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

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, November 17, 2016 1:00 - 5:00 PM
HP Conference Room
4070 27th Ct. SE
Salem, OR 97302

MEETING AGENDA

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

	I. CALL TO ORDER	
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. CMS Annual Report	R. Citron (OSU)
	B. Quarterly Utilization Reports	R. Citron (OSU)
	C. ProDUR Report	R. Holsapple (HPE)
	D. RetroDUR Report	T. Williams (OSU)
	E. Oregon State Drug Reviews	K. Sentena (OSU)
	1. Who Benefits from Calcium and Vitamin D Supplementation?	
	2. Pharmacist Prescribed Contraceptives	
	3. Vaccine Update 2016	
	4. Endocrine Therapy for Breast Cancer	
	F. Dose Consolidation Lettering Program	T. Williams (OSU)
	III. DUR NEW BUSINESS	
1:45 PM	A. Synagis® (palivizumab) Drug Policy	D. Engen (OSU)
	1. Prior Authorization Criteria Review	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	
1:50 PM	B. Procysbi® (cysteamine delayed-release) Drug Policy	D. Moretz (OSU)

1. Prior Authorization Criteria Review
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

1:55 PM	C. H.P. Acthar Gel® (repository corticotropin inj) Drug Policy 1. Prior Authorization Criteria Review 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
	IV. PREFERRED DRUG LIST NEW BUSINESS	
2:00 PM	A. Oral Cystic Fibrosis Modulators Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
2:30 PM	B. Opioid Analgesics Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	A. Gibler (OSU)
3:00 PM	BREAK	
3:10 PM	C. Multiple Sclerosis Drug Class Update 1. DERP Summary Review/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
3:30 PM	D. TALTZ (ixekizumab) New Drug Evaluation 1. New Drug Evaluation 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	A. Gibler (OSU)
3:45 PM	E. Non-statin Lipid-lowering Agents Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
4:05 PM	V. EXECUTIVE SESSION	
4:40 PM	VI. RECONVENE for PUBLIC RECOMMENDATIONS	
5:00 PM	VII. 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, September 29, 2016 1:00-5:00 PM
Hewlett-Packard Building
Salem, OR 97302

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: Bill Origer, MD; Tracy Klein, PhD, FNP; Rich Clark, MD, MPH; James Slater, PharmD; Walter Hardin, D.O., MBA; Caryn Mickelson, PharmD; Kelley Burnett, D.O; Cathy Zehrung, RPh; Stacy Ramirez, PharmD

Members Present by Phone:

Staff Present: Andrew Gibler, PharmD; Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD, BCPS; Dee Weston; Dave Engen, PharmD, CGP; Sarah Servid, PharmD; Kim Wentz, MD; Deanna Moretz, PharmD, BCPS; Lindsay Newton; Amber Vester;

Staff Present by Phone: Kathy Sentena, PharmD

Audience: Barrt Benson/Merck; *Brian Carlson/Ipsen; *May Kwong/Janssen; *Anthony Wheeler/Lilly; Venus Holder/Lilly; Teresa Blair/Ipsen; Todd Gavin/Indiveor; Rick Frees/Vemex; Jim Graves/BMS; *Anthony Hager/BMS; Lisa Boyle/WVP Health Authority; Stephanie Yamamoto/Janssen; *Cheri Lindberg/Indiveor; *Margaret Olmon/AbbVie; Cheryl Fletchor/AbbVie; *Raulo Frear/Merck; *Marc Jensen/Pfizer; *Stuart O'Brochta/Gilead; Becky Gonzales/Viiv Healthcare; *Andrea Scherschel/BMS; Emily Church/Salud Medical Center; Cassandra Miller/CareOregon; Tony Koehn/CareOregon; Martha Groeneveld/Synergy Pharma; Jennifer Snidler/SanofiGergne; Wisam Younis/Providence Health Plan; *Rose Mullen/Alkermes; Tim McFerron/Alkermes; *Mary Kemhus/Novartis; Wm Kennon/Primary Health; (Cannot make out name)/Pharmacy Student; Brian Heapde/Abbne; Luis Gonzalez/Salud Medical Center; Dean Haxby/OSU; Kerry Kostman Bonilla/AZ; Allison Naumoski/AZ; Hival Patel/AZ; Amy Burns/AllCare; Melissa Snider/Biomarin; Michael Estoos/Pfizer; *Sara Love/CCO Oregon; Kaysen Bala/Novo Nordisk; *Lorren Sandt; Kristel Jordan; *John McIlveen/OHA; *BJ Caunor/One in Four ChronicHealthy; Kerrie Fowler/Umpqua Health Alliance; *Kent Benner; Amy Bowman/Gilead; Tamatha Tracer/IHN CCO

(*) Provided verbal testimony

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:04 pm. Introductions were made by Committee members and staff.

B. Mr. Citron reported there were no new conflicts of interest to declare.

C. Approval of agenda and July minutes presented by Mr. Citron. (pages 4 - 9)

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

D. Department updates for OHA presented by Dr. Jim Rickards.

II. DUR OLD BUSINESS

A. Botulinum Toxins (page 10)
   1. Approve updated botulinum toxin PA criteria

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

III. PREFERRED DRUG LIST NEW BUSINESS

A. Newer Diabetes Agents Drug Class Update (pages 34 – 47)
   Dr. Sentena presented the class update and following recommendations:

   1. No changes to the PMPDP based on the clinical evidence
   2. Continue current clinical PA criteria
   3. Approve GLP-1 receptor agonist PA modification
   4. Evaluate comparative costs in executive session

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

B. Asthma/COPD Drug Class Update (pages 48 - 82)
   Dr. Sentena presented the scan and the following recommendations:

   1. No changes to the PMPDP based on the clinical evidence
   2. Continue current clinical PA criteria and add “without COPD” to Q#3 in LAMA/LABA criteria
   3. Evaluate comparative costs in executive session

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

C. Biologics Drug Class Update (pages 83 – 117)
   Dr. Gibler presented the scan and following recommendations:

1. DERP Summary Review/Prior Authorization Criteria
2. Approve modifications to Biologics PA criteria and add “biologic” DMARD to Q#13
3. Evaluate comparative costs in executive session

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

D. Substance Use Disorders Class Update (pages 118 – 143)
Dr. Gibler presented the scan and the following recommendations:

1. Approve modifications to buprenorphine & buprenorphine/naloxone products and injectable naltrexone PA criteria. Amend Vivitrol PA length to 6 months and add same PDMP language.
2. Remove buprenorphine sublingual tablets from PMPDP and restrict use to pregnant women and females actively trying to conceive
3. Evaluate comparative costs in executive session

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

E. Class Literature Scans (pages 144 – 155)
Dr. Moretz and Dr. Gibler presented the following scans and recommendations:

1. Growth Hormones Scan
    a. No further research is needed at this time
    b. Maintain current PA criteria
    c. Evaluate comparative costs in executive session
2. Parental Antipsychotics Scan
    a. No further research is needed at this time
    b. Maintain current PA criteria
    c. Evaluate comparative costs in executive session

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

F. Hepatitis C Class Update (pages 156 – 202)
Dr. Herink presented the new drug evaluations and class update along with the following recommendations:

a. Approve recommended fibrosis blood testing-**All in favor**
b. Amend expected survivalfrom non-HCV-associated morbidities from 5 years to 1 year-**Majority not in favor**
c. Allow treatment to F2-**deferred to a future meeting for more discussion**
d. Allow specialist for F2-**deferred to a future meeting for more discussion**
e. Training around F2-**deferred to a future meeting for more discussion**
f. Approve changes to alcohol and SUD criteria-**Majority in favor**
g. Include NS5A polymorphism testing-**All in favor**

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

V. EXECUTIVE SESSION

VI. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. Newer Diabetes Agents Drug Class Update (pages 34 – 47)
***ACTION:** Recommend no changes to the PMPDP
Motion, 2nd, All in Favor. Approved.

B. Asthma/COPD Drug Class Update (pages 48 - 82)
***ACTION:** Make Ipratropium/Albuterol (Combivent Respimat) non-preferred and grandfather current users for 6 months; Make Ventolin HFA preferred on the PMPDP.
Motion, 2nd, All in Favor. Approved.

C. Biologics Drug Class Update (pages 83 – 117)
***ACTION:** Make Canakinumab-pf non-preferred on the PMPDP.
Motion, 2nd, All in Favor. Approved.

D. Substance Use Disorders Class Update (pages 118 – 143)
***ACTION:** Recommend no changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

E. Growth Hormone Scan (pages 144 – 149)
***ACTION:** Make Saizen non-preferred and Genotropin preferred on the PMPDP.
Motion, 2nd, All in Favor. Approved.

