIN	N	
ORAL	SOLUTION	LYRICA	PREGABALIN	N	
ORAL	SOLUTION	NEURONTIN	GABAPENTIN	N	
ORAL	SOLUTION	VIMPAT	LCM	N	
ORAL	TAB ER 24H	KEPPRA XR	LEVETIRACETAM	N	
ORAL	TAB ER 24H	LEVETIRACETAM ER	LEVETIRACETAM	N	
ORAL	TAB ER 24H	OXTELLAR XR	OXCARBAZEPINE	N	
ORAL	TABLET	APTIOM	ESLICARBAZEPINE ACETATE	N	
ORAL	TABLET	FELBAMATE	FELBAMATE	N	
ORAL	TABLET	FELBATOL	FELBAMATE	N	
ORAL	TABLET	FYCOMPA	PERAMPANEL	N	
ORAL	TABLET	GABAPENTIN	GABAPENTIN	N	
ORAL	TABLET	NEURONTIN	GABAPENTIN	N	
ORAL	TABLET	ONFI	CLOBAZAM	N	
ORAL	TABLET	POTIGA	EZOGABINE	N	
ORAL	TABLET	SABRIL	VIGABATRIN	N	
RECTAL	KIT	DIAZEPAM	DIAZEPAM	N	
ORAL	TABLET ER	HORIZANT	GABAPENTIN ENACARBIL	N	
ORAL	SYRINGE	VALPROIC ACID	VALPROIC ACID (AS SODIUM SALT)	N	Y
ORAL	TAB ER 24H	GRALISE	GABAPENTIN	N	
ORAL	TABLET	ONFI	CLOBAZAM	N	
ORAL	TABLET ER	HORIZANT	GABAPENTIN ENACARBIL	N	

Appendix 2: New Clinical Trials

A total of 107 citations were manually reviewed from the literature search. After further review, 105 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 2 trials are briefly described in the table below. Full abstracts are included in **Appendix 3.**

Table 1: Description of Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Razazian, et al. Randomized, double-blind, parallel group design 4 weeks	Carbamazepine 200 mg po bid vs Pregabalin 75mg po bid vs Venlafaxine 75mg po bid	Adults over 18 years of age, metabolically stable type 1 or 2 diabetes with peripheral diabetic neuropathic pain for at least 3 months with visual analog score ≥ 40	Subjective pain as assessed by the visual analogue scale (VAS).	Carbamazepine: Mean VAS baseline: 74.5, mean VAS score on day 35: 39.6 ($p< 0.0001$) Pregablin: Mean VAS baseline: 82.3, mean VAS score on day 35: 33.4 ($p< 0.0001$)
Werhahn, et al. Randomized, double-blind, parallel group design 58 weeks	Carbamazepine controlled release 200-1200mg per day vs Lamotrigine 50-300mg per day vs Levetiracetam 500- 3000mg per day Flexible dosing	Patients ≥60 years with new-onset focal epilepsy	Primary outcome was the retention to treatment at week 58.	Retention Rates at week 58: Carbamazepine CR 45.8% Lamotrigine 55.6% Levetiracetam 61.5%

Appendix 3: Abstracts of Clinical Trials

Razazian N, Baziyar M, Moradian N, Afshari D, Bostani A, Mahmoodi M. Evaluation of the efficacy and safety of pregabalin, venlafaxine, and carbamazepine in patients with painful diabetic peripheral neuropathy. A randomized, double-blind trial. *Neurosciences*. 2014 Jul; 19(3):192-8

Background. To evaluate the efficacy and safety of carbamazepine, pregabalin, and venlafaxine in patients with painful diabetic neuropathy (PDN)

Methods. Randomized, double-blind, parallel-group clinical trial between December 2012 and December 2013 at Kermanshah University of Medical Sciences, Kermanshah, Iran. Two hundred and fifty-seven patients with clinically definite PDN were randomized to receive, carbamazepine, venlafaxine, or pregabalin. The primary outcome was subjective pain as assessed by the visual analogue scale (VAS). Secondary outcomes consisted of sleep, mood, and work interference assessments, and a percentage of patients achieving at least 50% reduction in pain intensity.

Results. Means of VAS scores for carbamazepine, pregabalin, and venlafaxine treatment groups at the baseline (74.5, 82.3, and 74.5) and endpoint (39.6, 33.4, and 46.6) revealed significant reduction, although pregabalin was more efficacious than carbamazepine, and venlafaxine. Improvements in means scores of sleep, mood, and work interferences were identified in all treatment groups.

Conclusions. This study showed the efficacy of venlafaxine, pregabalin, and carbamazepine in pain reduction in patients with diabetic neuropathy, although pregabalin was shown to be superior to carbamazepine, and venlafaxine in relieving pain, no significant superiority was shown between carbamazepine, and venlafaxine.

Konrad J. Werhahn, Eugen Trinka, et al. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. *Epilepsia*. Volume 56, Issue 3, pages 450–459, March 2015.

Background. To compare the effectiveness of controlled-released carbamazepine (CR-CBZ) to levetiracetam (LEV) and to lamotrigine (LTG) in elderly patients with newly diagnosed focal epilepsy.

Methods. Randomized, double-blind, parallel-group trial conducted between January 2007 and August 2011, in 47 ambulatory or hospital sites in Germany, Austria, or Switzerland. Eligible participants were aged ≥60, had new-onset epilepsy, had no acute illness as the cause of their seizures, and had no contraindication to the drugs in the trial. Patients were randomized 1:1:1 to CR-CBZ, LTG, or LEV. Doses were up-titrated for 6 weeks and could be maintained or adjusted depending on seizure relapse or tolerability over an additional period of 52 weeks. Primary outcome was the retention to treatment at week 58; secondary measures related to seizure and adverse event frequency.

Results. Of 361 randomized patients, 359 were included (CR-CBZ n = 121, LTG n = 117, LEV n = 122) in the modified intent-to-treat population (mean age [range] 71.4 [60–95] years). At week 58, the retention rate for LEV was significantly higher than for CR-CBZ (61.5% vs. 45.8%, p = 0.02), and similar to LTG (55.6%). Seizure freedom rates at weeks 30 and 58 were not different across the groups. Twice as many patients receiving CR-CBZ discontinued due to adverse events or death compared to those in the LEV group (32.2% vs. 17.2%; odds ratio 2.28, 95% confidence interval [CI] 1.25–4.19, p = 0.007), whereas discontinuation was intermediate for LTG (26.3%). Median daily doses of completers (n = 195) were CR-CBZ 380.0 mg/day (333.0–384.0), LTG 95 mg/day (94.0–97.0), and LEV 950 mg/day (940.0–985.0).

Conclusions. In the initial monotherapy of focal epilepsy in the elderly, 1-year retention to LEV was higher compared to CR-CBZ due to better tolerability. Retention of LTG was intermediate and close to LEV, but did not differ significantly from either comparators.

Appendix 4: Medline Search Strategy

Ovid Medline (R) without Revisions 1996 to April Week 1 2016

1 exp Epilepsy/dt [Drug Therapy] 18598
2 exp Anticonvulsants/ad, ae, ct, pk, pd, tu, to [Administration & Dosage, Adverse Effects, Contraindications, Pharmacokinetics, Pharmacology, Therapeutic Use, Toxicity] 45806
3 1 and 2 15473
4 (2015 or 2016*).dp. 530554*
5 3 and 4 613
6 exp Carbamazepine 5333
7 3 and 4 and 6 50
8 Clobazam.mp 394
9 3 and 4 and 8 17
10 Diazepam/ 4342
11 3 and 4 and 10 19
12 valproic acid/ 7128
13 limit 12 to humans 5656
14 3 and 4 and 13 63
15 Eslicarbazepine.mp 141
16 limit 15 to humans 141
17 3 and 4 and 16 7
18 Ethosuximide/ 259
19 limit 18 to humans 120
20 3 and 4 and 19 1
21 Ethotoin.mp 2
22 Ezogabine.mp 0
23 Felbamate.mp 464
24 limit 23 to humans 359
25 Gabapentin.mp 4445
26 limit 25 to humans 3563
27 3 and 4 and 26 7
28 LCM.mp 402
29 limit 28 to humans
30 3 and 4 and 29 23
31 Lamotrigine.mp 3882
32 limit 31 to humans 3366
33 3 and 4 and 32 42
34 Levetiracetam.mp 2027
35 limit 34 to humans
36 3 and 4 and 35 61

37 Methsuximide.mp 17
38 limit 37 to humans 15
39 Oxcarbazepine.mp 1161
40 limit 39 to humans 1161
41 3 and 4 and 40 18
42 Perampanel.mp 115

43 limit to humans 104
44 3 and 4 and 43 17
45 Phenobarbital/ 2916
46 limit 45 to humans 1333
47 3 and 4 and 46 13
48 Phenytoin/ 3107
49 limit 48 to humans 2339
50 3 and 4 and 49 24
51 Pregablin.mp 8
52 limit 51 to humans 7
53 Primidone/ 155
54 limit 53 to humans 118
55 3 and 4 and 54 0
56 Rufinamide.mp 155
57 limit 56 to humans 145
58 3 and 4 and 57 4
59 Tiagabine.mp 785
60 limit 59 to humans
61 3 and 4 and 60 1
62 Topiramate.mp 3486
63 limit 62 to humans 3091
64 3 and 4 and 63 23
65 Valproic Acid.mp 8562
66 limit 65 to humans 6840
67 3 and 4 and 65 90
68 Vigabatrin/ 998
69 limit to 68 to humans 745
70 3 and 4 and 69 11
71 Zonisamide.mp 909
72 limit 71 to humans 773
73 3 and 4 and 71 13
74 limit 5 to (humans and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 107
75 6 or 8 or 10 or 12 or 15 or 18 or 21 or 22 or 23 or 25 or 28 or 31 or 34 or 37 or 39 or 42 or 45 or 48 or 51 or 53 or 56 or 59 or 59 or 62 or 65 or 68 or 71 33738
76 limit 75 to ((clinical study 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 meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews) and last 2 years) 551

Clobazam

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- 12 months

Requires PA:

- Clobazam

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 client have a diagnosis of Lennox-Gastaut syndrome and is 2 years of age or older?	**Yes:** Go to #3.	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication?	**Yes:** Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness

Limitations of Use:

• Clobazam is not indicated for other epilepsy syndromes other than Lennox-Gastaut.

P&T Review: *7/16 (DM); 3/15; 5/12*
Implementation: *8/12*

Topiramate

Goal(s):

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

Length of Authorization:

90 days to lifetime

Requires PA:

- Non-preferred topiramate products

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does patient have diagnosis of epilepsy (ICD-10 G40101-G40311; G40401-G40509; G40802; G40804; G40901-G40919; R569 or S069X9S)?	**Yes:** Approve for lifetime (until 12-31-2036)	**No:** Go to #3
3. Does the patient have a diagnosis of migraine (ICD10 G43001-G43919; G43A0; G43B0; G43C0; G43D0; G43A1; G43B1; G43C1; G43D1)?	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime*	**No:** Go to #4
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder? • ICD-10 F30.10-F33.9 and subsets • ICD-10 F259 and subsets	**Yes:** Go to #5	**No:** Go to #6

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

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

Drug Class Review

Newer Oral Anticoagulant Drugs

Final Original Report

Executive Summary

May 2016

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

Marian McDonagh, PharmD
Ian Blazina, MPH
Brittany Holzhammer, MPH

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator
Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

INTRODUCTION

Inappropriate clotting can result in deep vein thrombosis (DVT) and pulmonary embolism (PE) in the venous system and heart attack and thromboembolic stroke in the arterial system, causing significant morbidity and mortality. The burden of disease due to inappropriate clotting in the United States is high. Risk factors for DVT and PE include immobilization (e.g., long plane flights and major orthopedic surgery), cancer, pregnancy, oral contraceptives, and smoking. The Centers for Disease Control and Prevention (CDC) estimates that as many as 900,000 people (1 to 2 per 1,000) could be affected by venous thromboembolism (VTE) each year in the United States. An estimated 60,000 to 100,000 Americans die of VTE, with 10% to 30% of people dying within 1 month of diagnosis. It is estimated that among people who have a DVT, approximately 50% will have long-term complications, and approximately 33% of people with DVT/PE will have a recurrence within 10 years.

Historically, medications to treat or prevent blood clots were primarily low-molecular weight heparins and warfarin. These drugs inhibit clotting through indirect mechanisms and require injection (in the case of heparins) and laboratory monitoring for dose adjustment and have multiple drug-drug interactions (in the case of warfarin). Several "novel" direct-acting oral anticoagulant pharmacotherapies (NOACs) have been developed in recent years that have the theoretical advantages of oral administration, not requiring laboratory monitoring for dose adjustment, and not having numerous drug-drug interactions. These are 3 oral factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban) and a direct thrombin inhibitor (dabigatran) (Table A). This review compares the effectiveness and harms of NOACs with each other and focuses on the uses of these drugs for the acute treatment of venous thromboembolic events in adults, for extended treatment to prevent recurrence of venous thromboembolic events in adults at increased risk, and for the prevention of thromboembolic events in adults with atrial fibrillation or venous thromboembolic events in adults who have undergone orthopedic surgery.

Scope and Key Questions

The goal of this report is to compare the benefits and harms of newer oral anticoagulant drugs. The Pacific Northwest Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, outcomes of interest, and, based on these, eligibility criteria for studies. A draft of these questions and inclusion and exclusion criteria were posted on the Drug Effectiveness Review Project website for public comment. The draft was reviewed and revised by representatives of the organizations participating in the Drug Effectiveness Review Project. Revision took into consideration input from the public and the organizations' desire for the key questions to reflect populations, drugs, and outcome measures of interest to clinicians and patients. These organizations approved the following key questions to guide the review for this report:

1. What is the evidence on the effectiveness and harms of the direct-acting oral anticoagulants compared with each other or with other anticoagulants for treatment of a venous thromboembolic event in adults?
2. What is the evidence on the effectiveness and harms of the direct-acting oral anticoagulants compared with each other or with other anticoagulants for extended treatment to prevent recurrence of thromboembolic events in adults at increased risk?

3. What is the evidence on the effectiveness and harms of the direct-acting oral anticoagulants compared with each other or with other anticoagulants for prevention of thromboembolic events in adults with atrial fibrillation or venous thromboembolic events in adults who have undergone orthopedic surgery?
4. What is the evidence on whether there are subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one direct-acting oral anticoagulant is more effective or associated with fewer harms than another direct-acting oral anticoagulants or other anticoagulants?

METHODS

Inclusion Criteria

Populations

Adult populations for:

- Treatment of DVT or PE
- Extension of treatment for DVT or PE, to prevent recurrence in patients at increased risk (as defined by study, or according to guidelines)
- Prophylaxis to prevent VTE in patients undergoing orthopedic surgery
- Prophylaxis in patents with atrial fibrillation (valvular or non-valvular), to VTE.

Interventions

Table A. Interventions

Generic name	Trade name(s)	Forms
Direct Thrombin (Factor IIa) Inhibitors		
Dabigatran	Pradaxa®	Oral capsule
Direct Factor Xa Inhibitors		
Apixaban	Eliquis®	Oral tablet
Rivaroxaban	Xarelto®	Oral tablet
Edoxaban	Savaysa™ (US), Lixiana® (Japan)	Oral tablet

Comparators

- Other Factor Xa inhibitors
- Other anticoagulants (oral or injectable; including, but not limited to, warfarin, unfractionated heparin, low molecular weight heparins)
- Aspirin for patients unable to take warfarin
- Placebo for extended treatment to prevent recurrence of VTE (only).

Outcomes

Effectiveness outcomes

- Mortality (all-cause and cardiovascular)
- Symptomatic thromboembolic event (ischemic stroke, recurrent/initial DVT or PE)
- Cardiovascular events (including, but not limited to, MI)
- Functional capacity (e.g., return to work, ability to work)
- Quality of life (e.g., SF-36).

Harms outcomes

- Overall adverse events reported
- Overall withdrawals due to adverse events
- Major adverse events (including, but not limited to, major bleeding, intracranial bleeding [including intracerebral hemorrhage], readmission, reoperation)
- Specific adverse events or withdrawals due to specific adverse events (including, but not limited to, any bleeding, gastrointestinal symptoms, hypersensitivity reactions, etc.).

Study Designs

- Efficacy/effectiveness: head-to-head or active-controlled randomized trials and good-quality systematic reviews
- Harms: head-to-head or active-controlled randomized trials, good-quality systematic reviews, as well as cohort or case-control observational studies

We followed standard DERP methods for literature searching, study selection, data abstraction, validity assessment, data synthesis, and grading the strength of the body of evidence. Detailed methods can be found in the full report. We searched electronic databases through September 24, 2015. We attempted to identify additional studies through searches of ClinicalTrials.gov and the US Food and Drug Administration's website for medical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from pharmaceutical companies.

We conducted network meta-analyses of data from trials of NOACs compared with warfarin in patients with nonvalvular atrial fibrillation, and indirect comparison meta-analyses of data from trials of NOACs compared with enoxaparin in patients undergoing orthopedic surgery. We combined studies that were homogeneous enough that combining their results could be justified. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. When meta-analysis could not be performed, the data were summarized qualitatively. Caution should be used in interpreting the results of indirect and network meta-analyses, particularly where there may be variation at baseline (e.g. duration of study or risk-level of participants). In this report, the analyses are rated low-strength evidence at best for these reasons.

RESULTS

Table B. Summary of the evidence by key question for benefits and harms of newer oral anticoagulant drugs

Comparison	Population	Strength of evidence	Conclusions
Key Question 1. Comparative effectiveness and harms of treatment of VTE in adults			
VTE recurrence, DVT, and PE			
Indirect comparisons of edoxaban 30 or 60 mg qd or bid, apixaban 5 mg bid, rivaroxaban 15 mg bid, and dabigatran 150 mg bid	Treatment for VTE	Insufficient	No statistically significant difference.
Major bleeding			

Comparison	Population	Strength of evidence	Conclusions
Indirect comparisons of edoxaban 30 or 60 mg qd, apixaban 5 mg bid, and dabigatran 150 mg bid	Treatment for VTE	Low	Significantly lower risk with apixaban 5 mg bid vs. edoxaban 30 or 60 mg qd (**HR 0.37, 95% CI 0.15 to 0.89**) and dabigatran 150 mg bid (**HR 0.42, 95% CI 0.17 to 0.99**)
Key Question 2. Comparative effectiveness and harms of extended treatment to prevent recurrence of VTE			
VTE recurrence, all-cause mortality, acute coronary syndrome (individual outcomes)			
Indirect comparisons of apixaban 2.5 mg or 5 mg bid, rivaroxaban 20 mg qd, and dabigatran 150 mg bid	Extended treatment for VTE	Insufficient	No statistically significant difference.
Major bleeding			
Indirect comparisons of apixaban 2.5 mg or 5 mg bid, rivaroxaban 20 mg qd, and dabigatran 150 mg bid	Extended treatment for VTE	Insufficient	No statistically significant difference.
Clinically-relevant non-major bleeding			
Indirect comparisons of apixaban 2.5 mg and 5 mg bid, rivaroxaban 20 mg qd, dabigatran 150 bid	Extended treatment for VTE	Low	Significantly lower risk with apixaban 2.5 mg (**OR 0.23, 95% CI 0.084 to 0.62**) or 5 mg (**OR 0.31, 95% CI 0.11 to 0.82**) compared with rivaroxaban 20 mg
			Significantly lower risk with apixaban 2.5 mg than dabigatran 150 mg (**OR 0.40, 95% CI 0.168 to 0.97**).
Indirect comparisons of apixaban 5 mg bid, rivaroxaban 20 mg qd, and dabigatran 150 mg twice daily.		Insufficient	No statistically significant difference.
Key Question 3. Comparative effectiveness and harms in atrial fibrillation and orthopedic surgery			
Stroke or systemic embolism (composite outcome)			
Indirect comparisons of edoxaban 30 mg and 60 mg, apixaban 5 mg, rivaroxaban 15 mg and 20 mg, and dabigatran 110 mg and 150 mg	Atrial fibrillation (non-valvular)	Low	Edoxaban 30 mg results in statistically significantly higher risk than apixaban 5 mg (**OR 1.38, 95% CI 1.07 to 1.80**), rivaroxaban 15 mg (**OR 2.24, 95% CI 1.07 to 4.93**), or dabigatran 150 mg (**OR 1.64, 95% CI 1.23 to 2.20**).
			Rivaroxaban 20 mg resulted in statistically significantly higher risk than dabigatran 150 mg (**OR 1.32, 95% CI 1.01 to 1.74**); the risk for ischemic stroke (alone) was not increased significantly (OR 1.31, 95% CI 0.94 to 1.77), while the risk for hemorrhagic stroke was significantly increased (**OR 2.45, 95% CI 1.05 to 5.17**).
All other comparisons		Insufficient	No statistically significant difference.
Myocardial infarction			
Indirect comparisons of edoxaban 30 mg and 60 mg, apixaban 5 mg, rivaroxaban 15 mg and 20 mg, and dabigatran 110 mg and 150 mg	Atrial fibrillation (non-valvular)	Low	Apixaban 5 mg (**OR 0.62, 95% CI 0.40 to 0.95**), edoxaban 60 mg (**OR 0.68, 95% CI 0.46 to 1.01**) and rivaroxaban 20 mg (**OR 0.56, 95% CI 0.37 to 0.86**) had significantly lower risk than dabigatran 150 mg.
			Apixaban 5 mg (**OR 0.64, 95% CI 0.41 to 0.99**) and rivaroxaban 20 mg (**OR 0.58, 95% CI 0.38 to 0.88**) had statistically significantly lower risk than dabigatran 110 mg
			Edoxaban 30 mg had a statistically significantly greater risk than edoxaban 60 mg (**OR 1.27, 95% CI 1.01 to 1.60**).
All other comparisons		Insufficient	No statistically significant difference.

Comparison	Population	Strength of evidence	Conclusions
Major bleeding			
Indirect comparisons of edoxaban 30 mg and 60 mg, apixaban 5 mg, rivaroxaban 15 mg and 20 mg, and dabigatran 110 mg and 150 mg	Atrial fibrillation (non-valvular)	Low	Apixaban 5 mg resulted in statistically significantly lower risk than dabigatran 150 mg (**OR 0.74, 95% CI 0.60 to 0.91**) and rivaroxaban 20 mg (**OR 0.67, 95% CI 0.55 to 0.83**).
			Edoxaban 30 mg resulted in lower risk than apixaban 5 mg (**OR 0.67, 95% CI 0.54 to 0.83**), dabigatran 110 mg (**OR 0.58, 0.46 to 0.72**) or 150 mg (**OR 0.50, 95% CI 0.40 to 0.61**), and rivaroxaban 20 mg (**OR 0.45, 95% CI 0.37 to 0.56**).
			Edoxaban 60 mg had lower risk than rivaroxaban 20 mg (**OR 0.77, 95% CI 0.63 to 0.94**).
			Rivaroxaban 20 mg had higher risk than dabigatran 110 mg (**OR 1.28, 95% CI 1.04, 1.58**).
			Edoxaban 30 mg resulted in 41% lower risk of major bleeding than the higher dose, 60 mg (**OR 0.59, 95% CI 0.50 to 0.69**).
All other comparisons		Insufficient	No statistically significant difference.
Total VTE and all-cause mortality (composite outcome)			
Indirect comparisons of apixaban 2.5 mg bid or rivaroxaban 10 mg qd vs. dabigatran 150 mg qd or 220 mg qd	Orthopedic surgery: hip	Low	Significantly lower risk with apixaban 2.5 mg bid (**OR 0.28, 95% CI 0.08 to 0.94**) vs. dabigatran 150 mg qd, as well as for rivaroxaban 10 mg qd vs. dabigatran 150 mg qd (**OR 0.30, 95% CI 0.12 to 0.77**) or 220 mg qd (**OR 0.43, 95% CI 0.20 to 0.94**) in patients undergoing hip surgery.
	Orthopedic surgery: knee	Low	Significantly lower risk with apixaban 2.5 mg bid (**OR 0.64, 95% CI 0.42 to 0.97**) vs. dabigatran 150 mg qd, as well as for rivaroxaban 10 mg qd vs. dabigatran 150 mg qd (**OR 0.44, 95% CI 0.22 to 0.90**) or 220 mg qd (**OR 0.49, 95% CI 0.24 to 0.99**)
Indirect comparison of other drugs and doses	Orthopedic surgery	Insufficient	No statistically significant differences.
Symptomatic DVT and all-cause mortality (individual outcomes)			
Indirect comparisons of NOACs	Orthopedic surgery	Insufficient	No statistically significant differences.
Major bleeding			
Indirect comparisons of apixaban 2.5 mg bid to rivaroxaban 10 mg qd	Orthopedic surgery: knee	Low	Significantly lower risk with apixaban 2.5 mg bid vs. rivaroxaban 10 mg qd (**OR 0.35, 95% CI 0.13 to 0.91**).
Indirect comparison of other drugs and doses	Orthopedic surgery	Insufficient	No statistically significant differences.
Key Question 4. Comparative effectiveness and harms in subgroups			
Sub-group analyses of large RCTs of individual NOACs compared with warfarin (except edoxaban – no studies)	Majority of evidence in atrial fibrillation patients	Insufficient	No comparative evidence. Findings on age, sex, ethnicity similar to findings in overall studies populations. Findings in patients with diabetes taking dabigatran, patients on hemodialysis taking rivaroxaban or dabigatran (observational study), patients taking rivaroxaban and amiodarone, and patients taking dabigatran and an antiplatelet drug suggest further study is needed.

Limitations of this Report

As with other types of research, the limitations of this systematic review are important to recognize. Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and not being able to search additional electronic databases. While the search of the US Food and Drug Administration

documents and request for information from the manufacturers of the drugs is an important step in searching for unpublished studies and supplemental data, another possible limitation is the lack of a specific search for gray literature. As noted above, the lack of direct head-to-head comparisons seriously limits the ability to draw solid conclusions.

CONCLUSIONS

Evidence directly comparing NOACs is unavailable; current evidence is limited to indirect comparisons. Low-strength evidence suggests apixaban and rivaroxaban had lower risk of VTE and mortality in orthopedic patients. In atrial fibrillation, edoxaban 30 mg had a higher risk of stroke or embolism, and rivaroxaban had higher risk than dabigatran (higher dose). Differences in effectiveness were not found among the drugs in initial or extended treatment of VTE. Apixaban, edoxaban, and lower dose dabigatran have lower rates of major bleeding. Evidence on other comparisons and outcomes was insufficient to draw conclusions. These findings are based on indirect comparisons and should be interpreted with caution as direct comparisons could alter these findings.