F. Parenteral Antipsychotics Scan (pages 150-155)
***ACTION:** Make Abilify Maintena and Aristada preferred on the PMPDP contingent upon executed supplemental rebate contracting.
Motion, 2nd, All in Favor. Approved

G. Hepatitis C Class Update (pages 156 – 202)
***ACTION:** Make Zepatier the preferred regimen for GT1 and GT4, except decompensated; and make Epclusa preferred for GT2 and GT3 on the PMPDP.
Motion, 2nd, All in Favor. Approved

VII. ADJOURN

Drug Use Research & Management Program
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Pharmacy Utilization Summary Report: April 2015 - March 2016

Eligibility	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Avg Monthly
Total Members (FFS & Encounter)	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	1,045,449	1,066,593	1,076,454	1,053,431
FFS Members	130,455	132,476	126,047	135,197	145,013	138,135	143,529	146,793	125,393	132,175	136,513	132,588	135,360
OHP Basic with Medicare	29,480	29,794	29,983	30,262	30,466	30,646	30,825	30,889	30,968	31,349	31,408	31,594	30,639
OHP Basic without Medicare	16,978	16,784	16,112	15,354	14,992	14,714	14,234	14,190	13,045	13,175	12,913	13,091	14,632
ACA	83,997	85,898	79,952	89,581	99,555	92,775	98,470	101,714	81,380	87,651	92,192	87,903	90,089
Encounter Members	950,789	946,363	923,597	894,902	908,964	913,045	912,071	872,206	907,705	913,274	930,080	943,866	918,072
OHP Basic with Medicare	39,566	39,496	39,527	39,574	39,754	39,815	40,037	39,946	39,951	39,907	40,356	40,276	39,850
OHP Basic without Medicare	116,337	113,941	97,164	92,850	90,593	85,877	84,019	73,277	73,440	72,813	72,503	71,622	87,036
ACA	794,886	792,926	786,906	762,478	778,617	787,353	788,015	758,983	794,314	800,554	817,221	831,968	791,185

Gross Cost Figures for Drugs	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	YTD Sum
Total Amount Paid (FFS & Encounter)	$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	$68,669,508	$70,743,134	$76,319,106	$807,576,046
Mental Health Carve-Out Drugs	$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	$11,123,379	$11,458,425	$10,394,145	$131,073,507
OHP Basic with Medicare	$12,864	$11,878	$13,598	$11,082	$8,812	$3,611	$1,048	$778	$1,762	$1,137	$427	$367	$67,363
OHP Basic without Medicare	$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	$4,791,959	$4,967,765	$4,386,778	$59,115,702
ACA	$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	$6,256,573	$6,416,493	$5,943,549	$71,364,748
FFS Physical Health Drugs	$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	$3,188,212	$3,393,454	$3,604,498	$38,629,060
OHP Basic with Medicare	$228,025	$230,736	$232,816	$263,038	$225,706	$218,199	$212,525	$207,563	$211,099	$217,345	$219,277	$230,855	$2,697,184
OHP Basic without Medicare	$1,049,568	$949,612	$1,008,770	$991,645	$989,033	$953,819	$1,045,522	$996,771	$900,139	$960,103	$990,844	$1,031,917	$11,867,742
ACA	$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	$1,911,703	$2,067,953	$2,237,456	$23,068,422
FFS Physician Administered Drugs	$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	$1,803,052	$1,633,654	$1,830,237	$18,855,944
OHP Basic with Medicare	$291,911	$253,746	$267,061	$282,746	$273,243	$276,877	$270,912	$243,594	$316,105	$446,125	$407,852	$524,971	$3,855,142
OHP Basic without Medicare	$406,258	$247,313	$385,423	$244,257	$312,171	$280,485	$240,283	$216,877	$286,929	$294,235	$333,944	$348,587	$3,596,763
ACA	$697,970	$874,688	$728,455	$865,415	$776,570	$699,925	$771,655	$579,491	$526,759	$772,339	$635,533	$679,557	$8,608,356
Encounter Physical Health Drugs	$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	$43,937,904	$45,732,953	$50,858,399	$524,827,999
OHP Basic with Medicare	$275,801	$267,863	$280,483	$202,208	$212,016	$145,132	$152,195	$141,102	$138,151	$121,894	$130,785	$135,689	$2,203,319
OHP Basic without Medicare	$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	$11,862,705	$12,203,935	$13,579,887	$146,895,354
ACA	$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	$31,568,491	$33,021,545	$36,686,363	$372,792,258
Encounter Physician Administered Drugs	$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	$8,616,962	$8,524,648	$9,631,827	$94,189,536
OHP Basic with Medicare	$186,892	$169,577	$164,069	$162,748	$124,937	$169,114	$121,616	$90,054	$138,295	$250,094	$257,772	$199,043	$2,034,210
OHP Basic without Medicare	$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	$1,915,802	$2,194,607	$2,334,465	$25,029,465
ACA	$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	$6,246,768	$5,900,618	$6,912,222	$65,514,218

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: October 19, 2016

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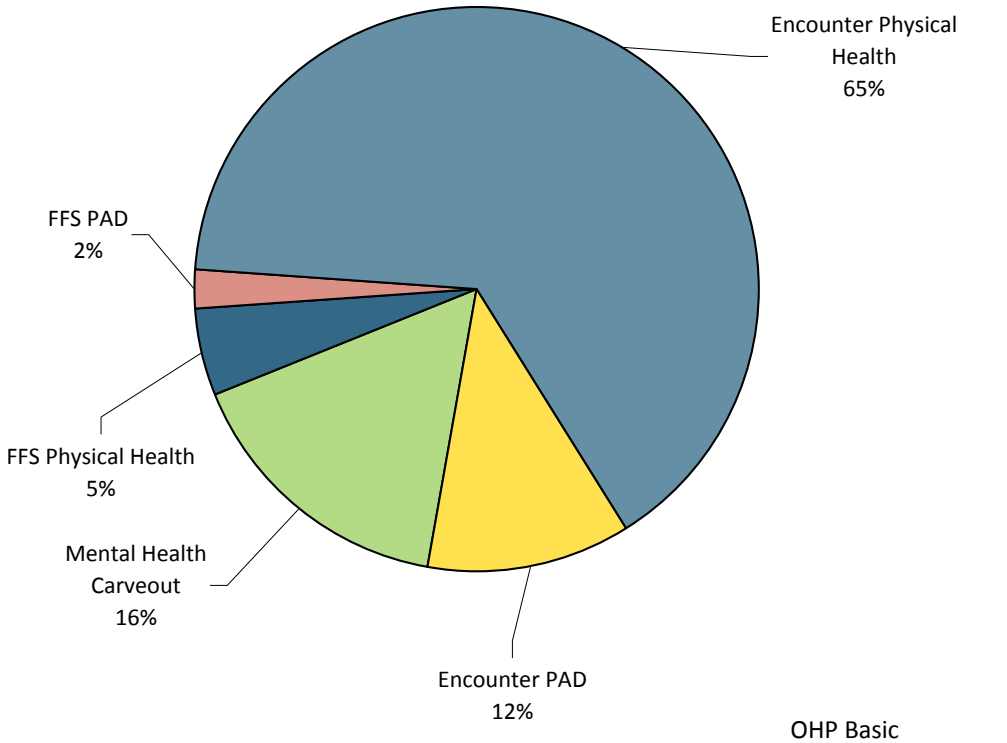
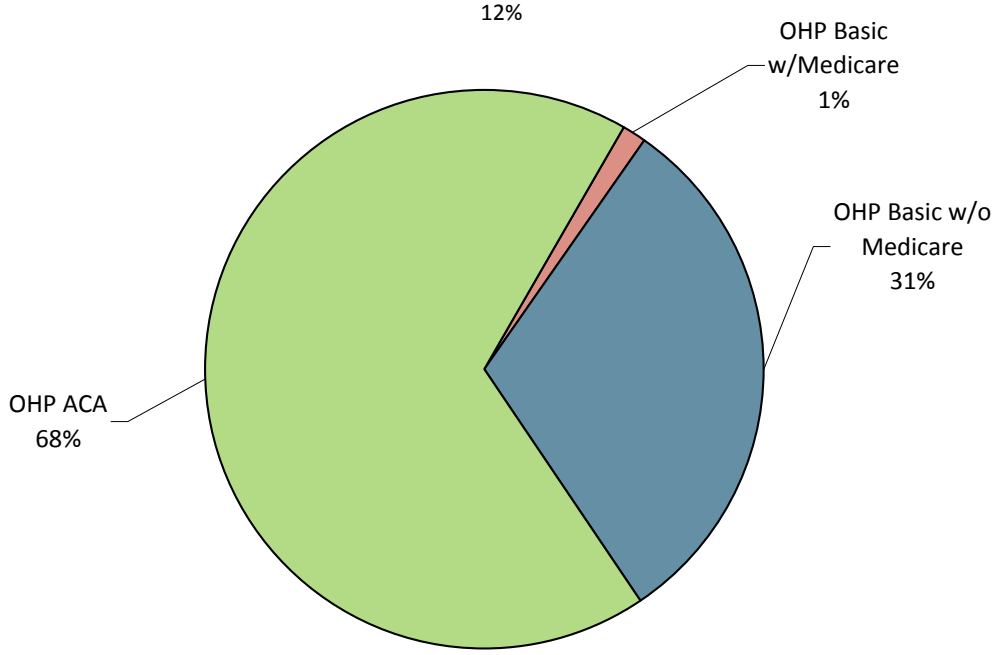
Pharmacy Utilization Summary Report: April 2015 - March 2016