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

Direct-acting Oral Anticoagulants
Drug Effectiveness Review Project Summary Report

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

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

Research Questions:
1. What is the evidence on the effectiveness and harms of the novel direct-acting oral anticoagulants (NOACs) compared with each other or with other anticoagulants for treatment of a venous thromboembolic (VTE) event in adults?
2. What is the evidence on the effectiveness and harms of the NOACs compared with each other or with other anticoagulants for extended treatment to prevent recurrence of thromboembolic events in adults at increased risk?
3. What is the evidence on the effectiveness and harms of the NOACs compared with each other or with other anticoagulants for prevention of thromboembolic events in adults with atrial fibrillation (AF) or venous thromboembolic events in adults who have undergone orthopedic surgery?
4. What is the evidence on whether there are subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one NOAC is more effective or associated with fewer harms than another NOAC or other anticoagulants?

Conclusions:
- There is insufficient evidence on the direct comparisons of NOACs. All NOAC efficacy and safety outcome comparisons were based on indirect data.
- There is low strength of evidence that there were no differences in all-cause mortality risks between the NOACs when used in patients with non-valvular atrial fibrillation (NVAF) and in patients undergoing hip or knee replacement surgery. There was insufficient evidence to develop conclusions on all-cause mortality risk between the NOACs when used for VTE prevention during extended treatment. Mortality was not assessed in NOAC treatment for VTE.
- For the composite outcome of VTE and mortality in orthopedic patients undergoing hip or knee surgery, there is low-strength of evidence that apixaban and rivaroxaban were associated with the lowest risk when compared to once daily dabigatran based on low strength of evidence. There is low strength of evidence that apixaban 2.5 mg twice daily was associated with less major bleeding than rivaroxaban 10 mg daily (OR 0.35; 95% CI, 0.13 to 0.91).
- In patients with NVAF there is low strength of evidence that edoxaban 30 mg is associated with a higher risk of the composite outcome of stroke or systemic embolism compared to apixaban 5 mg and dabigatran 150 mg (OR 1.38 and OR 1.64, respectively). Rivaroxaban 20 mg daily was found to have a higher risk of stroke and systemic embolism than dabigatran (OR 1.32, 95% CI, 1.01 to 1.74) based on low strength of evidence. Apixaban and edoxaban were associated with the lowest risk of major bleeds compared to the other NOACs.
- For the treatment of VTE there were no differences found in NOAC comparisons, based on insufficient evidence, for the following outcomes: VTE recurrence, DVT and PE. There is low strength of evidence in this population that major bleeding was less with apixaban compared to edoxaban and dabigatran.

- No differences were found in VTE recurrence, all-cause mortality, acute coronary syndrome, or major bleeding when comparing apixaban, rivaroxaban and dabigatran in patients being treated for prevention of recurrent VTE for an extended period (insufficient evidence). Apixaban was associated with less major bleeding than rivaroxaban and dabigatran.
- The evidence of superior efficacy or harms in patient subgroups was insufficient, preventing meaningful conclusions.

Recommendations:
- Evidence from the DERP report supports our current PDL and no changes are recommended.
- Recommend to continue access to all NOACs without prior authorization criteria.

Previous Conclusions:
- Canadian Cardiovascular Society Guidelines strongly recommend the DOAs in preference to warfarin, based on high-quality evidence from primary literature and meta-analyses, for patients with NVAF requiring anticoagulation. This recommendation was based on evidence of non-inferiority to warfarin, with similar or less major bleeding and less risk of intracranial hemorrhage. American Academy of Neurology Prevention of Stroke in NVAF and the European Primary Care Cardiovascular Society (EPCCS) Consensus Guidance on Stroke Prevention in AF (SPAF) recommends all of the oral anticoagulant options, without preference, for patients with NVAF. These recommendations were based on evidence from phase 3 trials.
- There is moderate strength of evidence of no difference in efficacy between DOAs and standard therapy (enoxaparin and warfarin) in treating VTE, supported by indirect comparisons from four new systematic reviews.
- There is moderate strength of evidence from a meta-analysis of 10 randomized controlled trials (RCT) that patients with mild (n=28,971) and moderate (n=11,722) renal insufficiency and AF, acute DVT or PE, or extended treatment of VTE that the DOAs are non-inferior to conventional anticoagulants with similar or less major bleeding or clinically relevant non-major bleeding (CRNM).
- There is low strength of evidence that LMWH are superior to warfarin and placebo for the primary prophylaxis of VTE in patients with cancer.
- Low strength of evidence demonstrated that DOA use in patients with VTE and cancer reduced the incidence of recurrent VTE and major bleeding when compared to conventional treatment of enoxaparin and warfarin.
- There is moderate strength of evidence that edoxaban 60 mg daily and 30 mg daily are non-inferior to warfarin for the prevention of strokes and systemic embolism in patients with NVAF. There is moderate strength of evidence, based on one good quality trial, that edoxaban 60 mg daily is non-inferior to warfarin for the treatment of VTE. Edoxaban is not recommended for patients with a CrCl >95 mL/min due to enhanced renal clearance, resulting in reduced efficacy in this population.
- Common adverse reactions (≥1%) seen with edoxaban are: bleeding, anemia, rash and abnormal liver function tests. There is moderate strength of evidence that both doses of edoxaban were associated with significantly less major bleeding and intracranial bleeds than warfarin in patients with NVAF and significantly more gastrointestinal (GI) bleeds in the high dose edoxaban group compared to warfarin.

Previous Recommendations:
- Atrial Fibrillation: Recommend removing the PA requirement for the DOAs, which are currently not preferred. Recommend all DOAs equally as an option for patients with NVAF and consider comparative pricing in executive session.
- VTE treatment: Recommend that all DOAs as options for the treatment of VTE and consider comparative pricing in executive session.
- Orthopedic Prophylaxis: Recommend all DOAs approved for orthopedic prophylaxis as options and consider comparative pricing in executive session.

Methods:
The May 2016 Drug Class Review on newer oral anticoagulants by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

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

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

Summary Findings:
A 2016 DERP summary of NOACs identified 53 good or fair quality studies which compared the NOACs to placebo, warfarin, heparins, or aspirin. Forty-four were randomized controlled trials, 4 were observational studies and 5 were systematic reviews. Table 1 identifies the drugs included in the review. All NOAC comparison were indirect due to lack of direct comparative evidence.

Table 1.0 Anticoagulants Included in the DERP Review

Generic Name	Trade Name	Formulation
Dabigatran	Pradaxa®	Oral capsule
Apixaban	Eliquis®	Oral tablet
Rivaroxaban	Xarelto®	Oral tablet
Edoxaban	Savaysa™	Oral tablet

Effectiveness/Efficacy and Safety of NOACs:

Venous Thromboembolism

- A meta-analysis of six randomized trials found no differences in the NOACs for the outcomes of VTE recurrence, DVT, and PE for the following indirect comparisons (trials directly compared NOAC to LMWH and warfarin) based on insufficient evidence:
  - Edoxaban 30 mg or 60 mg once daily compared to Apixaban 5 mg twice daily
  - Edoxaban 30 mg or 60 mg once daily compared to Rivaroxaban 15 mg twice daily
  - Edoxaban 30 mg or 60 mg once daily compared to Dabigatran 150 mg twice daily
  - Apixaban 5 mg twice daily compared to Rivaroxaban 15 mg twice daily
  - Apixaban 5 mg twice daily compared to Dabigatran 150 mg twice daily
  - Rivaroxaban 15 mg twice daily compared to Dabigatran 150 mg twice daily

- Apixaban 5 mg was associated with less major bleeding than edoxaban 30 or 60 mg once daily (HR 0.37; 95% CI, 0.15 to 0.89) and dabigatran 150 mg twice daily (HR 0.42; 95% CI, 0.17 to 0.99).

- An indirect comparison of data from 3 trials studying extended treatment of VTE prevention, which included the drugs apixaban, dabigatran and rivaroxaban, found no differences for the outcomes of VTE recurrence, all-cause mortality, acute coronary syndrome or major bleeding, based on insufficient evidence.
- This analysis also found apixaban 2.5 mg and 5 mg twice daily to be associated with less clinically relevant non-major bleeding compared to rivaroxaban 20 mg daily (OR 0.23; 95% CI, 0.08 to 0.62 and OR 0.31; 95% CI) and apixaban 2.5 mg daily compared to dabigatran 150 mg twice daily (OR 0.40; 95% CI, 0.17 to 0.97).

Non-Valvular Atrial Fibrillation

- A meta-analysis of 10 trials indirectly comparing the NOACs when used for non-valvular atrial fibrillation (NVAF) (from trial data of NOACs vs warfarin) found no differences in all-cause mortality risk.
- For the composite outcomes of stroke or systemic embolism (SE) edoxaban 30 mg was found to have a higher risk than apixaban 5 mg (OR 1.38; 95% CI 1.07 to 1.80), rivaroxaban 15 mg (OR 2.24, 95% CI 1.07 to 4.93) or dabigatran 150 mg twice daily (OR 1.64; 95% CI 1.23 to 2.20).
- Rivaroxaban 20 mg was associated with a higher risk of stroke or SE compared to dabigatran 150 mg twice daily (OR 1.32; 95% CI, 1.01 to 1.74) with significant differences found in hemorrhagic stroke favoring dabigatran (OR 2.45; 95% CI 1.05 to 5.17).
- All NOACs had a lower risk of stroke or systemic embolism compared to warfarin.
- The risk of myocardial infarction (MI) was lower with rivaroxaban 20 mg, apixaban 5 mg, and edoxaban 60 mg compared to dabigatran 150 mg. Apixaban 5 mg and rivaroxaban 20 mg also had a lower risk than dabigatran 110 mg.
- Edoxaban 30 mg was associated with a higher risk of MI compared to edoxaban 60 mg (1.27; 95% CI, 1.01 to 1.60).
- Intracranial hemorrhage was higher with rivaroxaban 20 mg compared to dabigatran 110 mg and edoxaban 30 mg had a lower risk than rivaroxaban 20 mg. Apixaban 5 mg had less risk of intracranial hemorrhage than dabigatran 150 mg.
- Gastrointestinal (GI) bleeding risk was lower with edoxaban 30 mg compared to both doses of dabigatran and rivaroxaban 20 mg. Risk of GI bleeds were higher with rivaroxaban compared to apixaban and higher with edoxaban 60 mg compared to edoxaban 30 mg.
- Apixaban 5 mg was associated with less major bleeding than dabigatran 150 mg and rivaroxaban 20 mg, however, edoxaban 30 mg had a lower risk than apixaban 5 mg, both doses of dabigatran and rivaroxaban.
- Major bleeds were less with edoxaban 60 mg compared to rivaroxaban 20 mg.
- Rivaroxaban 20 mg had a higher risk of major bleeds than dabigatran 110 mg.
- Edoxaban 30 mg had 41% lower risk of major bleeds than edoxaban 60 mg (OR 0.59; 95% CI, 0.50 to 0.69).
- All NOACs were associated with less risk of major bleeding than warfarin, except rivaroxaban 20 mg. In a sensitivity analysis rivaroxaban 20 mg was found to have an equivalent bleeding risk to warfarin.

Orthopedic Surgery

- Twenty-one orthopedic surgery trials indirectly compared the NOACs to heparins and warfarin.
- For the composite outcome of VTE and all-cause mortality in patients undergoing hip surgery apixaban 2.5 mg twice daily was found to have a lower risk compared to dabigatran 150 mg once daily (OR 0.28; 95% CI, 0.08 to 0.94).
- Rivaroxaban 10 mg twice daily was found to have a lower risk of VTE and all-cause mortality in hip surgery patients compared to dabigatran 150 mg once daily and dabigatran 220 mg once daily (OR 0.30 and 0.43, respectively).
- In patients undergoing knee surgery, apixaban 2.5 mg once daily was superior to dabigatran 150 mg once daily for VTE and all-cause mortality and rivaroxaban 10 mg once daily was superior to dabigatran 150 mg once daily and 220 mg once daily.

- In knee surgery patients apixaban 2.5 mg twice daily was associated with less major bleeding than rivaroxaban 10 mg once daily.
- There was insufficient evidence to determine differences in the all-cause mortality and symptomatic DVT rates between the NOACs.

Subgroup Analysis of NOACs
- All evidence for subgroup comparisons came from indirect data.
- In the treatment of VTE, the history of presence of cancer did not change efficacy or bleeding outcomes.
- Aspirin and non-steroidal anti-inflammatory use increased risk of clinically relevant bleeding with rivaroxaban or enoxaparin use.
- Age or Asian ethnicity had no effect on outcomes when used in patients with AF and taking rivaroxaban, dabigatran or apixaban.
- Use of dabigatran 110 mg and dabigatran 150 mg in patients with AF and diabetes demonstrated superior efficacy for the primary outcome of stroke or systemic embolism compared to warfarin but absolute risk reductions were small (0.54% and 0.38%, respectively).
- No efficacy differences between dabigatran, rivaroxaban or apixaban were found in patients with AF who also had the following comorbidities: heart failure, hypertension, or coronary artery disease.
- In patients with mild to moderate renal dysfunction, no differences were seen in outcomes in patients being treated for AF taking rivaroxaban, dabigatran or apixaban. Patients taking warfarin on hemodialysis were found to have less risk of hospitalization or death due to bleeding compared to rivaroxaban or dabigatran based on observational data.
- Patients with AF taking dabigatran 150 mg and antiplatelet drugs experienced a higher risk of stroke or systemic embolism and major bleeds.

New Safety Alerts:
No new safety alerts identified.

New Formulations or Indications:
In November of 2015, the FDA approved dabigatran (Pradaxa®) for prophylaxis of DVT and PE in patients who have undergone hip replacement surgery. The approval for the added indication came from evidence from 2 randomized, double-blind, non-inferiority trials in 5428 patients. Patients received dabigatran 75 mg orally 1-4 hours after surgery followed by 150 mg daily or 110 mg 1-4 hours after surgery followed by 220 mg daily or enoxaparin 40 mg subcutaneously once daily initiated the evening before surgery. Venous thromboembolism was confirmed by bilateral venography of the lower extremities. Dabigatran 110 mg given 1-4 hours after surgery and followed by 220 mg daily was found to be non-inferior to enoxaparin for the endpoint of VTE and all cause death.

Reference: Pradaxa® (dabigatran) [product information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc., November 2015.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	ELIQUIS	APIXABAN	Y
ORAL	CAPSULE	PRADAXA	DABIGATRAN ETEXILATE MESYLATE	Y
ORAL	TABLET	SAVAYSA	EDOXABAN TOSYLATE	Y
ORAL	TABLET	XARELTO	RIVAROXABAN	Y
ORAL	TAB DS PK	XARELTO	RIVAROXABAN	Y
ORAL	TABLET	COUMADIN	WARFARIN SODIUM	Y
ORAL	TABLET	JANTOVEN	WARFARIN SODIUM	Y
ORAL	TABLET	WARFARIN SODIUM	WARFARIN SODIUM	Y

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: July 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

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Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use 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

Class Review with New Drug Evaluations: Monoclonal Antibodies for Asthma

Date of Review: July 2016

Purpose for Class Review:
To review evaluate the place in therapy for 2 new monoclonal antibodies approved for severe asthma, mepolizumab and reslizumab, in addition to the evidence and guideline recommendations for omalizumab.

Research Questions:
1. Does mepolizumab or reslizumab have superior efficacy to placebo and are they more effective than alternative drugs in clinically relevant outcomes for the treatment of severe asthma?
2. Is mepolizumab or reslizumab safer than currently utilized drugs in the treatment of severe asthma?

Conclusions:
- Moderate quality evidence over 32 weeks supports the efficacy of mepolizumab 100 mg administered subcutaneously (SC) every 4 weeks in reducing about one clinically significant asthma exacerbation (an exacerbation that requires use of systemic corticosteroids, an emergency department visit, and/or hospitalization) in patients with severe eosinophilic asthma (broadly defined as peripheral blood count ≥300 cells/µL in past year or ≥150 cells/µL immediately before trial initiation) compared to placebo. This statistically significant difference amounted to about a 50% relative reduction with mepolizumab. All patients received standard of care for severe asthma (i.e., high dose inhaled corticosteroid [ICS], long-acting beta-agonist [LABA] and a rescue short-acting bronchodilator).
- Low quality evidence suggests mepolizumab 100 mg SC every 4 weeks may also reduce the rate of exacerbations that require hospitalization or emergency department visits compared with placebo, with a relative risk reduction of 61% (95% CI, 17 to 82%; p=0.02).
- Low quality evidence suggests mepolizumab may be associated with a statistically significant and clinically meaningful improvement in quality of life. The difference in total St. George's Respiratory Questionnaire scores from baseline between mepolizumab and placebo was -7.0 points (95% CI, -10.2 to -3.8). Low quality evidence also suggests mepolizumab may be associated with a statistically significantly symptom improvement. The difference in total Asthma Control Questionnaire (ACQ) scores from baseline between mepolizumab and placebo was -0.44 points (95% CI, -0.61 to -0.23); however, this difference did not exceed the minimal clinically important difference of 0.5 points.
- Low quality evidence also suggests mepolizumab may decrease chronic daily doses of oral corticosteroids (OCS). Mepolizumab resulted in 50% or greater reduction of OCS dose in 54% of patients versus 33% with placebo (OR 2.26; 95% CI, 1.10-4.65; p=0.03). However, there was no statistically significant difference in the number of patients able to discontinue chronic OCS use between the 2 groups.
- There is insufficient evidence to differentiate differences in efficacy between mepolizumab and other monoclonal antibodies approved for severe asthma.

- Safety data from Phase 3 trials and 2 long-term safety studies for mepolizumab reveal no major safety concerns at 1 to 3.5 years of treatment. Adverse events of interest for mepolizumab are similar to other monoclonal antibodies and include allergic reactions, local injection site reactions, serious cardiac events, infections, malignancy, and immunogenicity.
- The mepolizumab and placebo groups had similar frequencies of serious adverse events, with the majority of events related to asthma exacerbations. However, patients 12 to 17 years of age, elderly patients, and non-white racial groups were underrepresented in clinical trials. Therefore, the safety of mepolizumab in these populations is unclear.
- There is insufficient evidence to differentiate differences in safety between mepolizumab and other monoclonal antibodies for severe asthma of any phenotype.
- Moderate quality evidence over 52 weeks supports the efficacy of reslizumab 3 mg/kg intravenous (IV) infusion every 4 weeks in reducing the number of patients experiencing at least one asthma exacerbation in adults (≥18 years) with severe eosinophilic asthma (broadly defined as peripheral blood count ≥400 cells/µL) compared to placebo (32% vs. 50%, respectively; RR 0.64; 95% CI 0.5 to 0.7) with an absolute risk reduction (ARR) of 18% and a number-needed-to-treat (NNT) of 5 over 52 weeks. An exacerbation was defined as an event that required use of systemic corticosteroids, a 2-fold increase in the dose of either inhaled corticosteroid (ICS) or oral corticosteroids (OCS) for 3 or more days, an emergency department (ED) visit, and/or hospitalization or unscheduled physician's office visit. All patients received standard of care for severe asthma (i.e., high dose ICS, long-acting beta-agonist [LABA] and a rescue short-acting bronchodilator).
- Low quality evidence suggests reslizumab 3 mg/kg IV every 4 weeks does not reduce the rate of exacerbations that require hospitalization or ED visits compared with placebo (RR 0.66; 95% CI 0.38 to 1.16).
- Moderate quality evidence suggests reslizumab is associated a clinically meaningful improvement in quality life, defined as a 0.5 point reduction or more in the Asthma Control Questionnaire (ACQ) and the Asthma Quality of Life Questionnaire (AQLQ).
- There are insufficient data to support reslizumab use in pediatric patients under 18 years of age. Although the sample size was small, there was an increase in asthma exacerbation rates among adolescents. Reslizumab should not be used in this patient population until evidence of benefit is clear.
- Reslizumab is associated with similar frequencies of serious adverse events as placebo, with the majority of events related to asthma exacerbations. However, pediatric and elderly patients, U.S. patients, and non-white racial groups were underrepresented in clinical trials. Therefore, the safety of reslizumab in these populations is unclear.
- There is insufficient evidence to differentiate differences in efficacy or safety between reslizumab and other monoclonal antibodies for severe asthma of any phenotype.
- Overall, there is moderate quality evidence that omalizumab is more effective than placebo in reducing exacerbations and hospitalizations as adjunctive therapy to standard therapy in IgE-mediated moderate to severe asthma. Effects were less profound when only participants with severe disease were included and evidence remains insufficient for the treatment of severe, oral corticosteroid dependent asthma. Limited evidence is available in children.
- Although distinctly different, there is no evidence to support using omalizumab in combination with either reslizumab or mepolizumab.

Recommendations:

- Designate mepolizumab and reslizumab as a non-preferred drug subject to Prior Authorization (PA) criteria in **Appendix 2**.

Background:

An estimated 22 million Americans have asthma, which affects people of all ages and can have a significant impact on quality of life and daily functioning.[1] Only 5-10% of people with asthma have severe asthma but they account for about 50% of all healthcare costs associated with asthma. [1] Severe asthma is characterized by daily symptoms, awakening most nights due to symptoms and significant limitations in normal activities.[1,2] The European Respiratory Society

(ERS)/American Thoracic Society (ATS) defines severe asthma as asthma that (1) requires treatment with high dose ICS plus a second controller (e.g., LABA) during the previous year and/or use OCS for 50% or more of the previous year or (2) remains uncontrolled despite this therapy.[3] However, chronic use of OCS may result in other complications, including growth suppression in children, osteoporosis, Cushing's syndrome, adrenal insufficiency, diabetes, and increased risk for infections. [1]

Clinical trials may further define patients with severe asthma as those whose asthma worsens when high dose ICS or OCS are tapered but do not otherwise meet criteria for uncontrolled asthma and patients with evidence of any one of the 4 following criteria for uncontrolled asthma who are currently on high dose ICS therapy: (1) poor symptom control (ACQ score consistently greater than 1.5 or Asthma Control Test [ACT] score less than 20; (2) frequent severe exacerbations that have required use of OCS for more than 3 days on 2 separate occasions in the previous year; (3) serious exacerbations that resulted in at least 1 hospitalization in the previous year; or (4) airflow limitation (pre-bronchodilator forced expiratory volume in 1 second (FEV_1) less than 80% of the normal predicted volume with a reduced FEV_1/Forced Vital Capacity (FVC) defined as less than the lower limit of normal.[3] However, uncontrolled asthma is multifactorial, and issues such as incorrect diagnosis, comorbidities and nonadherence to prescribed therapy, and psychosocial issues are major causes for treatment failure.[2] The Global Initiative for Asthma (GINA) guidelines recommend patients with severe asthma, despite correct inhaler use and adherence to standard of care, be seen by an asthma specialist.[4] These patients should be seen 1 to 3 months after starting specific treatment for eosinophilic severe asthma, and every 3–12 months thereafter.[4] All patients should be seen within 1 week after an exacerbation.[4]

Clinically relevant outcomes for severe asthma include reduction in asthma exacerbations that result in: 1) decreased emergency department (ED) visits or hospitalizations; 2) decreased chronic use of OCS; 3) improved quality of life; and 4) improved symptom management. Four instruments are commonly used in clinical trials to assess quality-of-life and symptom management related to asthma. These tests are self-administered and subject to recall bias but have been validated with highly consistent reproducibility between users. The ACQ is a 5- or 7-item questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.[5] Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 the minimally clinical important difference. [5] The Asthma Quality of Life Questionnaire (AQLQ) is a 32-item quality-of-life instrument that assesses both physical and emotional impact of disease.[6] Scores range from 1 (severely impaired) to 7 (not impaired at all), with higher scores indicating better quality of life. [6] A difference of 0.5 overall and for each item is the minimally clinical important difference for this instrument. [6] The St. George's Respiratory Questionnaire (SGRQ) is a 50-item quality-of-life tool for patients with obstructive airway disease.[7] The questionnaire is composed of 2 parts. Part 1 assesses symptoms and part 2 assesses limitation of activities and its social and psychological impact. [7] Scores range from 0 to 100, with higher scores indicating more limitations. [7] A change of 4 points is associated with slightly efficacious treatment, 8 points for moderately efficacious treatment, and 12 points for very efficacious treatment. [7] Lastly, the ACT is a tool used to identify patients with poorly controlled asthma.[8] The test contains 5 items that assess the frequency of shortness of breath and general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control. [8] Scores range from 5 (poor control of asthma) to 25 (complete control of asthma). [8] An ACT score greater than 19 indicates well-controlled asthma, with a change of 3 points the minimally clinical important difference over time. [8]

Omalizumab is a monoclonal antibody that has been available for over a decade to help manage severe allergic asthma with use of other asthma controllers (e.g., ICS, LABA, etc.).[9] Omalizumab is also approved for the treatment of chronic idiopathic urticaria, a condition that is not funded by the Oregon Health Plan (OHP). Mepolizumab and reslizumab are humanized monoclonal antibodies recently approved to manage severe asthma. These agents are approved and studied in patients with severe asthma and eosinophilic phenotype, though this phenotype has not been clearly defined outside of these trials and a consensus has not been developed to identify this phenotype in a clinically useful way.[10–12] Eosinophilic asthma is found in patients with both non-severe and severe disease and is often associated with response to corticosteroids.[13,14]However, some patients with eosinophilic asthma may not sufficiently respond to OCS .[13,14] Persistence of eosinophils in the airways despite ICS therapy has been associated with severe asthma, and higher airway and blood eosinophil counts have been

associated with increased risk for asthma exacerbations.[14–16] Mepolizumab and reslizumab bind to interleukin-5 (IL-5), which decreases IL-5 signaling and decreases eosinophils in the blood and tissue.[17] They were studied as add on therapy for patients inadequately controlled on traditional controller medications, which may include inhaled corticosteroids, long-acting inhaled beta-agonists, mast cell stabilizers and leukotriene modifiers. Reslizumab was studied in patients with asthma with sputum eosinophil count ≥3%. However, in clinical trials blood eosinophil was used a surrogate to sputum eosinophilia because it is more accessible.

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.