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

Last Updated: October 19, 2016

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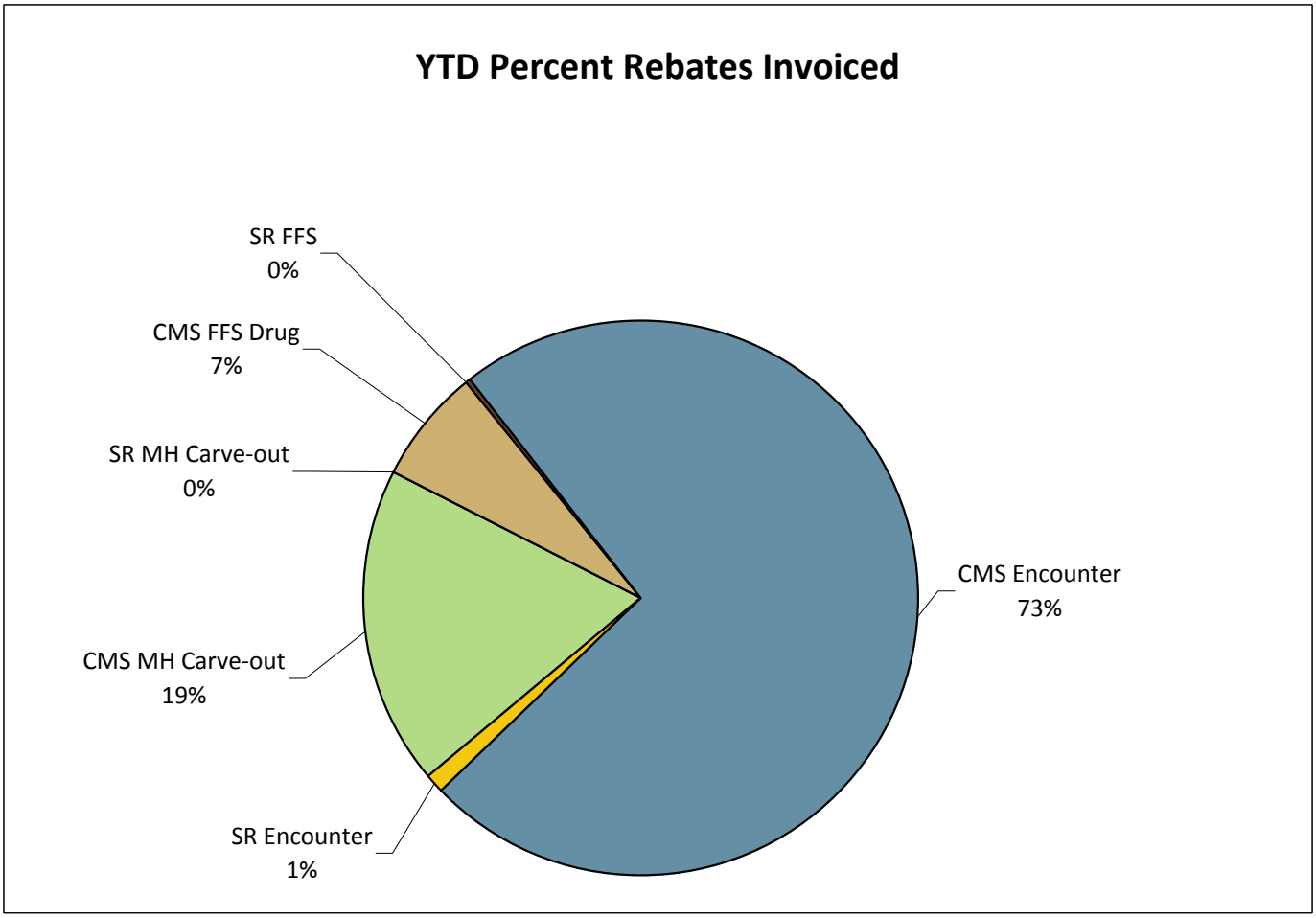
Pharmacy Utilization Summary Report: April 2015 - March 2016

Quarterly Rebates Invoiced	2015-Q2	2015-Q3	2015-Q4	2016-Q1	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$96,619,220	$93,552,958	$96,235,037	$108,879,829	$395,287,044
CMS MH Carve-out	$18,975,370	$17,375,190	$18,188,211	$19,035,117	$73,573,887
SR MH Carve-out					$0
CMS FFS Drug	$6,121,743	$6,157,546	$5,856,800	$7,941,284	$26,077,372
SR FFS	$227,898	$250,196	$334,651	$360,608	$1,173,354
CMS Encounter	$70,093,281	$68,012,508	$70,477,233	$80,958,446	$289,541,468
SR Encounter	$1,200,928	$1,757,518	$1,378,142	$584,374	$4,920,962

Quaterly Net Drug Costs	2015-Q2	2015-Q3	2015-Q4	2016-Q1	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$99,096,781	$103,047,261	$103,293,041	$106,851,919	$412,289,002
Mental Health Carve-Out Drugs	$13,954,327	$14,886,308	$14,718,152	$13,940,833	$57,499,620
FFS Phys Health + PAD	$7,633,009	$7,977,438	$7,472,618	$7,151,214	$30,234,278
Encounter Phys Health + PAD	$77,509,445	$80,183,515	$81,102,272	$85,759,873	$324,555,105



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

Last Updated: October 26, 2016

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Pharmacy Utilization Summary Report: April 2015 - March 2016

PMPM Drug Costs (Rebates not Included)	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$59.73	$59.74	$63.52	$64.17	$61.67	$62.31	$62.95	$62.52	$67.15	$65.68	$66.33	$70.90	$63.89
Mental Health Carve-Out Drugs	$10.46	$9.91	$10.42	$10.50	$10.13	$10.24	$10.34	$10.27	$11.16	$10.64	$10.74	$9.66	$10.37
FFS Physical Health Drugs	$23.53	$21.57	$25.57	$25.74	$20.92	$23.29	$22.99	$22.20	$23.96	$24.12	$24.86	$27.19	$23.83
FFS Physician Administered Drugs	$12.41	$11.87	$13.02	$11.83	$10.93	$10.64	$10.29	$8.86	$10.57	$13.64	$11.97	$13.80	$11.65
Encounter Physical Health Drugs	$42.97	$44.25	$46.58	$47.20	$46.39	$46.66	$47.94	$47.99	$50.62	$48.11	$49.17	$53.88	$47.65
Encounter Physician Administered Drugs	$8.14	$7.88	$8.51	$8.90	$8.29	$8.16	$7.71	$7.83	$8.33	$9.44	$9.17	$10.20	$8.55

Claim Counts	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Avg Monthly
Total Claim Count (FFS & Encounter)	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	1,027,353	1,052,074	1,139,353	1,036,121
Mental Health Carve-Out Drugs	154,149	148,814	152,199	152,180	150,978	151,853	153,828	146,402	157,690	152,943	153,452	164,662	153,263
FFS Physical Health Drugs	70,967	68,496	72,311	73,666	67,651	69,915	72,180	70,902	67,797	68,137	70,586	74,543	70,596
FFS Physician Administered Drugs	14,451	14,173	15,144	15,582	14,583	14,617	13,335	11,850	12,083	18,270	17,698	17,830	14,968
Encounter Physical Health Drugs	737,507	716,143	713,608	692,850	690,397	700,265	718,215	673,982	721,607	697,271	720,931	787,091	714,156
Encounter Physician Administered Drugs	85,933	84,377	84,980	81,171	79,628	79,208	80,309	74,051	72,650	90,732	89,407	95,227	83,139

Amount Paid per Claim (Rebates not Included)	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$60.76	$62.45	$64.22	$65.10	$64.79	$64.48	$64.02	$65.20	$67.23	$66.84	$67.24	$66.98	$64.94
Mental Health Carve-Out Drugs	$73.34	$71.85	$71.83	$71.11	$70.72	$70.88	$70.93	$71.49	$73.11	$72.73	$74.67	$63.12	$71.32
FFS Physical Health Drugs	$43.26	$41.71	$44.58	$47.23	$44.85	$46.02	$45.71	$45.95	$44.31	$46.79	$48.08	$48.35	$45.57
FFS Physician Administered Drugs	$112.00	$110.97	$108.35	$102.63	$108.68	$100.59	$110.78	$109.70	$109.69	$98.69	$92.31	$102.65	$105.59
Encounter Physical Health Drugs	$55.40	$58.47	$60.29	$60.96	$61.08	$60.83	$60.88	$62.11	$63.68	$63.01	$63.44	$64.62	$61.23
Encounter Physician Administered Drugs	$90.04	$88.37	$92.46	$98.10	$94.63	$94.03	$87.56	$92.18	$104.07	$94.97	$95.35	$101.15	$94.41

Amount Paid per Claim - Multi Source Drugs (Rebates not Included)	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$27.64	$28.11	$28.15	$27.85	$27.59	$27.72	$27.59	$27.40	$27.38	$27.25	$27.37	$25.40	$27.45
Mental Health Carve-Out Drugs	$55.49	$54.13	$53.49	$51.87	$51.26	$50.98	$50.72	$51.07	$51.29	$51.56	$51.94	$39.57	$51.11
FFS Physical Health Drugs	$21.54	$21.57	$21.00	$22.13	$21.41	$21.74	$22.54	$21.26	$21.07	$22.17	$21.89	$22.65	$21.75
Encounter Physical Health Drugs	$22.22	$23.16	$23.30	$23.01	$22.84	$23.07	$22.93	$22.72	$22.58	$22.25	$22.52	$22.60	$22.77

Amount Paid per Claim - Single Source Drugs (Rebates not Included)	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$476.20	$498.99	$517.15	$530.56	$524.35	$484.53	$476.63	$515.55	$551.73	$571.36	$572.10	$582.87	$525.17
Mental Health Carve-Out Drugs	$480.88	$478.31	$493.52	$510.14	$514.25	$522.36	$518.39	$521.50	$547.36	$553.03	$577.17	$585.89	$525.23
FFS Physical Health Drugs	$324.16	$302.02	$349.17	$375.40	$353.06	$354.74	$325.34	$359.08	$354.23	$371.21	$383.39	$378.49	$352.53
Encounter Physical Health Drugs	$490.44	$520.58	$537.05	$549.43	$541.70	$491.96	$486.11	$530.33	$569.51	$593.05	$590.01	$601.76	$541.83