Table 1. Indications and Dosing

Drug Name	Indications	Strength/Route	Dose and Frequency
Cinqair (reslizumab)[18]	Add-on for severe eosinophilic asthma (≥18 y/o)	Intravenous infusion	3 mg/kg every 4 weeks
Nucala (mepolizumab)[17]	Add-on for severe eosinophilic asthma (≥12y/o)	Subcutaneous Injection	100 mg SubQ every 4 weeks
Xolair (omalizumab)[9]	Moderate-to-severe persistent and uncontrolled asthma (≥12 y/o) Chronic idiopathic urticarial (≥12 y/o)	Subcutaneous Injection	150 to 375 mg SubQ every 2 or 4 weeks

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Boxed Warnings and Risk Evaluation Mitigation Strategies. For drugs recently approved, the manufacturer's summary prescribing information is provided.

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 OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

Systematic Reviews:

A Cochrane systematic review evaluated the use of omalizumab compared to placebo or conventional therapy for the treatment for asthma in adults and children.[19] A total of 25 RCTs were included in the review. Studies including participants on subcutaneous omalizumab with moderate or severe asthma who were on background ICS therapy demonstrated a significant reduction (moderate quality evidence) in asthma exacerbations (OR 055; 95% CI 0.42 to 0.60; n=3261) and hospitalizations (OR 0.16; 95% CI 0.06 to 0.42; n=1824). Little effect on exacerbations was seen when only participants with severe asthma were included (OR 1.00; 95% CI 0.50 to 1.99). Participants were also more likely to be able to withdraw their ICS compared to those treated with placebo (OR 2.50; 95% CI 2.00 to 3.13). However, there was no significant difference between omalizumab and placebo in the number of participants who were able to withdraw from oral corticosteroid therapy (OR 1.18; 95% CI 0.53 to 2.63). There were fewer serious adverse events reported in the omalizumab group compared to placebo (OR 0.72; 95% CI 0.57 to 0.91) but more injection site reactions. Overall, omalizumab was found to be more effective in reducing exacerbations and hospitalizations as adjunctive therapy to inhaled steroids and during steroid tapering. Effects were less profound when only participants with severe disease were included and evidence remains insufficient for the treatment of severe, oral corticosteroid dependent asthma. Limited evidence is available in children.

Another systematic review and economic evaluation was performed by the Health Technology Assessment program of the National Institute for Health Research on omalizumab for the treatment of severe persistent allergic asthma.[20] Studies with omalizumab as add-on therapy to standard care compared with standard therapy alone in adults and children were included. Eleven RCTs and 15 observational trials were included. Studies had variable inclusion criteria but most required ICS background therapy. In adults and adolescents aged 12 years and older, omalizumab reduced the rate of clinically significant exacerbations (RR 0.74; 95% CI 0.55 to 1.00) but did not reach statistical significance, and severe exacerbations (RR 0.50; 95% CI 0.32 to 0.78). There was insufficient evidence that omalizumab reduced the use of oral corticosteroids. Only one trial in children demonstrated a decrease in clinically significant exacerbations (RR 0.67; 95% CI 0.44 to 0.995). Evidence on the safety of omalizumab in children was limited. There is no direct evidence comparing omalizumab to oral corticosteroids as add-on therapy.

Lastly, omalizumab treatment for adults and children with allergic asthma was reviewed by the Canadian Agency for Drugs and Technologies in Health (CADTH) in the form of a rapid response.[21] Consistent with previous reviews, the authors found that the evidence suggests omalizumab decreases asthma exacerbations and hospitalizations in adults and adolescents with moderate to severe allergic asthma inadequately controlled by standard therapy with less evidence in children. In addition, omalizumab was found to improve asthma symptoms and be associated with a reduction in inhaled corticosteroid use compared to placebo. A meta-analysis was not done, but rather existing evidence was summarized. They also summarized economic evaluations. Evaluations in the UK and Japan did not find omalizumab to be cost-effective as add-on to standard of care while evaluations by the Dutch and Spanish did find it to be cost effective.

In addition to asthma, omalizumab is also FDA approved for the treatment of chronic idiopathic urticaria (CIU). CADTH also conducted a systematic review evaluating the beneficial and harmful effects of omalizumab or the treatment of CIU in adults and adolescents who remain symptomatic despite H_1 anthistamine treatment.[22] The review included 3 RCTs that compared omalizumab to placebo in 978 adult and adolescent patients with CIU refractory to antihistamines. The primary outcomes were improvement in the Weekly Itch Severity Score (ITSS) and the Uticaria Activity Score over 7 days (UAS7). These have been validated for use in CIU and were considered clinically relevant by the authors. All 3 trials showed improvements in CIU symptoms as measured by both the UAS7 and WISS. Results were not pooled, but one major trial showed an improvement in UAS7 of -10.02 (95% CI -13.17 to -6.86) with omalizumab 300 mg compared to placebo and in WISS of -4.52 (95% CI -5.97 to -3.08) at week 12. The authors found these results to be clinically significant based on published minimal clinically important differences for these outcomes. The 150 mg dose in trials failed to show a clinically significant response compared to placebo. Omalizumab also appeared to significantly improve quality of life. However, outcomes assessed after the 16-week treatment free follow up period showed that the majority of efficacy outcomes did not maintain statistically improvements compared to placebo. Due to the chronic nature of the disease, it remains possible that long-term

therapy is necessary; however, there are no data on the efficacy and safety of re-treatment or to define the optimal interval between treatment courses. Patients receiving omalizumab were more likely to experience adverse effects overall, and headaches in particular than those in placebo.

Guidelines:
2014 guidelines from the Scottish Intercollegiate Guidelines Network (SIGN) recommends that "omalizumab treatment should only be initiated in specialist centers with experience of evaluation and management of patients with severe and difficult asthma."[23] They also recommend omalizumab is only used in patients on high-dose ICS and LABA who have impaired lung function, are symptomatic with frequent asthma attacks, and have allergy as an important cause of their asthma.

Guidelines from The National Institute for Health and Clinical Excellence (NICE) from 2013 recommend omalizumab similarly as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimized standard therapy in people aged 6 years and older who need continuous or frequent treatment with oral corticosteroids (Defined as 4 or more courses in the previous year).[24] This recommendation is consistent with the guidelines from the National Heart, Lung and Blood Institute (NHLBI) asthma guidelines.

Mepolizumab NEW DRUG EVALUATION**:**

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
The FDA approved mepolizumab based on data from 3 short-term, GSK-sponsored, placebo-controlled, international trials (Studies 97, 88, and 75).[16] Most study sites occurred outside North America and non-white racial groups were uniformly underrepresented in the trials. Applicability of the trials was further limited by extensive inclusion and exclusion criteria and limited duration of study in a relatively few number patients. However, the studies evaluated clinically relevant endpoints and had an overall low or unclear risk of bias for the domains assessed (see Table 1). In all 3 trials, mepolizumab was compared with placebo and all patients received standard of care for severe asthma, which included high dose ICS, a LABA (or other long-acting controller), and a rescue bronchodilator.

The FDA-approved dose of 100 mg SC every 4 weeks is supported by the data and corresponds to the lowest tested intravenous (IV) dose of 75 mg that provided meaningful reduction of exacerbations versus placebo.[16] Statistically significant reductions in asthma exacerbation rates were seen in 2 exacerbation studies for all mepolizumab doses but with no significant dose-response beyond the 75 mg IV dose, and no significant difference between the mepolizumab 75 mg IV dose and 100 mg SC dose.[16] Overall rates of exacerbations requiring ED visits or hospitalizations were low across all treatment groups in all studies (approximately 1 in every 5 to 10 exacerbations required ED visits or hospitalization).[16] However, exacerbations that did require an ED visit or hospitalization occurred less frequently in groups assigned to mepolizumab compared to the placebo groups.[16] The benefit of mepolizumab on asthma exacerbations was demonstrated in Studies 97 and 88, in which patients were selected based on a previous history of exacerbation and presence of an eosinophilic phenotype.[16] Study 97 used one or more criteria to identify the eosinophil phenotype.[16] However, analysis of the various criteria used to screen patients for enrollment found that number of asthma exacerbations in the prior year and peripheral blood eosinophil threshold (≥300 cells/µL in past year or ≥150 cells/µL at baseline) were the criteria that best selected for patients that showed benefit in asthma exacerbations.[16] In Study 75 (OCS reduction study), the same blood eosinophil threshold was prospectively used to screen patients for enrollment.[16]

Study 97 was a 52-week, multicenter, double-blind, phase 2, placebo-controlled, dose-ranging study of IV mepolizumab every 4 weeks in which the key phenotypic characteristics of the target population for the drug were investigated.[10] Patients recruited were on chronic high-dose ICS therapy with an additional controller agent with or without maintenance OCS. [10] Patients had a history of 2 or more exacerbations per year and eosinophilic airway inflammation, defined by serum eosinophil count (≥300 cells/μL), sputum eosinophils (≥3%), exhaled nitric oxide concentration (≥50 ppb) or loss of asthma control after 25% or more reduction in regular maintenance ICS or OCS dose. [10] The primary outcome was the annualized rate of asthma exacerbations. [10] Quality-of-life and asthma control were assessed by the AQLQ and ACQ questionnaires, respectively, as secondary outcomes.[11] The rate of clinically significant exacerbations (reported as per patient per year) for mepolizumab 75 mg IV every 4 weeks was 1.24 compared to 2.40 for the placebo group, a difference of -1.16 asthma exacerbations (rate ratio [RR] 0.52; 95% CI, 0.39 to 0.69; p<0.001). The rate of exacerbations that resulted in ED visits or hospitalization was reduced by 0.26 exacerbations for the 75 mg IV dose compared to placebo (RR 0.40; 95% CI, 0.19 to 0.81). However, no significant difference in total ACQ scores (Mean Difference [MD] -0.16 (95% CI, -0.39 to 0.07) or total AQLQ scores (MD –0.08 (95% CI, –0.16 to 0.32) were found.

Study 88 was a 32-week, multicenter, randomized, double-blind, double-dummy, phase 3, placebo-controlled exacerbation study of SC (100 mg) and IV (75 mg) mepolizumab every 4 weeks in patients with severe asthma, most of whom did not yet require daily OCS.[11] The key characteristics used to identify eligible patients included a blood eosinophil count (≥150 cells/μL at screening or ≥300 cells/μL in the past 12 months), number of previous exacerbations (≥2), and high-dose ICS use plus an additional controller with or without OCS. [11] The primary outcome was the annualized rate of asthma exacerbations.[12] Quality-of-life and asthma control were assessed by the SGRQ and ACQ-5 questionnaires, respectively, as secondary outcomes. [11] The IV and SC groups had statistically significant 47% (95% CI, 28 to 60%) and 53% (95% CI, 36 to 65%) relative reductions in the mean rate of exacerbations, respectively, compared with placebo. [11] The SC group also experienced a statistically significant mean reduction in the rate of exacerbations requiring hospitalization or ED visits when compared with placebo (61%; 95% CI, 17 to 82%; p=0.02) but the IV group did not. [11] Both the IV and SC mepolizumab groups had statistically significant and clinically meaningful[7] improved total SGRQ scores versus placebo, with differences of –6.4 (95% CI, –9.7 to –3.2) and –7.0 (95% CI, –10.2 to –3.8), respectively. [11] Both the IV and SC mepolizumab groups also had statistically significantly improved ACQ scores versus placebo, with differences of –0.42 (95% CI, –0.61 to –0.23) and –0.44 (95% CI, –0.61 to –0.23), respectively; [11] however, these differences did not exceed the minimal clinically important difference of 0.5 points.[5]

Study 75 was a 24-week, multicenter, randomized, double-blind, phase 3, placebo-controlled study designed to investigate whether SC mepolizumab 100 mg every 4 weeks would allow patients on chronic OCS for severe eosinophilic asthma to reduce their OCS dose without loss of asthma control.[12] Eligible patients were on an OCS for at least 6 months equal to 5 to 35 mg daily of prednisone or its equivalent) and had presence of eosinophilic inflammation (blood eosinophil level ≥300 cells/μL anytime during the preceding 12 months before screening or 150 cells/μL at screening). [12] The primary outcome was reduction in OCS dose. [12] Quality-of-life and asthma control were assessed by the SGRQ and ACQ questionnaires, respectively, as secondary outcomes. [12] Before randomization, patient's OCS doses were tapered to the lowest effective dose that did not result in a clinically meaningful increase of 0.5 points in ACQ scores. These doses were used as a baseline measure from which dose reductions were made over a 16-week period. After 20 weeks on mepolizumab or placebo, 14% on mepolizumab completely stopped OCS compared to 8% on placebo and 23% of patients on mepolizumab had a 90-100% reduction in OCS compared to 11% on placebo. Overall, 36% of patients on mepolizumab had no reduction in OCS dose, developed uncontrolled asthma or withdrew from treatment, compared to 56% on placebo. The proportion of patients who had a reduction in OCS dose of 50% or more after 20 weeks was greater in patients on mepolizumab versus placebo (54% vs. 33%, respectively; odd ratio [OR] 2.26; 95% CI, 1.10 to 4.65; p=0.03; number-needed-to-treat = 5). Similarly, the proportion of patients who had a reduction in OCS dose equivalent to 5 mg or less daily of prednisone was greater in patients on mepolizumab versus placebo (54% vs. 32%, respectively; OR 2.45; 95% CI, 1.12 to 5.37; p=0.02; number-needed-to-treat = 5). Clinically meaningful improvements in asthma control (ACQ -0.52 points; 95% CI, -0.87 to -0.17; p=0.004) and quality-of-life (SGRQ -5.8 points; 95% CI, -10.6 to -1.0; p=0.02) were also noted in patients who received mepolizumab versus placebo.