Multi-Source Drug Use Percentage	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Avg Monthly
Multi-Source Drug Use Percentage	93.4%	93.4%	93.3%	93.3%	93.2%	92.6%	92.5%	92.8%	93.0%	93.4%	93.3%	93.2%	93.1%
Mental Health Carve-Out Drugs	95.8%	95.8%	95.8%	95.8%	95.8%	95.8%	95.7%	95.7%	95.6%	95.8%	95.7%	95.7%	95.7%
FFS Physical Health Drugs	92.8%	92.8%	92.8%	92.9%	92.9%	92.7%	92.3%	92.7%	93.0%	92.9%	92.8%	92.8%	92.8%
Encounter Physical Health Drugs	92.9%	92.9%	92.8%	92.8%	92.6%	91.9%	91.8%	92.2%	92.5%	92.9%	92.8%	92.7%	92.6%

Preferred Drug Use Percentage	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Avg Monthly
Preferred Drug Use Percentage	86.52%	86.45%	86.48%	86.33%	86.45%	86.45%	86.80%	86.84%	86.74%	86.61%	86.85%	87.01%	86.6%
Mental Health Carve-Out Drugs	76.81%	76.71%	76.57%	76.24%	76.38%	76.26%	76.12%	76.10%	76.20%	76.25%	75.91%	77.59%	76.4%
FFS Physical Health Drugs	94.61%	94.59%	94.89%	95.23%	95.40%	95.42%	95.17%	95.84%	95.57%	95.45%	95.37%	95.38%	95.2%
Encounter Physical Health Drugs	87.82%	87.74%	87.79%	87.54%	87.71%	87.72%	88.19%	88.15%	88.12%	87.95%	88.29%	88.14%	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: October 19, 2016

Drug Use Research & Management Program
DHS - Division of Medical Assistance Programs
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Top 40 Drugs by Gross Amount Paid (FFS Only) - Third Quarter 2016

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$3,430,924	9.2%	3,622	$947	V
2	STRATTERA	ADHD Drugs	$1,930,210	5.2%	4,580	$421	Y
3	SEROQUEL XR	Antipsychotics, 2nd Gen	$1,842,229	5.0%	2,877	$640	V
4	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$1,562,504	4.2%	12,369	$126	V
5	INVEGA SUSTENNA	Antipsychotics, Parenteral	$1,358,251	3.7%	842	$1,613	V
6	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$697,417	1.9%	1,160	$601	V
7	DULOXETINE HCL	Antidepressants	$630,780	1.7%	25,614	$25	V
8	FLUOXETINE HCL	Antidepressants	$626,859	1.7%	30,306	$21	Y
9	HARVONI	Hepatitis C, Direct-Acting Antivirals	$581,201	1.6%	21	$27,676	Y
10	ABILIFY MAINTENA	Antipsychotics, Parenteral	$577,268	1.6%	356	$1,622	V
11	SAPHRIS	Antipsychotics, 2nd Gen	$541,454	1.5%	903	$600	V
12	PRISTIQ ER	Antidepressants	$485,159	1.3%	1,596	$304	V
13	BUPROPION XL	Antidepressants	$461,555	1.2%	17,845	$26	V
14	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$445,473	1.2%	1,379	$323	V
15	SERTRALINE HCL	Antidepressants	$430,524	1.2%	37,863	$11	Y
16	RISPERDAL CONSTA	Antipsychotics, Parenteral	$411,842	1.1%	504	$817	Y
17	TRAZODONE HCL	Antidepressants	$383,212	1.0%	35,784	$11	
18	VENLAFAXINE HCL ER	Antidepressants	$366,692	1.0%	1,921	$191	V
19	DIVALPROEX SODIUM ER	Antiepileptics (oral & rectal)	$362,265	1.0%	4,193	$86	Y
20	AMITRIPTYLINE HCL	Antidepressants	$306,989	0.8%	16,160	$19	Y
21	LANTUS	Diabetes, Insulins	$303,954	0.8%	883	$344	Y
22	VIIBRYD	Antidepressants	$297,961	0.8%	1,340	$222	V
23	INVEGA TRINZA	Antipsychotics, Parenteral	$294,447	0.8%	61	$4,827	V
24	LAMOTRIGINE	Antiepileptics (oral & rectal)	$292,065	0.8%	20,542	$14	Y
25	CITALOPRAM HBR	Antidepressants	$269,135	0.7%	27,721	$10	Y
26	VENLAFAXINE HCL ER	Antidepressants	$246,421	0.7%	14,367	$17	Y
27	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$240,655	0.6%	13,513	$18	
28	ENBREL	Biologics for Autoimmune Conditions	$238,644	0.6%	71	$3,361	Y
29	REXULTI	Antipsychotics, 2nd Gen	$234,145	0.6%	236	$992	V
30	ESCITALOPRAM OXALATE	Antidepressants	$233,897	0.6%	19,238	$12	Y
31	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$224,271	0.6%	556	$403	Y
32	BUPROPION HCL SR	Antidepressants	$218,602	0.6%	11,023	$20	Y
33	QUETIAPINE FUMARATE	Antipsychotics, 2nd Gen	$210,062	0.6%	12,409	$17	Y
34	HUMIRA PEN	Biologics for Autoimmune Conditions	$206,868	0.6%	55	$3,761	Y
35	Infliximab Injection	Physican Administered Drug	$198,108	0.5%	97	$2,042	
36	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$194,865	0.5%	3,351	$58	Y
37	METHYLPHENIDATE ER	ADHD Drugs	$192,285	0.5%	1,526	$126	N
38	TRINTELLIX	Antidepressants	$190,973	0.5%	593	$322	V
39	VRAYLAR	Antipsychotics, 2nd Gen	$182,134	0.5%	191	$954	V
40	CLOZAPINE	Antipsychotics, 2nd Gen	$175,786	0.5%	3,059	$57	Y
		Top 40 Aggregate:	**$22,078,084**		**330,727**	**$1,341**	
		All FFS Drugs Totals:	**$37,170,188**		**675,268**	**$424**	

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: October 19, 2016

ProDUR Report for July through September 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	31	9	0	22	0.00%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,083	292	1	790	1.47%
DD (Drug/Drug Interaction)	Set alert/Pay claim	146	42	0	104	0.17%
ER (Early Refill)	Set alert/Deny claim	49,303	10,801	67	38,415	68.97%
ID (Ingredient Duplication)	Set alert/Pay claim	14,350	4,278	18	10,032	20.07%
LD (Low Dose)	Set alert/Pay claim	564	126	0	437	0.73%
LR (Late Refill/Underutilization)	Set alert/Pay claim	3	2	0	2	0.00%
MC (Drug/Disease Interaction)	Set alert/Pay claim	496	127	0	369	0.67%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	868	264	5	594	1.17%
PG (Pregnancy/Drug Interaction)	Set alert/Deny claim	16	8	0	8	0.00%
TD (Therapeutic Duplication)	Set alert/Pay claim	4,566	1,448	0	3,111	6.37%
	Totals	**71,426**	**17,397**	**91**	**53,884**	**99.60%**

ProDUR Report for July through September 2016

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
DC	Diazepam	150	36	114	6,384	2.3%	24.0%
	Haloperidol	399	99	300	2,064	19.3%	24.8%
	Wellbutrin (Bupropion)	1,392	282	1,110	26,691	5.2%	20.3%
DD	Geodon (Ziprasidone)	126	33	93	3,279	3.8%	26.2%
ER	Remeron (Mirtazapine)	1,803	291	1,512	6,402	28.2%	16.1%
	Hydrocodone/APAP	255	81	174	4,014	6.4%	31.8%
	Oxycodone	354	126	228	3,627	9.8%	35.6%
	Lorazepam	2,187	594	1,593	14,691	14.9%	27.2%
	Alprazolam	1,638	324	1,314	11,112	14.7%	19.8%
	Lamictal (Lamotrigine)	6,294	1,263	5,031	21,090	29.8%	20.1%
	Abilify (Aripiprazole)	3,795	783	3,012	13,431	28.3%	20.6%
	Seroquel (Quetiapine)	4,494	939	3,552	14,952	30.1%	20.9%
	Risperdal (Risperidone)	3,294	708	2,586	10,080	32.7%	21.5%
	Wellbutrin (Bupropion)	6,045	987	5,058	26,691	22.6%	16.3%
	Zoloft (Sertraline)	7,869	1,494	6,375	31,905	24.7%	19.0%
	Prozac (Fluoxetine)	5,916	1,041	4,875	25,215	23.5%	17.6%
	Celexa (Citalopram)	4,665	726	3,939	22,035	21.2%	15.6%
	Trazodone	7,722	1,368	6,354	30,144	25.6%	17.7%
	Cymbalta (Duloxetine)	5,097	870	4,227	21,450	23.8%	17.1%
ID	Lamictal (Lamotrigine)	2,178	654	1,524	21,090	10.3%	30.0%
	Seroquel (Quetiapine)	2,025	603	1,419	14,952	13.5%	29.8%
	Abilify (Aripiprazole)	798	363	735	13,431	5.9%	45.5%
	Risperdal (Risperidone)	1,440	375	1,065	10,080	14.3%	26.0%
	Zoloft (Sertraline)	1,677	438	1,236	31,905	5.3%	26.1%
	Prozac (Fluoxetine)	1,641	417	1,224	25,215	6.5%	25.4%
TD	Lamictal (Lamotrigine)	1,011	327	684	21,090	4.8%	32.3%
	Depakote (Divalproex Sodium)	582	180	402	9,132	6.4%	30.9%
	Seroquel (Quetiapine)	1,212	396	813	14,952	8.1%	32.7%
	Zyprexa (Olanzapine)	705	147	558	9,024	7.8%	20.9%