Mepolizumab has not been studied against other monoclonal antibodies for comparative efficacy in severe asthma. It is also unknown whether the efficacy demonstrated in these trials would be sustained long-term. The trials included only 28 patients 12 to 17 years of age and only 38 patients at least 65 years of age.[16] The number of young and elderly patients was insufficient to determine whether this population would respond differently to mepolizumab.

Clinical Safety:

The safety of mepolizumab can be assessed over a time frame of 1 to 3.5 years from Studies 97, 88, and 75, and the ongoing safety extension Studies 61 and 66, where patients from the Studies 97, 88 and 75 were enrolled.[16] Adverse events of interest for monoclonal antibodies include allergic reactions, local injection site reactions, serious cardiac events, infections, malignancy, and immunogenicity. The mepolizumab and placebo groups had similar frequencies of serious adverse events (SAEs), with the majority of SAEs related to asthma exacerbation. [16] In patients who received at least 1 dose of study drug, discontinuation rates were low (about 1 to 3%). Common adverse events leading to early withdrawal were worsening of asthma, fatigue, and headache (<1% for each). [16]

Treatment groups had similar safety profiles, with the exception of injection site reaction (8% with mepolizumab 100 mg SC vs. 3% with placebo). Other common adverse reactions found with mepolizumab 100 mg SC are noted in **Table 1**.[17]

Table 2. Adverse Reactions with Mepolizumab with ≥3% Incidence and More Common than Placebo. [17]

Adverse Reaction	Mepolizumab 100 mg SC (n=263)	Placebo (n=257)
Headache	19%	18%
Injection site reaction	8%	3%
Back pain	5%	4%
Fatigue	5%	4%
Influenza	3%	2%
Urinary tract infection	3%	2%
Upper abdominal pain	3%	2%
Pruritus	3%	2%
Eczema	3%	<1%
Muscle spams	3%	<1%

The studies did not report any cases of anaphylaxis. [16] Non-anaphylactic allergic reactions occurred in 2% of less of all patients, with similar rates similar between mepolizumab and placebo groups. [16] Once case was a Type 4 delayed hypersensitivity reaction. [16]

Study 97 had a numerical imbalance in the number of serious cardiac events with 7 events in the mepolizumab group and only 1 patient in the placebo group. [16] All but one patient had cardiovascular risk factors at baseline; this finding was not seen in subsequent studies 88 and 75 or in the ongoing safety extension studies, with a 3% overall frequency of cardiac events in both mepolizumab and placebo groups. [16]

The mepolizumab and placebo groups had similar frequencies of infections, including serious infections and opportunistic infections (57% and 58%, respectively). [16] However, 2 patients treated with mepolizumab 100 mg SC had serious herpes zoster infection compared to none in placebo groups. Therefore, prescribing information recommend the varicella vaccination, when appropriate, before starting mepolizumab. [16] The overall risk of infections will be clarified with long-term use of mepolizumab.

The FDA considers the risk of malignancy with mepolizumab to be lower than for other monoclonal antibodies because IL-5 inhibition is unlikely to induce general immunosuppression. In the controlled severe asthma studies, treatment groups had similar frequencies of benign or malignant neoplasms ranging from 0% to 2%. Three cases of malignancies were reported in the placebo groups and 2 cases were reported in mepolizumab groups. No reports of lymphoma or lymphoproliferative cancers occurred, which can suggest general immunosuppression. [16] The overall risk of malignancy will be clarified with long-term use of mepolizumab.

Clinical trials included only 28 patients 12 to 17 years of age and older and only 38 patients at least 65 years of age. [16] The number of elderly patients was insufficient to determine whether this population would respond differently to mepolizumab. The risk of helminth infection is unknown because patients with, or at risk for, parasitic infections were excluded.

Table 3: Pharmacology and Pharmacokinetic Properties: [17]

Parameter	
Mechanism of Action	The mechanism of action has not been firmly established. Mepolizumab is an antagonist of IL-5, the cytokine predominantly responsible for the eosinophil production, recruitment, activation, and survival. By binding to IL-5, mepolizumab blocks IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the cell surface of eosinophils. This inhibition of IL-5 signaling reduces eosinophil production and survival.
Distribution and Protein Binding	Vd 3.6 L in 70 kg individual
Metabolism	Proteolytic enzymes widely distributed in the body
Half-Life	16 to 22 days
Elimination	Clearance 0.28 L daily in 70 kg individual

Abbreviations: IL-5 = interleukin 5; kg = kilograms; L = liters; Vd = volume of distribution

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Hospitalizations due to exacerbations
2) Emergency Department visits due to exacerbations
3) Quality of life
4) Asthma symptoms
5) Reduction/elimination in systemic corticosteroid use
6) Serious adverse events
7) Discontinuations due to adverse events

Primary Study Endpoints:
1) Studies 97 and 88: The rate of clinically significant asthma exacerbations, which were defined as worsening of asthma requiring use of OCS for ≥3days, hospital admission, or an ED visit.
2) Study 75: Percentage reduction in daily OCS dose during weeks 20 to 24 as compared to baseline.

Table 4. Clinical Efficacy Evidence Table.

Ref./ Study Design	Drug Regimen/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARI/ NNH	Quality Rating Risk of Bias/Applicability
1. Pavord, et al.[10] MC, DB, PC, RCT Phase 3 STUDY 97	1. MEP 75 mg IV Q4 wk 2. MEP 250 mg IV Q4 wk 3. MEP 750 mg IV Q4 wk 4. PBO IV Q4 wk 52 weeks	Demographics: Mean age: 49 y Females: 63% White: 90% Hospitalizations due to asthma in past year: 38% Severe exacerbations in past year: 3.6 Chronic OCS: 30% Key Inclusion Criteria: -age ≥12 y and wt ≥45 kg -asthma w/ FEV_1 <80% predicted for adults; FEV_1 <90% predicted; or FEV_1/FVC <0.8 for adolescents <18 y -≥1 of the following: FEV_1 w/ >12% reversibility; + methacholine challenge; or ≥20% FEV_1 variability -h/o ≥2 asthma exacerbations requiring OCS past 12 months -ICS equiv. to ≥880 mcg fluticasone plus an additional controller -blood eosinophil ≥300 cell/µL or sputum eosinophils ≥3% or FE_{NO} ≥50 ppb or rapid deterioration of asthma control after ≥25% reduction in ICS or OCS dose in past 12 months Key Exclusion Criteria: -current smokers or h/o ≥10 pack years -concurrent respiratory disease -liver disease -pregnancy/lactation	mITT 1. 153 2. 152 3. 156 4. 155 Attrition 1. 0.6% 2. 0% 3. 0% 4. 2.5%	Primary Endpoint: Rate of clinically significant exacerbations per patient per year* 1. 1.24 (SE log 0.12) 2. 1.46 (SE log 0.11) 3. 1.15 (SE log 0.12) 4. 2.40 (SE log 0.11) 1 vs. 4: RR 0.52 (95% CI, 0.39 to 0.69) 2 vs. 4: RR 0.61 (95% CI, 0.46 to 0.81) 3 vs. 4: RR 0.48 (95% CI, 0.36 to 0.64) Key Secondary Endpoints: Rate of hospitalizations or ED visits per patient per year from exacerbation: 1. 0.17 (SE log 0.30) 2. 0.25 (SE log 0.25) 3. 0.22 (SE log 0.26) 4. 0.43 (SE log 0.24) 1 vs. 4: RR 0.40 (95% CI, 0.19 to 0.81) 2 vs 4: RR 0.58 (95% CI, 0.30 to 1.12) 3 vs. 4: RR 0.52 (95% CI, 0.27 to 1.02) Δ ACQ from baseline (0-6): 1. -0.75 (SE log 0.09) 2. -0.87 (SE log 0.09) 3. -0.80 (SE log 0.09) 4. -0.59 (SE log 0.0.9) 1 vs. 4 MD -0.16 (95% CI, -0.39 to 0.07) 2 vs. 4 MD -0.27 (95% CI, -0.51 to 0.04) 3 vs. 4 MD -0.20 (95% CI, -	 NA NA NA NA NS NS NS NS NS	Safety Outcomes (0-56 weeks) D/C due to AE: 1. 3% 2. 5% 3. 6% 4. 4% SAE (includes asthma-related AE): 1. 13% 2. 16% 3. 12% 4. 16% Fatal AE: 1. 0% 2. 1.3% 3. 0.6% 4. 0% Serious Infection: 1. 5% 2. 2% 3. 3% 4. 3% Infusion-related reactions: 1. 5% 2. 8% 3. 12% 4. 6%	NA for all	**Risk of Bias** (low/high/unclear): Selection bias: (low) randomized 1:1:1:1 by centralized computer-generated, permuted-block schedule. Stratified by chronic OCS. Baseline ACQ and exacerbations requiring hospitalization higher in PBO arm at baseline. Performance bias: (low) MEP and PBO identical in appearance and administered by staff unaware of group assignments. However, staff that prepared study drugs were aware of group assignments. Detection bias: (unclear) statisticians and GSK personnel blinded to data; power assumptions are not referenced; specific statistical tests utilized unclear. Attrition bias: (low) overall attrition low and similar across groups based on mITT analysis; imputation of missing data unclear for several dropouts. Appropriate statistical tests used. Reporting bias: (unclear) funded by GSK; data analyzed by GSK. Pre-specified primary outcome reported as relative risk. **Applicability**: Patient: extensive inclusion criteria may limit applicability of study results. Eosinophil asthma broadly defined w/ multiple criteria. Intervention: IV infusion of MEP was not approved by FDA; 10-fold difference in dose tested but no dose-response observed. Comparator: PBO allows investigators to assess efficacy of MEP, but a direct comparison with other monoclonal antibodies for severe asthma would be helpful to understand place in therapy. Outcomes: clinically significant asthma exacerbation defined as a composite of many outcomes but it is unclear what criteria primarily drove the reduction in exacerbations; no clear dose-response observed across doses. Short study duration. Setting: 81 centers in 13 countries (Argentina, Australia, Canada, Chile, France, Germany, South Korea, Poland, Romania, Russia, Ukraine, U.K. and U.S.

				0.43 to 0.03)				
2. Ortega, et al.[11] MC, DB, PC, PG, RCT Phase 3 STUDY 88	1. MEP 75 mg IV + PBO SC Q4 wk 2. MEP 100 mg SC + PBO IV Q4 wk 3. PBO IV + SC Q4 wk 32 weeks	Baseline Demographics: Mean age: 50 y Females: 57% White: 78% SGRQ: 46.4 ACQ-5: 2.22 Chronic OCS: 25% Key Inclusion Criteria: -age ≥12 y and wt ≥45 kg -asthma w/ FEV_1 <80% predicted for adults; FEV_1 <90% predicted or FEV_1/FVC <0.8 for adolescents <18 y -≥1 of the following tests results: FEV_1 w/ >12% reversibility; + methacholine challenge; or ≥20% FEV_1 variability -≥2 asthma exacerbations in past 1 year while on ≥880 mcg/d of ICS fluticasone (or equiv.) requiring OCS -≥3 months of additional controller besides ICS -blood eosinophil >150 cell/µL at screening or ≥300 cell/µL in past year Key Exclusion Criteria: -current smokers or h/o ≥10 pack years -concurrent respiratory disease -liver disease -HF (EF<30%; NYHA Class IV; hospitalized in past year) or angina -immunodeficiency (HIV) -monoclonal antibody drug for asthma -pregnancy/lactation	mITT 1. 191 2. 194 3. 191 Attrition 1. NR 2. NR 3. NR (total 0.6%)	Primary Endpoint: Rate of clinically significant asthma exacerbations* 1. 0.93 2. 0.83 3. 1.74 1 vs. 3: RRR 47% (95% CI, 28 to 60%; p<0.001) 2 vs. 3: RRR 53% (95% CI, 36 to 65%; p<0.001) Key Secondary Endpoints: Mean annual rate of asthma exacerbations requiring hospitalization or ED visit: 1. 0.14 2. 0.08 3. 0.20 1 vs. 3: RRR 32% (95% CI, -41 to 67%; p=0.30) 2 vs. 3: RRR 61% (95% CI, 17 to 82%; p=0.02) Δ SGRQ from baseline (0-100): 1. -15.4 (SE 1.2) 2. -16.0 (SE 1.1) 3. -9.0 (SE 1.2) 1 vs. 3: ARR -6.4% (95% CI, -9.7 to -3.2%; p<0.001) 2 vs. 3: ARR -7.0% (95% CI, -10.2 to -3.8; p<0.001) Δ ACQ from baseline (0-6): 1. -0.92 (SE 0.07) 2. -0.94 (SE 0.07) 3. -0.50 (SE 0.07) 1 vs. 3: ARR -0.42% (95% CI, -0.61 to -0.23%; p<0.001) 2 vs. 3: ARR -0.44% (95% CI, -0.63 to -0.25; p<0.001)	NA NA NA NA NA NA NA	Safety Outcomes (0-40 weeks) Any non-asthma AE: 1. 84% 2. 78% 3. 82% Drug-related AE: 1. 17% 2. 20% 3. 16% D/C due to AE: 1. 0% 2. 1% 3. 2% SAE (includes asthma-related AE): 1. 7% 2. 8% 3. 14% Anti-MEP antibodies: 1. 4% 2. 5% 3. 2% Injection-site AE: 1. 3% 2. 9% 3. 3%	NA for all	**Risk of Bias** (low/high/unclear): Selection bias: (low) randomized 1:1:1 by centralized computer-generated, permuted-block schedule. Performance bias: (low) See Pavord, et al. Detection bias: (low) statisticians and GSK personnel blinded to data. Power assumptions appropriate. Appropriate statistical tests utilized. Attrition bias: (low) overall attrition low and similar across groups based on mITT analysis; imputation of missing data unclear but few dropped out early. Appropriate statistical tests used. Reporting bias: (unclear) funded by GSK; data analyzed by GSK. Pre-specified primary outcome reported as relative risk reduction. **Applicability**: Patient: About 1/4 of patients on chronic OCS and 1/3 were former smokers. Average duration of asthma was about 20 years. Patients remained on ICS and at least one other controller agent. Intervention: SC dose approved and available in U.S.; IV dose was not approved and appeared to be associated with more AEs w/o additional efficacy vs. SC dose. Comparator: See Pavord, et al. Outcomes: composite primary endpoint is clinically relevant but results were nearly all driven by use of ≥3 days of OCS and not hospitalizations or ED visits. Mean dose and duration of OCS for each exacerbation between groups unknown. Short study duration. Setting: 16 countries in Europe (n=270); South and Central America (n=68); USA (n=67); Japan (n=50); Korea (n=45); Canada (n=35); Australia/Russia/Ukraine (n=41).