ProDUR Report for July through September 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)	1,803	291	6,402	6	33	84	0	168	0
	Hydrocodone/APAP	255	81	4,014	3	0	30	0	48	0
	Oxycodone	354	126	3,627	0	3	60	3	60	0
	Lorazepam	2,187	594	14,691	45	12	222	0	315	0
	Alprazolam	1,638	324	11,112	33	21	96	0	174	0
	Lamictal (Lamotrigine)	6,294	1,263	21,090	84	72	429	0	678	0
	Abilify (Aripiprazole)	3,795	783	13,431	72	66	168	0	477	0
	Seroquel (Quetiapine)	4,494	939	14,952	36	78	291	0	534	0
	Risperdal (Risperidone)	3,294	708	10,080	33	39	192	6	438	0
	Wellbutrin (Bupropion)	6,045	987	26,691	93	132	246	0	516	0
	Zoloft (Sertraline)	7,869	1,494	31,905	165	141	609	3	576	0
	Prozac (Fluoxetine)	5,916	1,041	25,215	90	81	339	0	531	0
	Celexa (Citalopram)	4,665	726	22,035	93	120	228	0	285	0
	Trazodone	7,722	1,368	30,144	72	111	576	3	606	0
	Cymbalta (Duloxetine)	5,097	870	21,450	75	87	291	0	417	0

Drug Use Research & Management Program
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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	15
		Profiles Sent	10	18	7	7
		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

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Retro-DUR Intervention History by Quarter FFY 2015 - 2016

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

Oregon State University
College of Pharmacy

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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%	1,065	2,398	44%			
Five or more concurrent psychotropics	188	10,624	2%	202	11,375	2%	184	10,708	2%			
Three or more concurrent psychotropics	1,985	10,624	19%	1,989	11,375	17%	2,003	10,708	19%			
Two or More Concurrent Antipsychotics	97	10,624	1%	79	11,375	1%	80	10,708	1%			
Under 18 years old on any antipsychotic	2,419	10,624	23%	2,477	11,375	22%	2,414	10,708	23%			
Youth five years and younger on psychotropics	143	10,624	1%	163	11,375	1%	146	10,708	1%			

11/14/2016

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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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%	302	493	61%			
Five or more concurrent psychotropics	31	2,138	1%	41	2,648	2%	31	2,449	1%			
Three or more concurrent psychotropics	332	2,138	16%	357	2,648	13%	359	2,449	15%			
Two or More Concurrent Antipsychotics	17	2,138	1%	18	2,648	1%	17	2,449	1%			
Under 18 years old on any antipsychotic	442	2,138	21%	499	2,648	19%	480	2,449	20%			
Youth five years and younger on psychotropics	35	2,138	2%	39	2,648	1%	37	2,317	2%			

11/14/2016

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

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Who Benefits from Calcium and Vitamin D Supplementation

By Kathy Sentena, Pharm.D, OSU College of Pharmacy Drug Use Research and Management

The use of calcium and vitamin D products in Oregon fee-for-service patients account for over 44,000 claims annually.[1] Suggestion of benefit for many common disorders, from depression to cancer, have led to increased utilization of both supplements. As with any supplement or medication, prudent use should be supported by evidence of benefit. Additionally, the financial implications of the high utilization of calcium and vitamin D requires justification. This newsletter will examine the evidence of benefits and harms associated with calcium and vitamin D products and offer suggestions for optimal use.

Background - Calcium is important for adequate bone formation with a suggested recommended daily allowance (RDA) of 700-1,300 mg daily, depending on age.[2,3] Calcium is prevalent in many foods and adequate RDAs may be met through diet alone. If supplementation is required, calcium supplements should be dosed based on elemental calcium. The National Osteoporosis Foundation endorses the Institute of Medicine (IOM) recommendations of 1,000 mg daily of calcium for men aged 51-70 years and 1,200 mg daily for men 71 years and older and for women 51 years and older.[3] The World Health Organization (WHO) recommends 1,500-2,000 mg of calcium daily for pregnant women.[4]

Vitamin D is needed for intestinal absorption of calcium and phosphorous.[5] Vitamin D is produced in the skin as vitamin D3 through exposure to sunlight; alternatively, vitamin D can be supplemented as vitamin D_3 (cholecalciferol), vitamin D_2 (ergocalciferol) or obtained through diet (oily fish, etc.).[2] Absorption of vitamin D can vary depending on several factors.[2,4] The U.S. Preventative Services Task Force (USPSTF) recommends against routine screening of asymptomatic adults, but other guidelines recommend screening individuals at high risk for vitamin D deficiency.[5,7] Low sun exposure, obesity, fat malabsorption syndromes, bariatric patients, nephrotic syndrome, certain medications and endocrine disorders increase the risk of vitamin D deficiency.[5] There is no consensus on optimal vitamin D levels and commonly used assays have high levels of variability.[8] The IOM recommends a serum 25-hydroxyvitamin D [25(OH)D] level of ≥20 ng/mL for adequate bone health.[3] However, the Endocrine Society, National Osteoporosis Foundation and International Osteoporosis Foundation suggest 25(OH)D levels of ≥30 ng/mL.[5] Recommended vitamin D intake via diet and/or supplementation is presented in Table 1.[5]

Table 1. Recommended Vitamin D Intake by Age*[5]

Population			
1-70 years	≥ 600 IU	Over 70 years	≥ 800 IU
Risk of Deficiency			
0-1 years	400 – 1,000 IU	19-50 years	1,500 – 2,000 IU
1-18 years	600 - 1,000 IU	>50 years	1,500 – 2,000 IU
Pregnant or Lactating		600 - 2000 IU	
Vitamin D Deficient			
1-18 years	Treatment: 2,000 IU/day or 50,000 IU D_2 once weekly for 6 weeks Maintenance: 600 - 1,000 IU/day		
> 18 years	Treatment: 6,000 IU/day or 50,000 IU D_2 or D_3 once weekly for 8 weeks Maintenance: 1,500 - 2,000 IU/day		
* Daily dose unless otherwise stated / IU - International Units			

CALCIUM

Bone – The benefits of calcium supplementation on bone health have recently been evaluated. A high-quality systematic review (n=26 trials) with meta-analysis found supportive evidence for the use of calcium supplementation in elderly women. There was a lower risk of total body fractures (any non-vertebral fractures) versus control groups (11% vs. 12%, respectively; relative risk [RR] 0.89; 95% CI, 0.81 to 0.96; P=0.004) and fewer vertebral fractures versus controls (1.3% vs. 1.5%, respectively; RR 0.86; 95% CI, 0.74 to 1.00; P=0.04) regardless of calcium dose.[9] No benefit was seen in hip or forearm fractures. Calcium with vitamin D had similar results as calcium monotherapy. Studies of dietary calcium (milk powder and hydroxyapatite) had no effect on fracture rates.[9] A second systematic review (n=59 trials) of women under 70 years of age found bone mineral density (BMD) increased by 0.7-1.8% in the hip, lumbar spine, femoral neck, forearm and total body with calcium supplementation dosed 250-2,500 mg daily.[5] In contrast, anti-resorptive therapy (e.g., bisphosphonates) increased BMD by 6-9% over 3 years.[5]

Pregnancy - Calcium has been thought to lower the risk of pre-eclampsia, pre-term birth and blood pressure in pregnant women. A systematic review of 13 trials (n=15,730) found moderate evidence that calcium supplementation (≥1 g/day) decreases the risk of pre-eclampsia during pregnancy (RR 0.45; 95% CI, 0.31 to 0.65), with an incidence rate of 65/1000 in controls (placebo or no treatment) compared to 29/1000 in women treated with calcium.[10] The greatest benefits were seen in women with diets low in calcium and women who had a high risk of pre-eclampsia. Calcium supplementation was also found to reduce the risk of hypertension in this population compared to placebo (RR 0.65; 95% CI, 0.53 to 0.81) as well as decrease the incidence of pre-term birth (79/1000 vs. 104/1000, respectively; RR 0.76; 95% CI, 0.60 to 0.97).[10] However, calcium supplementation did not reduce the occurrence of pre-term birth in women not at increased risk for pre-eclampsia.[11]

VITAMIN D

Bone – Evidence suggests that vitamin D has limited benefit for fracture prevention. A Cochrane Review found vitamin D alone, compared to control (placebo, no intervention or calcium alone), does not prevent hip fractures (RR 1.12; 95% CI, 0.98 to 1.29) or new bone fractures (RR 1.03; 95% CI 0.96 to 1.11) in trials of predominately elderly women.[12] These results were supported by the USPSTF which found insufficient evidence to determine the benefits and harms of vitamin D_3 400 IU or more and calcium 1000 mg or more. Doses of vitamin D_3 400 IU or less and calcium 1000 mg or less were not found to be beneficial for primary prevention of fractures in postmenopausal women.[7]

Falls - There is evidence of fall prevention with vitamin D supplementation. Vitamin D doses of 400-1000 IU were found to decrease the number of falls compared to placebo (41.6% vs. 55.8%, respectively; RR 0.66; 95% CI, 0.50 to 0.88) in elderly women.[13] Limited evidence suggests an increased risk of falls with high doses (500,000 IU annually and >24,000 IU monthly) of vitamin D.[14,15] The USPSTF concluded that for patients 65 years and older at risk of falls, vitamin D supplementation may be beneficial for fall prevention.[7,13]

Cancer - Evidence from a systematic review and meta-analysis in primary and secondary prevention patients (n=50,623) that were cancer-free at study initiation found no benefit of vitamin D supplementation compared to placebo on cancer rates.[16] A modest 0.4% reduction in cancer-related mortality was found with vitamin D supplementation compared to controls (2.5% vs. 2.9%, respectively; RR 0.94; 95% CI, 0.91 to 0.98; p=0.002).[16]