3. Bel, et al.[12] MC, DB, PC, PG, RCT Phase 3 STUDY 75	1. MEP 100 mg SC Q4 wk 2. PBO SC Q4 wk 4 Phases: Optimization: taper OCS to lowest effective dose Induction: post-randomization (weeks 0-4) Reduction: reduce OCS by 1.25-10 mg/d Q4 wk (weeks 4-20) Maintenance: no change in OCS dose (weeks 20-24)	Baseline Demographics: Mean age: 50 y Females: 55 % White: 95% Hospitalizations due to asthma in past year: 17% Severe exacerbations in past year: 3.1 Key Inclusion Criteria: -age ≥12 y and wt ≥45 kg -chronic (≥6 months) OCS equiv. to 5-35 mg/d of prednisone -blood eosinophil >150 cell/µL at screening or ≥300 cell/µL in past year -ICS equiv. to ≥880 mcg fluticasone except ≥440 mcg adolescents <18 y -≥3 months of additional controller besides ICS -asthma w/ FEV_1 <80% predicted for adults; FEV_1 <90% predicted or FEV_1/FVC <0.8 for adolescents <18 y -≥1 of the following tests results: FEV_1 w/ >12% reversibility; + methacholine challenge; or ≥20% FEV_1 variability Key Exclusion Criteria: See Ortega, et al.	mITT 1. 69 2. 66 Attrition 1. 0% 2. 0%	Primary Endpoint: % reduction of daily OCS dose from baseline to weeks 20-24 (MEP vs. PBO): 90 to 100%: 23% vs. 11% 75 to <90%: 17% vs. 8% 50 to <75%: 13% vs. 15% >0 to <50%: 10% vs. 11% OR 2.39 (95% CI, 1.25-4.56; p=0.008) Key Secondary Endpoints (weeks 20-24): ≥50% reduction of OCS dose: 1. 54% 2. 33% OR 2.26 (95% CI, 1.10-4.65; p=0.03) Reduction of daily OCS dose to ≤5 mg: 1. 54% 2. 32% OR 2.45 (95% CI, 1.12-5.37; p=0.02) Off OCS: 1. 14% 2. 8% OR 1.67 (95% CI, 0.49-5.75; p=0.41)	NA 21/5 22/5 NS	Safety Outcomes (0-32 weeks) Any non-asthma AE: 1. 83% 2. 91% Drug-related AE: 1. 30% 2. 18% D/C due to AE: 1. 4% 2. 5% SAE (includes asthma-related AE): 1. 1% 2. 18% Anti-MEP antibodies: 1. NR 2. NR (4% total cohort) Injection-site AE: 1. 6% 2. 3%	NA for all	**Risk of Bias** (low/high/unclear): Selection bias: (low) randomized 1:1 by centralized computer-generated, permuted-block schedule, stratified by country. Baseline SGRQ lower and OCS dose higher in PBO arm than MEP arm. Performance bias: (low) See Ortega, et al. Detection bias: (low) See Ortega, et al. Attrition bias: (high) imputation of missing data unclear; mITT performed but 26% of subjects in run-in optimization phase did not get randomized. Reporting bias: (unclear) See Ortega, et al. **Applicability**: Patient: Patients remained on maintenance asthma drug regimen used prior to study, including ICS and ≥1 other controller agent. Intervention: FDA-approved dose and formulation studied. Comparator: See Pavord, et al. Outcomes: Mean daily OCS doses at weeks 20-24 were 10.5 mg and 8.6 mg for PBO and MEP, respectively; median doses were 10.0 and 3.1 mg, respectively. Only 40% had >75% reduction in OCD dose vs. 19% with PBO. No difference in more moderate dose reductions. Short study duration. Setting: 38 sites in Germany (n=8); France (5); Czech Republic (5); U.S. (5); U.K. (4); Australia (3); Canada (3); Netherlands (2), Poland (2); and Mexico (1).

Abbreviations [alphabetical order]: ACQ = 5-item Asthma Control Questionnaire (scale 0-6); AQLQ = 32-item Asthma Quality of Life Questionnaire (scale 1-7); ARI = absolute risk increase; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; EF = ejection fraction; FDA = U.S. Food and Drug Administration; FE_{NO} = exhaled nitric oxide concentration; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HF = heart failure; h/o = history of; ICS = inhaled corticosteroid; ITT = intention to treat; IV = intravenous; MC = multi-centered; MD = mean difference; MEP = mepolizumab; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; NYHA = New York Heart Association; OCS = oral corticosteroid; OR = odds ratio; PC = placebo-controlled; PBO = placebo; PC20 = provocative concentration of inhaled methacholine needed to reduce FEV1 by 20%; PEF = peak expiratory flow; PG = parallel group; PP = per protocol; RR = relative risk; RRR = relative risk reduction; SAE = serious adverse event; SC = subcutaneous; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; wk = weeks; wt = weight; y = years; µL = microliters.

*Worsening of asthma which requires use of systemic corticosteroids (IV or oral steroid for ≥3 days or a single IM dose; for subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for ≥3 days) and/or hospitalization and/or emergency department visits

Reslizumab NEW DRUG EVALUATION:

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:

Reslizumab was approved by the FDA based on 3 phase 3 studies (3081, 3082, and 3083).[25] Study 3081 was a lung function study and studies 3082 and 3083 were exacerbation studies. Patients were required to have a blood eosinophil count ≥400 cells/µl. This cutoff is based on data suggesting that a blood eosinophil count of at least 400 cells/µl had a high positive predictive value for the presence of sputum eosinophils of 3% or greater. However, this threshold is not definitive nor widely accepted.[25] The studied dose was 3 mg/kg IV every 4 weeks. However, the FDA notes that dose-ranging data are not as robust for reslizumab, and only a single dose was studied in all phase 3 studies.[25] Study sites were in North America (including the U.S.), South America, Asia and Europe. In the 3 primary studies (3081, 3082, 3083), only 20% of sites were within the US. Studies included patients with mean asthma duration of around 20 years or more with a mean of 2 exacerbations in the previous year.[25] All patients were on standard of care treatment based on disease severity, including ICS and LABA with inadequate control based on an ACQ score of ≥1.5.[25]

Study 3081 was a dose-ranging lung function study over 16 weeks. It remains unpublished and cannot be adequately assessed for quality. It included patients taking medium- to high-dose ICS with or without another controller with inadequate control based on an ACQ score of ≥1.5.[25] This was the only study investigating more than one dose of reslizumab (0.3 mg/kg and 3 mg/kg IV). Overall, both groups had a significant improvement in FEV1 from baseline compared to placebo (0.127, 0.238, and 0.286 L for placebo, 0.3 mg/kg and 3 mg/kg, respectively). Both doses demonstrated improvement in FEV1 but the treatment effect was modestly greater in the 3.0 mg/kg treatment group (FEV1 of 0.159 L) compared to the 0.3 mg/kg group (FEV1 of 0.111 L), both demonstrated efficacy. Both doses demonstrated improvements in the ACQ and AQLQ. A dose-dependent reduction of blood eosinophil count was seen with the higher dose (92%) compared to the lower dose (68%) and placebo (14%), but whether this endpoint translates into clinical outcomes remains unknown.[25] An additional study was designed to evaluate for an interaction between change from baseline in FEV1 and baseline eosinophil count and no significant interaction was found.[25] Additionally, an FDA exploratory analysis of studies 3082 and 3083 found no relationship between blood eosinophil count and exacerbation benefit.[25]

Studies 3082 and 3083 were identical phase 3 studies evaluating the frequency of exacerbations over 52 weeks with similar inclusion criteria as study 3081 in addition to requiring at least one exacerbation during the previous year. Use of OCS was permitted.[26] Studies only included the 3 mg/kg dose despite the FDA suggesting inclusion of more than one dose.[25] Pooled data from 3082 and 3083 demonstrated a decrease in the number of patients experiencing at least one asthma exacerbation compared to placebo (32% vs. 50%, respectively; RR 0.64; 95% CI 0.5 to 0.7) with an ARR of 18% and a NNT of 5 over 52 weeks.[26] There was no significant difference in the rate of episodes requiring hospitalizations or ED visits per patient per year between reslizumab and placebo (0.077 vs. 0.12; RR 0.66; 95% CI 0.38 to 1.16).[26] However, ED/hospitalization rates were low across all treatment groups (approximately 1 for every 5-10 exacerbations).[25] There was a significant improvement in patient-reported measures of the ACQ (pooled mean difference -0.25; 95% CI -0.343 to 0.156) and significantly more patients achieved a clinically significant reduction of 0.5 points on the ACQ in the reslizumab group compared to placebo, despite a large placebo effect.[26] Both studies demonstrated an increased change in FEV1 over placebo at week 52 (0.145 L in study 3082 and 0.123 L in study 3083).

Study data did not show a consistent benefit in patients 12 to 17 years of age; therefore, reslizumab is only approved for adults ages 18 years or older.[25] A total of 40 pediatric patients ages 12 to 17 years were included in studies 3081, 3082 and 3083 and the FDA advisory committee did not find the data adequate to support approval. In addition, an increase in asthma exacerbation rates was observed for adolescents, Blacks, and U.S. patients, which could be driven by the small sample size in these subgroups. Further data are needed in these populations.

Clinical Safety:
Overall dropouts and early discontinuations were low. The most common adverse event leading to discontinuation in all groups was worsening asthma. The most common adverse events, those that occurred in more than 5% of patients who received reslizumab, were worsening of asthma symptoms, nasopharyngitis, upper respiratory tract infections, sinusitis, influenza and headache.

Anaphylaxis was reported in 3 patients who received reslizumab. Malignancy also occurred with reslizumab, and a transient increase in creatine phosphokinase (CPK) suggest potential for muscle toxicity. Elevated CPK levels higher than 10-times the upper limit of normal occurred more frequently in the reslizumab arm (0.8%) than the placebo arm (0.4%). Musculoskeletal pain, muscle spasm, myalgia, muscle fatigue and rhabdomyolysis also occurred more with reslizumab than placebo. However, overall differences were small and there was an imbalance in baseline CPK values between the groups.

Table 5: Pharmacology and Pharmacokinetic Properties:

Parameter	
Mechanism of Action	IL-5 antagonist; thereby reducing the production and survival of eosinophils.
Distribution and Protein Binding	Volume of distribution of 5 L, suggesting minimal distribution to the extravascular tissues.
Metabolism	Metabolized by enzymatic proteolysis into small peptides and amino acids.
Half-Life	Approximately 24 days.
Elimination	Clearance approximately 7 mL/hour.

Abbreviations: IL-5 = interleukin 5; L = liters; ml =milliliters

Comparative Clinical Efficacy:
Clinically Relevant Endpoints:
1) Hospitalizations due to exacerbations
2) Emergency Department visits due to exacerbations
3) Quality of life
4) Asthma symptoms
5) Reduction/elimination in systemic corticosteroid use
6) Serious adverse events
7) Discontinuations due to adverse events

Primary Study Endpoint:
1) Frequency of clinical asthma exacerbations per patient during the 52 week treatment period.

Table 6. Clinical Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Castro, et al.[26] MC, DB, PC, RCT Phase 3 Study 3082	1. RES 3 mg/kg IV Q 4 weeks 2. Placebo IV Duration: 52 weeks	Demographics: Mean age: 49 y Females: 62% White: 73% Chronic OCS: 19% LABA use: 85% Mean ACQ: 2.71 Key Inclusion Criteria: Age 12-75 years blood eosinophil ≥ 400 cells/ µL; ACQ-7 score ≥1.5, at least medium dose ICS, ≥1 exacerbation in year prior Key Exclusion Criteria: Any clinically meaningful comorbidity, other lung disease, current smoker, any inadequately controlled medical factors (diabetes, GERD), pregnant or nursing females, HIV, drug and alcohol abuse.	ITT: 1. 245 2. 244 Attrition: 1. 0 2. 0	Primary Endpoint: Rate of asthma exacerbations per patient per year* 1. 0.90 2. 1.80 RR 0.50 (95% CI 0.37 to 0.67) Patients with ≥ 1 clinical asthma exacerbation (CAE) 1. 92 (38%) 2. 132 (54%) RR 0.69 (95% CI 0.56 go 0.85) Secondary Endpoints: Proportion of patients achieving a 0.5 point reduction in ACQ score from baseline: 1. 184 (76%) 2. 152 (63%) OR 0.5; 95% CI 0.3 to 0.8 Proportion of patients achieving a 0.5 point reduction in AQLQ score from baseline: 1. 75% 2. 65% OR 0.6; 95% CI 0.4 to 0.9) Rate of CAE requiring hospitalization or ER treatment per patient per year: 1. 0.14 2. 0.21 RR 0.66 (95% CI 0.32 to 1.36) P=0.26	NA 16/6 13/7 10/10 NS	Outcome: D/C due to AE: 1. 4 (1.6%) 2. 8 (3.3%) SAE (includes asthma-related AE): 1. 10% 2. 14%	NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized 1:1 by computerized central randomization and interactive response technology. Performance Bias: (low) patients and investigators remained masked. RES and PBO identical volume and in appearance. Detection Bias: (unclear) Funder's clinical staff masked until analysis; unclear of outcome assessors blinded. Attrition Bias: (low) overall attrition low and similar across groups based on mITT analysis; imputation of missing data unclear for several dropouts. Appropriate statistical tests used. Reporting Bias: (unclear) Funded by Teva. Teva employees were involved in all steps of study design and data analysis and had access to all study data and were involved in writing and publishing of the manuscript. **Applicability**: Patient: extensive and elusive exclusion criteria limits applicability of study results. Intervention: FDA suggested that multiple doses of RES studied in phase 3 trials. Unclear on optimal dose due to lack of dose response data. Comparator: PBO allows investigators to assess efficacy of RES, but a direct comparison with other monoclonal antibodies for severe asthma would be helpful to understand place in therapy Outcomes: clinically significant asthma exacerbation defined as a composite of many outcomes but it is unclear what criteria primarily drove the reduction in exacerbations; no clear dose-response observed across doses. Short study duration. Setting: 128 centers in Asia, Australia, North America, South America, South Africa, and Europe. Only 15% in the US.

2. Castro, et al.[26] MC, DB, PC, RCT Phase 3 Study 3083	1. RES 3 mg/kg IV Q 4 weeks 2. Placebo Duration: 52 weeks	Demographics: Mean age: 48 y Females: 63% White: 73% Chronic OCS: 12% LABA use: 82% Mean ACQ: 2.59 Key Inclusion Criteria: Age 12-75 years blood eosinophil ≥ 400 cells/ µL; ACQ-7 score ≥1.5, at least medium dose ICS, ≥1 exacerbation in year prior Key Exclusion Criteria: Any clinically meaningful comorbidity, other lung disease, current smoker, any inadequately controlled medical factors (diabetes, GERD), pregnant or nursing females, HIV, drug and alcohol abuse.	ITT: 1. 232 2. 232 Attrition: 1. 0 2. 0	Primary Endpoint: Rate of asthma exacerbations per patient per year* 1. 0.86 2. 2.11 RR 0.41 (95% CI 0.28 to 0.59) Patients with ≥ 1 clinical asthma exacerbation (CAE) 1. 59 (25%) 2. 105 (45%) RR 0.56 (95% CI 0.4 to 0.74) Secondary Endpoints: Proportion of patients achieving a 0.5 point reduction in ACQ score from baseline: 1. 178 (77%) 2. 140 (61%) OR 0.4; 95% CI 0.2 to 0.6 Proportion of patients achieving a 0.5 point reduction in AQLQ score from baseline: 1. 74% 2. 64% OR 0.6; 95% CI 0.4 to 1.0) Rate of CAE requiring hospitalization or ER treatment per patient per year: 1. 0.03 2. 0.05 RR 0.69 (95% CI 0.29 to 1.65)	NA 20/5 16/6 NS NS	Outcome: D/C due to AE: 1. 8 (3.4%) 2. 9 (3.9%) SAE (includes asthma-related AE): 1. 8% 2. 10%	NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized 1:1 by computerized central randomization and interactive response technology. Performance Bias: (low) patients and investigators remained masked. RES and PBO identical volume and in appearance. Detection Bias: (unclear) Funder's clinical staff masked until analysis; unclear of outcome assessors blinded. Attrition Bias: (low) overall attrition low and similar across groups based on mITT analysis; imputation of missing data unclear for several dropouts. Appropriate statistical tests used. Reporting Bias: (unclear) Funded by Teva. Teva employees were involved in all steps of study design and data analysis and were involved in writing and publishing **Applicability**: Patient: extensive and elusive exclusion criteria limits applicability of study results. Intervention: FDA suggested that multiple doses of RES studied in phase 3 trials. Unclear on optimal dose. Comparator: PBO allows investigators to assess efficacy of RES, but a direct comparison with other monoclonal antibodies for severe asthma would be helpful to understand place in therapy Outcomes: clinically significant asthma exacerbation defined as a composite of many outcomes but it is unclear what criteria primarily drove the reduction in exacerbations; no clear dose-response observed across doses. Short study duration. Setting: 128 centers in Asia, Australia, North America, South America, South Africa, and Europe. Only 7% in the US.

Abbreviations [alphabetical order]: ACQ = 5-item Asthma Control Questionnaire (scale 0-6); AQLQ = 32-item Asthma Quality of Life Questionnaire (scale 1-7); ARI = absolute risk increase; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; h/o = history of; ICS = inhaled corticosteroid; ITT = intention to treat; IV = intravenous; LABA = Long Acting Beta Agonist; MC = multi-centered; MD = mean difference; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; OCS = oral corticosteroid; OR = odds ratio; PC = placebo-controlled; PBO = placebo; PG = parallel group; PP = per protocol; RR = relative risk; RES = reslizumab; RRR = relative risk reduction; SAE = serious adverse event; y = years; µL = microliters.
*Worsening of asthma that resulted in use of systemic corticosteroids in patients not already receiving treatment, or 2-fold increase in the dose of either ICS or OCS for 3 or more days, or the need for emergency department or hospital admission or unscheduled physician's office visit.

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Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

NUCALA (mepolizumab) for injection, for subcutaneous use
Initial U.S. Approval: 2015

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

NUCALA is an interleukin-5 antagonist monoclonal antibody (IgG1 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. (1)

Limitations of Use:

- Not for treatment of other eosinophilic conditions. (1)
- Not for relief of acute bronchospasm or status asthmaticus. (1)

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

100 mg administered subcutaneously once every 4 weeks. (2)

- See Full Prescribing Information for instructions on reconstitution of lyophilized powder, and preparation and administration of the injection.

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

For injection: 100 mg of lyophilized powder in a single-dose vial for reconstitution. (3)

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

History of hypersensitivity to mepolizumab or excipients in the formulation. (4)

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

- Hypersensitivity reactions (e.g., angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Discontinue NUCALA in the event of a hypersensitivity reaction. (5.1)
- Do not use to treat acute bronchospasm or status asthmaticus. (5.2)
- Herpes zoster infections have occurred in patients receiving NUCALA. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA. (5.3)
- Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decrease corticosteroids gradually, if appropriate. (5.4)
- Treat patients with pre-existing helminth infections before therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue NUCALA until parasitic infection resolves. (5.5)

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

Most common adverse reactions (incidence greater than or equal to 5%) include headache, injection site reaction, back pain, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 11/2015

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

CINQAIR® (reslizumab) injection, for intravenous use
Initial U.S. Approval: 2016

WARNING: ANAPHYLAXIS
See full prescribing information for complete boxed warning.

- **Anaphylaxis occurred with CINQAIR infusion in 0.3% of patients in placebo-controlled studies (5.1)**
- **Patients should be observed for an appropriate period of time after CINQAIR infusion; healthcare professionals should be prepared to manage anaphylaxis that can be life-threatening (5.1)**
- **Discontinue CINQAIR immediately if the patient experiences anaphylaxis (5.1)**

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

CINQAIR is an interleukin-5 antagonist monoclonal antibody (IgG4 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype (1).

Limitations of Use: CINQAIR is **not** indicated for:

- treatment of other eosinophilic conditions (1)
- relief of acute bronchospasm or status asthmaticus (1)

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

- CINQAIR is for intravenous infusion only. Do not administer as an intravenous push or bolus (2.1)
- CINQAIR should be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis (2.2)
- Recommended dosage regimen is 3 mg/kg once every 4 weeks by intravenous infusion over 20-50 minutes (2.1)

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

Injection: 100 mg/10 mL (10 mg/mL) solution in single-use vials (3)

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

Known hypersensitivity to reslizumab or any of its excipients (4)

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

- Malignancy: Malignancies were observed in clinical studies. (5.3)
- Reduction in Corticosteroid Dosage: Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with CINQAIR. Decrease corticosteroids gradually, if appropriate. (5.4)
- Parasitic (Helminth) Infection: Treat patients with pre-existing helminth infections before therapy with CINQAIR. If patients become infected while receiving CINQAIR and do not respond to anti-helminth treatment, discontinue CINQAIR until the parasitic infection resolves. (5.5)

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

The most common adverse reaction (incidence greater than or equal to 2%) includes oropharyngeal pain. (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 03/2016

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

XOLAIR® (omalizumab) for injection, for subcutaneous use
Initial U.S. Approval: 2003

WARNING: ANAPHYLAXIS

See full prescribing information for complete boxed warning.

Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred after the first dose of Xolair but also has occurred beyond 1 year after beginning treatment. Closely observe patients for an appropriate period of time after Xolair administration and be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. (5.1)

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.1) 12/2015

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

Xolair is an anti-IgE antibody indicated for:

- Moderate to severe persistent asthma in patients (12 years of age and above) with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (1.1)
- Chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment (1.2)

Limitations of use:

- Not indicated for other allergic conditions or other forms of urticaria. (1.1, 1.2,)
- Not indicated for acute bronchospasm or status asthmaticus. (1.1, 5.3)

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

For subcutaneous (SC) administration only. (2.1, 2.2)
Divide doses of more than 150 mg among more than one injection site to limit injections to not more than 150 mg per site. (2.4)

- Asthma: Xolair 150 to 375 mg SC every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See the dose determination charts. (2.1)
- Chronic Idiopathic Urticaria: Xolair 150 or 300 mg SC every 4 weeks. Dosing in CIU is not dependent on serum IgE level or body weight. (2.2)

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

- For injection: Lyophilized, sterile powder in a single-use 5mL vial, 150 mg. (3)

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

- Severe hypersensitivity reaction to Xolair or any ingredient of Xolair. (4, 5.1)

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

- Anaphylaxis: Administer only in a healthcare setting prepared to manage anaphylaxis that can be life-threatening and observe patients for an appropriate period of time after administration. (5.1)
- Malignancy: Malignancies have been observed in clinical studies. (5.2)
- Acute Asthma Symptoms: Do not use for the treatment of acute bronchospasm or status asthmaticus. (5.3)
- Corticosteroid Reduction: Do not abruptly discontinue corticosteroids upon initiation of Xolair therapy. (5.4)
- Fever, Arthralgia, and Rash: Stop Xolair if patients develop signs and symptoms similar to serum sickness. (5.6)
- Eosinophilic Conditions: Be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.5)

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

- Asthma: The most common adverse reactions (≥1% more frequent in Xolair-treated patients) in clinical studies were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. (6.1)
- Chronic Idiopathic Urticaria: The most common adverse reactions (≥2% Xolair-treated patients and more frequent than in placebo) included the following: nausea, nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, arthralgia, headache, and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- No formal drug interaction studies have been performed. (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2015

Monoclonal Antibodies for Severe Asthma

Goal(s):

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

Length of Authorization:

Up to 12 months

Requires PA:

- Omalizumab
- Mepolizumab
- Reslizumab

Covered Alternatives:

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

Table 1. Maximum Adult Doses for Inhaled Corticosteroids.

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the claim for reslizumab in a patient under 18 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Is the diagnosis an OHP-funded diagnosis? Note: chronic urticaria is not an OHP-funded condition	**Yes:** Go to #5	**No:** Pass to RPh. Deny; not funded by the OHP.
5. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient required at least 2 hospitalizations or ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, aminophylline, theophylline)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the patient currently receiving another monoclonal antibody for asthma (e.g., omalizumab, mepolizumab or reslizumab)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #9

Approval Criteria		
9. If the claim is for omalizumab, can the prescriber provide documentation of allergic IgE-mediated asthma diagnosis, confirmed by a positive skin test or in vitro reactivity to perennial allergen?	**Yes:** Approve once every 2-4 weeks for up to 12 months. Document test and result:_____	**No:** Go to #10
10. If the claim is for mepolizumab or reslizumab, can the prescriber provide documentation of eosinophilic phenotype, confirmed by blood eosinophil count ≥300 cells/μL in the past 12 months?	**Yes:** Approve once every 4 weeks for up to 12 months. Document eosinophil count (date):_____	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the patient currently taking a maximally-dosed inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, aminophylline, theophylline)?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness.
2. Has the number of ED visits or hospitalizations in the last 12 months been reduced from baseline, or has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *7/16*
Implementation: *TBD*