Mortality – The evidence on the ability of vitamin D to reduce mortality has been inconsistent. The USPSTF found no significant effect of vitamin D on mortality compared to placebo (RR 0.83; 95% CI, 0.73 to 1.18).[13]This finding was substantiated by a second meta-analysis of high dose or intermittent dose vitamin D.[17] A Cochrane review found a 0.2% reduction in mortality with vitamin D supplementation, however, high levels of attrition cause concern over the reliability of the findings.[18]

Additional trial data found no beneficial effect of vitamin D for the following conditions: cystic fibrosis, pain scores, depression, systolic or diastolic blood pressure, asthma symptoms in children, and A1C in type 2 diabetes.[18-26] Outcomes related to pregnancy, such as pre-eclampsia and gestational diabetes were also not reduced by vitamin D supplementation.[27,28]

Harms of Calcium and Vitamin D - A recent retrospective review looked at emergency department (ED) visits related to dietary supplements.[29] Data was analyzed from 63 U.S. hospitals from 2004 to 2013. Deaths were not tracked

due to differences in reporting practices. Over 23,000 ED visits were identified. Of those, 32% were related to micronutrients. Calcium was associated with 3.4% (95% CI, 2.5% to 4.3%) of visits. In patients 65 years and older, iron, calcium and potassium accounted for one-third of all ED visits related to supplements. Visits due to calcium were primarily related to swallowing difficulties (combination of choking and pill-induced dysphagia or globus).[29]

A report by Canadian Agency for Drugs and Health Technologies in Health (CADTH) evaluated toxicities with vitamin D regimens.[30] Three systematic reviews, 24 randomized controlled trials (RCTs) and 6 non-randomized trials were evaluated. Hypercalcemia and hypercalciuria were the most commonly reported adverse events and nephrolithiasis was the most common kidney-related event. Combination therapy with calcium, hydrochlorothiazide or high dose vitamin D (>50,000 IU) were most notably associated with these adverse events. Reports of increased risk of prostate cancer and vitamin D supplementation have been reported but there is very limited evidence of this association.[30] Vitamin D regimens dosed less than 50,000 IU appear to be safe. Additional evidence found 25(OH)D levels greater than 50 ng/mL may be associated with a higher risk of mortality, cardiovascular disease, cancer and falls.[7] A second CADTH report found no link between combination calcium and vitamin D supplements and an increased risk of cardiovascular disease.[31]

OHP Recommendations - In March of 2016 the Oregon Health Plan (OHP) Pharmacy and Therapeutics Committee recommended vitamin D and calcium supplements be covered only for patients who are pregnant, have a nutrient deficiency, have a diagnosis of osteoporosis, or are 65 years of age or older and at increased risk for falls.[32] Evidence so far indicates these populations may benefit from supplementation with calcium and vitamin D. Additionally, it is recommended that patients receive a 90-day supply of these supplements to minimize the time and expense of multiple fills.

Peer Reviewed By: Robert Hughes, DO, Samaritan Family Medicine Resident Clinic and Nanette Bultemeier, Pharm D, Clinical Pharmacy Specialist, Providence Medical Group

References:

1. Drug Use Research and Management Program. Calcium/Vit D replacement, oral. Q1 2016 Market Share Report: fee-for-service claims. Accessed June 2, 2016.
2. Tai V, Leung W, Grey A, et al. Calcium intake and bone mineral density: systematic review and meta-analysis. *BMJ*. 2015;351:h4183. Doi: 10.1136/bmj.h4183.
3. Food, Nutrition Board. Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington DC: National Academy Press, 2010.
4. WHO. Guideline: Calcium supplementation in pregnant women. Geneva, World Health Organization, 2013.
5. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930. Doi: 10.1210/jc.2011-0385.
6. Perez-Lopez F, Pasupuleti V, Mezones-Holguin E, et al. Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized clinical trials. *Fertility and Sterility*. 2015;103 (5).
7. LeFevre ML; U.S. Preventive Services Task Force. Screening for vitamin D deficiency in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2015 Jan 20;162(2):133-40. doi: 10.7326/M14-2450.
8. Reid I, Bolland M, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. *Lancet* 2014;383:146-55.
9. Bolland M, Leung W, Tai V, et al. Calcium intake and risk of fracture: systematic review. *BMJ* 2015;351:h4580. Doi: 10.1136/bmj.h4580.
10. Hofmeyer GJ, Lawrie TA, Atallah AN, et al. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database of Systematic Reviews* 2014, Issue 6. Art. No.: CD001059. Doi: 10.1002/14651858.CD001059.pub4.
11. Buppasiri P, Lumbiganon P, Thinkhamrop J, et al. Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes. *Cochrane Database of Systematic Reviews* 2015, Issue 2. Art. No.: CD007079. Doi: 10.1002/14651858.CD007079.pub3.
12. Avenell A, Mak J, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: CD000227. Doi: 10.1002/14651858.CD000227.pub4.
13. LeBlanc E, Chou R, Zakher B, et al. Screening for vitamin D deficiency: systematic review for the U.S. Preventative Services Task Force Recommendation. Evidence Synthesis No.119. AHRQ Publication No. 13-05183-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2014
14. Bischoff-Ferrari H, Dawson-Hughes B, Orav J, et al. Monthly high-dose vitamin d treatment for the prevention of functional decline. JAMA Intern Med. 2016;176:175-183. Doi: 10.100/jamainternmed.2015.7148.
15. Sanders K, Stuart A, Williamson E, et al. Annual high-dose oral vitamin d and falls and fractures in older women. JAMA. 2010;303:1815-1822.
16. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of cancer in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 6. Art. No.: CD007469. Doi: 10.1002/14651858.CD007469.pub2.
17. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 1. Art. No.: CD007470. Doi: 10.1002/14651858.CD007470.pub3.
18. Ferguson JH, Chang AB. Vitamin D supplementation for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2014, Issue 5. Art. No.: CD007298. Doi: 10.1002/14651858.CD007298.pub4.
19. Gowda U, Mutowo M, Smith B, et al. Vitamin D supplementation to reduce depression in adults: meta-analysis of randomized controlled trials. *Nutrition*. 2015;31:421-429.
20. Zheng YT, Cui QQ, Hong YM, et al. A meta-analysis of high dose, intermittent vitamin D supplementation among older adults. *PLoS ONE*. 2015;10 (1):e0115850. Doi: 10.1371/journal.pone.0115850.
21. Straube S, Derry S, Straube C, et al. Vitamin D for the treatment of chronic painful conditions in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 5. Art. No.:CD007771. Doi: 10.1002/14651858.CD007771.pub3.
22. Gowda U, Mutowo M, Smith B, et al. Vitamin D supplementation to reduce depression in adults: meta-analysis of randomized controlled trials. *Nutrition*. 2015;31:421-429.
23. Beveridge L, Struthers A, Khan F, et al. Effect of vitamin D supplementation on blood pressure. *JAMA Intern Med*. 2015;175:745-754.
24. Krul-Poel Y, Westra S, Boekel E, et al. Effect of vitamin D supplementation on glycemic control in patients with type 2 diabetes (SUNNY trial): a randomized placebo-controlled trial. *Diabetes Care*. 2015;38:1420-1426. Doi: 10.2337/dc15-0323.
25. Litonjua A, Carey V, Laranjo N, et al. Effect of prenatal supplementation with vitamin D on asthma or recurrent wheezing in offspring by age 3 years. *JAMA*. 2016;315:362-370. Doi: 10.1001/jama.2015.18589.
26. Chawes B, Bonnelykke K, Stokholm J, et al. Effect of vitamin D3 supplementation during pregnancy on risk of persistent wheeze in the offspring. *JAMA*. 2016;315:353-361. Doi: 10.1001/jama.2015.18318.
27. De-Regil LM, Palacios C, Lombardo LK, et al. Vitamin D supplementation for women in pregnancy. *Cochrane Database of Systematic Reviews*. 2016, Issue 1. Art. No.: CD008873. Doi: 10.1002/14651858.CD008873.pub3.
28. Perez-Lopez F, Pasupuleti V, Mezones-Holguin E, et al. Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized clinical trials. *Fertility and Sterility*. 2015;103 (5).
29. Geller A, Shehab N, Weidel N, et al. Emergency department visits for adverse events related to dietary supplements. *N Eng J Med*. 2015; 373:1531-40. Doi: 10.1056/NEJMsa1504267.
30. Canadian Agency for Drugs and Technologies in Health. Vitamin D toxicity associated with different vitamin D dosing regimens: safety. Rapid Response Report: Summary of Abstracts. December 2, 2014. Available at: https://www.cadth.ca/sites/default/files/pdf/htis/dec-2014/RA0716%20Vitamin%20D%20Toxicity%20Final.pdf. Accessed June 3, 2016.
31. Canadian Agency for Drugs and Technologies in Health. Calcium and vitamin D for falls and osteoporosis prevention: safety. Rapid Response Report: Summary of Abstracts. August 19, 2011. Available at: https://www.cadth.ca/sites/default/files/pdf/htis/aug-2011/RB0407_Calcium_and_cardiac_risk_final.pdf. Accessed June 3, 2016.
32. Drug Use Research and Management Programs. Class update: calcium and vitamin D products. Oregon drug use review/Pharmacy and Therapeutics Committee Meeting. March 31, 2016. Available at: http://www.orpdl.org/durm/meetings/meetingdocs/2016_03_31/finals/2016_03_31_PnT_Complete.pdf. Accessed June 6, 2016.

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Pharmacist Prescribed Contraceptives

By Fiona Karbowicz, R.Ph. Pharmacist Consultant, Oregon Board of Pharmacy

Have you heard of House Bill 2879? It is a new law in Oregon that has already impacted hundreds of women and pharmacist providers in our state since its implementation on January 1, 2016.[1] This law allows pharmacists in Oregon to prescribe and dispense oral contraceptives or contraceptive patches to eligible women. State Representative Knute Buehler, a physician from Bend, conceptualized this law as a way of improving access to contraceptive care for women while leveraging the availability, knowledge, and unique skills of pharmacists. Pharmacist healthcare professionals have years of educational and clinical training related to pharmacology and pharmacotherapy, are recognized by the state as healthcare providers, but do not have broad prescribing privileges. Additionally, local pharmacies are present throughout our communities and often provide longer hours of access and availability than traditional medical clinics, creating a unique method of access.

The Oregon Board of Pharmacy partnered with members from the Oregon Medical Board, the Oregon State Board of Nursing, the Oregon Health Authority, and several women's healthcare clinicians to create the standard procedures for pharmacists to prescribe contraceptives. The end result was the creation of a standard procedures algorithm, which considers the American Congress of Obstetricians and Gynecologists (ACOG) position, in conjunction with the utilization of the Centers for Disease Control and Prevention (CDC) United States Medical Eligibility Criteria for Contraceptive Use (US MEC).[2,3] The US MEC provides guidance on the safety of contraceptive method use for women with specific characteristics and medical conditions.[3]

Changing of prescribing laws have been a result of providers believing that women should have greater access to contraception. In the United States almost 50% of pregnancies are unintended.[4] Additionally, there were 700,000 legal abortions performed in 2012.[4] Many physician groups support the concept of over-the-counter (OTC) access to contraception. The use of OTC contraception has been documented in the literature and determined to be safe.[5] However, contraception is not yet available OTC and the ability of the pharmacist to prescribe contraception will hopefully decrease unintended pregnancies and abortions.

Requirements of Pharmacists

In order to prescribe hormonal contraceptive therapy, a pharmacist must complete a one-time educational training program that refreshes a pharmacist's knowledge on important components of prescribing contraception. Currently there is only one program approved by the Oregon Board of Pharmacy and is offered through Oregon State University.[1] The 5-hour training program can be completed online for a fee of $250.[6]

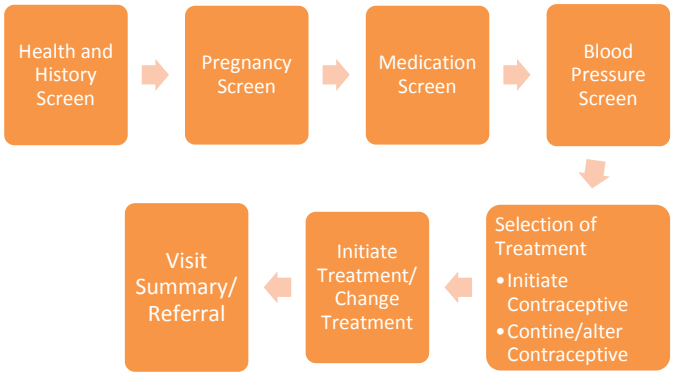
The Comprehensive Contraceptive Education and Training for Prescribing Pharmacists program is comprised of the following objectives:[6]

- Counseling women on the most appropriate and effective contraceptive method
- A comprehensive review of hormonal contraceptives, including the following:
  - Mechanism of action
  - Doses
  - Adverse reactions
  - Benefits
  - Harms
- Patient Education
  - Adherence
  - Missed doses
  - Drug interactions
  - Adverse reactions
- Training on the use of the self-assessment questionnaire as it is related to the US MEC
- Assessment of women's risk for the appropriateness of contraceptive therapy
- When to refer women to health provider
- Incorporation of hormonal contraceptive prescribing by pharmacist into a community or ambulatory care setting

Algorithm for Contraceptive Prescribing

Pharmacists trained to prescribe contraceptives are required to use the Standard Procedures Algorithm for Oregon RPh Prescribing of Contraceptives.[1] The algorithm consist of 7 steps. A simplified algorithm is presented in Figure 1.

Figure 1. Pharmacists Prescribing Algorithm[1]



In general, pharmacists are advised against prescribing contraceptives to women in which pregnancy cannot be ruled out, to women with certain health conditions present that require further evaluation and follow-up, to women taking medications or supplements that may alter the efficacy or safety of contraception, and to women with systolic blood pressure higher than 140 mmHg or diastolic blood pressure higher than 90 mmHg.[1]

Prescribing Logistics

Women seeking a prescription for contraception will follow a simple process. She is asked to fill out a questionnaire designed to identify potential medical contraindications (Figure 2).[1] The pharmacist determines eligibility for contraception by evaluating the questionnaire and determining whether she is eligible and using a summary chart of the US MEC to evaluate any concerning health issues. The US MEC summary chart is color coded to the Oregon self-screen questionnaire shown in Figure 2.[1] The color coded key helps to easily identify if the women has no restrictions to contraception, the advantages outweigh the theoretical or proven risks, theoretical or proven risks outweigh the advantages or there is an unacceptable health risk and contraception should not be used. After completion of the summary US MEC, the pharmacist asks a short series of questions to rule out pregnancy and performs a blood pressure reading. The pharmacist also reviews the woman's current medication regimen to confirm that she does not take any

medicine that could interact with or increase risk of harms of contraceptive hormones. At any the step of the process, if the woman is not eligible, the pharmacist shall refer her to a diagnostic clinician, such as a primary care provider or other women's healthcare provider. Once eligible, the pharmacist selects the most appropriate contraceptive option. Upon dispensing, the pharmacist shall provide a consultation to the patient. Each counseling session must include, at a minimum, instructions on when to begin therapy, expectations and management of potential side effects, information that patches and pills do not protect against sexually transmitted diseases (STDs), and strategies for adherence. Additionally, the pharmacist shall encourage routine health screenings and notification of the visit to her care provider.

Pharmacists are encouraged to explore billing options related to contraceptive prescribing. Of note, the Oregon Health Plan (OHP) reimburses pharmacists for consulting with women prescribed contraceptives.

Figure 2. Patient Self-Screening Questionnaire[1]

Hormonal Contraceptive Self-Screening Questionnaire

Name_____ Health Care Provider's Name _____ Date_____
Date of Birth_____ Age*_____ Weight_____ Do you have health insurance? Yes / No
What was the date of your last women's health clinical visit? _____
Any Allergies to Medications? *Yes / No* If yes, list them here: _____

Background Information:

1	Do you think you might be pregnant now?	Yes ☐ No☐
2	What was the first day of your last menstrual period?	___/___/___
3	Have you ever taken birth control pills, or used a birth control patch, ring, or injection?	Yes ☐ No ☐
	Have you previously had contraceptives prescribed to you by a pharmacist?	Yes ☐ No ☐
	Did you ever experience a bad reaction to using hormonal birth control?	Yes ☐ No ☐
	- If yes, what kind of reaction occurred?	_____
	Are you currently using any method of birth control including pills, or a birth control patch, ring or shot/injection?	Yes ☐ No ☐
	- If yes, which one do you use?	_____
4	Have you ever been told by a medical professional not to take hormones?	Yes ☐ No ☐
5	Do you smoke cigarettes?	Yes ☐ No ☐

Medical History:

6	Have you given birth within the past 6 weeks?	Yes ☐ No ☐
7	Are you currently breastfeeding?	Yes ☐ No ☐
8	Do you have diabetes?	Yes ☐ No ☐
9	Do you get migraine headaches? If so, have you ever had the kind of headaches that start with warning signs or symptoms, such as flashes of light, blind spots, or tingling in your hand or face that comes and goes completely away before the headache starts?	Yes ☐ No ☐
10	Do you have high blood pressure, hypertension, or high cholesterol? (Please indicate yes, even if it is controlled by medication)	Yes ☐ No ☐
11	Have you ever had a heart attack or stroke, or been told you had any heart disease?	Yes ☐ No ☐
12	Have you ever had a blood clot?	Yes ☐ No ☐
13	Have you ever been told by a medical professional that you are at risk of developing a blood clot?	Yes ☐ No ☐
14	Have you had recent major surgery or are you planning to have surgery in the next 4 weeks?	Yes ☐ No ☐
15	Have you had bariatric surgery or stomach reduction surgery?	Yes ☐ No ☐
16	Do you have or have you ever had breast cancer?	Yes ☐ No ☐
17	Do you have or have you ever had hepatitis, liver disease, liver cancer, or gall bladder disease, or do you have jaundice (yellow skin or eyes)?	Yes ☐ No ☐
18	Do you have lupus, rheumatoid arthritis, or any blood disorders?	Yes ☐ No ☐
19	Do you take medication for seizures, tuberculosis (TB), fungal infections, or human immunodeficiency virus (HIV)?	Yes ☐ No ☐
	- If yes, list them here:	
20	Do you have any other medical problems or take any medications, including herbs or supplements?	Yes ☐ No ☐
	- If yes, list them here:	

Do you have a preferred method of birth control that you would like to use?

☐ **A pill you take each day** ☐ **A patch that you change weekly** ☐ **Other (ring, injectable, implant, or IUD)**

Internal use only ☐ verified DOB* with valid photo ID ☐ BP Reading _____/_____
Pharmacist Name _____ Pharmacist Signature _____
☐ Drug Prescribed_____ Rx# _____ -or- ☐ Patient Referred-circle reason(s)
Sig: _____(Pharmacy Phone _____ Address _____)
Notes: _____ April 2016

The law allows pharmacists to prescribe oral and patch dosage forms, but it does not provide for implants, vaginal rings, or intrauterine devices (IUDs).[1] Women 18 years of age and older, or those under 18 years of age with evidence of a previous prescription from a primary or women's health care provider are eligible to receive pharmacist prescribed birth control. Pharmacists are prohibited from requiring patients to schedule appointments; prescribing beyond 3 years following the initial prescription without evidence the patient has had a clinical visit with her primary or women's health care provider; prescribing outside the algorithm; or prescribing for self or family members.[1]

Conclusion

Allowing OTC contraception to women is a noteworthy milestone in a women's ability to manage her health care. Pharmacists are positioned to offer this type of care based on their extensive knowledge of medications. While barriers for obtaining contraception still exist, Oregon is leading the way to improve the care offered to women.

For more information, please refer to the Oregon Board of Pharmacy's webpage dedicated to this program: http://www.oregon.gov/pharmacy/Pages/ContraceptivePrescribing.aspx

Peer Reviewed By: Lorinda Anderson, Pharm D., Pharmacy Instructor, OSU College of Pharmacy

References:

1. Oregon Board of Pharmacy. Oregon pharmacists prescribing contraceptive therapy. Available at: http://www.oregon.gov/pharmacy/Pages/ContraceptivePrescribing.aspx. Accessed July 18, 2016.
2. American College of Obstetricians and Gynecologists. Understanding and using the U.S. Medical Eligibility Criteria for contraceptive use, 2010. American College of Obstetricians and Gynecologists. Available at : http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Gynecologic-Practice/Understanding-and-Using-the-US-Medical-Eligibility-Criteria-for-Contraceptive-Use-2010. Accessed July 29, 2016.
3. Centers for Disease Control and Prevention. United States medical eligibility criteria (US MEC) for contraceptive use 2010. Available at: http://www.cdc.gov/reproductivehealth/unintendedpregnancy/usmec.htm. Accessed July 18, 2016.
4. Yang T, Kozhimannil K, Snowden J. Pharmacist-prescribed birth control in Oregon and other states. *JAMA*. 2016; 315:1567-1568.
5. Singh S, Sedgh G, Hussain R. Unintended pregnancy: worldwide levels, trends and outcomes. *Stud Fam Plann*. 2014;41:241-50.
6. Oregon State University Professional and Continuing Education. Comprehensive Contraceptive Education and Training for the Prescribing Pharmacist. Available at: https://pace.oregonstate.edu/catalog/comprehensive-contraceptive-education-and-training-prescribing-pharmacist. Accessed July 27, 2016.

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Vaccine Update 2016

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The Advisory Committee on Immunization Practices (ACIP) meets three times a year to discuss research focused on vaccine safety and efficacy. Their recommendations serve as public health guidance for storage, handling and administration of immunizations. The ACIP 2016 adult vaccine schedule includes updates for the human papillomavirus (HPV), pneumococcal and meningococcal vaccinations. In addition, ACIP revised some of their previous influenza recommendations for the upcoming 2016-17 season. A summary of ACIP immunization recommendations from the past year will be reviewed in this article.

Influenza Vaccine - Nasal Spray not recommended for 2016-17 flu season

In June 2016, ACIP reviewed its annual influenza vaccine recommendations. The committee voted to continue recommending all people 6 months and older be vaccinated annually against influenza. In a change from previous recommendations, ACIP voted that the live attenuated influenza vaccine (LAIV) nasal spray formulation not be used during the 2016-17 season.[1] The committee also voted to remove LAIV from the Vaccines for Children (VFC) program. This is an interim recommendation, as data may be subject to change in future influenza seasons. Final ACIP recommendations for the 2016-17 influenza season can be accessed at this web site: http://www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm?s_cid=rr6505a1_w

The vote was based on data collated by the U.S. Influenza Vaccine Effectiveness Network demonstrating poor efficacy of LAIV from 2013 through 2016. The Center for Disease Control (CDC) conducts vaccine effectiveness studies every flu season to evaluate the efficacy of the current influenza vaccine. Vaccine effectiveness can vary widely from season to season depending on the circulating viruses and the antigens contained in the vaccine manufactured for each influenza season. The CDC estimate of LAIV effectiveness against any influenza virus during the 2015-16 season amongst children 2 through 17 years of age was 3% (95% Confidence Interval (CI): -49 to 37). In other words, no protective benefit could be measured. In contrast, the inactivated influenza vaccine (IIV) contained in the intramuscular flu shot had a vaccine effectiveness estimate of 63% (95% CI: 52 to 72) in the same age group and time frame.[2] From 2010 through 2013, the influenza nasal spray was a trivalent vaccine. In late 2013, the quadrivalent formulation of the nasal spray was developed for influenza prophylaxis. In a CDC retrospective review it was noted that the LAIV formulation was substantially less effective than the IIV form of the vaccine in preventing Influenza A(H1N1)pdm09 in the 2010-11, 2013-14 and 2015-16 influenza seasons.[3]

Possible reasons for poor performance of LAIV in 2015-16 were theorized as follows:

- Suboptimal performance of the A/Bolivia/559/2013 (H1N1)pdm09 HA vaccine component[3]
- Potential interference among viruses in the quadrivalent vaccine [i.e., additional B vaccine component inhibits viral replication of A(H1N1)pdm09 virus][3]
- Reduced immunogenicity of LAIV as a result of more highly vaccinated population in recent years; compared with populations of earlier studies, in which it is likely that a higher proportion of children were vaccine-naïve[3]

Three recent studies evaluated the seasonal effectiveness of LAIV compared to IIV. A retrospective analysis of the U.S. Influenza Effectiveness Network data from 2010 through 2014 evaluated the relative effectiveness of LIAV compared with IIV in preventing influenza.[4] The odds of influenza were not statistically different between 2010 through 2013 between LAIV and IIV for all types of influenza. However, in the 2013-14 season the odds of influenza were significantly higher for LAIV compared to IIV in patients aged 2-17 years (OR = 2.88; 95% CI: 1.62-5.12) and for patients aged 2-8 years (OR = 5.36, 95% CI: 2.37-12.13).[4] Notably, for the age range between 9 and 17 the odds ratio was not statistically significant.

When the odds ratios were calculated by virus type, a higher proportion of LAIV patients aged 2-17 years tested positive for Type A(H1N1)pdm09 virus compared to the IIV patients (OR = 5.53, 95% CI: 1.35-22.76) in 2010-11.[4] Similar patterns were seen in 2013-14 in the same age range (OR = 2.65, 95% CI: 1.34-5.27).[4] There were no statistically significant differences noted for A/H3N2 or Type B viruses. This analysis suggests lower effectiveness of LAIV was related to the influenza type A(H1N1)pdm09 virus.[4] Current circulating strains of influenza A are subcategorized as either H1N1 or H3N2 viruses. In the spring of 2009, a new strain of influenza A(H1N1) was identified as causing the first flu pandemic in over 40 years.[5] This particular viral strain replaced the previously circulating influenza Type A virus and continues to circulate each season. Influenza Type A tends to cause more severe disease and mortality in older patients, while children and young adults seem to be more susceptible to influenza Type B infections.

An observational trial was conducted in 1033 children aged 2-17 years during the 2013-14 influenza season at 4 separate geographic sites.[6] Seventy four percent of the influenza cases were due to A(H1N1)pdm09 strains, 21% were due to influenza B, and 4% were due to influenza H3N2. LAIV did not show significant effectiveness against A(H1N1)pdm09 (Vaccine effectiveness (VE) = 13%, 95% CI: −55 to 51) but was effective against B strains (VE = 82%, 95% CI: 12–96).[6] Inactivated influenza vaccine was effective against A(H1N1)pdm09 (VE = 74% , 95% CI: 50–86) and type B (VE = 70%, 95% CI: 18–89).[6] The authors concluded LAIV provided significant protection against type B influenza but not against A(H1N1)pdm09 in children aged 2–17 years during the 2013–2014 season.

In another observational trial, influenza vaccine effectiveness was evaluated during the 2013-14 season against the Type A(H1N1)pdm09 strain of the influenza virus at 5 different sites in adults and children.[7] Of the 1197 confirmed influenza cases assessed in the study, 85% were positive for A(H1N1)pdm09, 9% had the A/H3N2 virus, and 6% tested positive for the Type B strain. Vaccine effectiveness for LAIV was estimated in children aged 2–17 years as very few adults received LAIV. The LAIV VE against A(H1N1)pdm09-related respiratory illness was 18% (95% CI, −38% to 51%) and not statistically significant. LAIV VE against A(H1N1)pdm09 was not significant in any age-stratified model. Among the youngest children, aged 2–4 years, 11% of those who were negative for influenza virus had received LAIV4, compared with 18% of those with confirmed A(H1N1)pdm09; this difference was not statistically significant (p = 0.23).[7]

A recently published randomized controlled trial (RCT) directly compared the trivalent formulation of LAIV to IIV in a rural Canadian population to assess if one formulation provided more effective protection against influenza than the other.[8] A total of 4611 participants were enrolled in the study over a 3 year period from 2012 through May, 2015. The primary outcome was the presence of laboratory confirmed influenza A or B. Influenza infection occurred in 5.3% of the LAIV group compared to 5.2% of the IIV group.[8] The nonsignificant hazard ratio comparing LIAV to IIV was 1.03 (95% CI 0.85-1.24).[8] The investigators concluded immunizing with LAIV does not provide better community protection again influenza than IIV.[8] When comparing the results of this RCT to observational trials it must be noted that the study period took place during different years (2012-2015) and with the trivalent

forms of the flu vaccine. The poor performance of LAIV in the United States was observed in the 2015-16 season with the quadrivalent formula. Finally, the study population was a small, isolated rural community which may not reflect influenza transmission in larger, urban populations.

In conclusion, there is mounting evidence that the influenza nasal spray does not provide adequate effectiveness in preventing influenza when compared to the injectable form. For this reason, the ACIP Advisory Committee voted 13-1 that the nasal spray should not be used during the 2016-17 influenza season. However, annual flu vaccination with the injectable flu vaccine continues to be an ACIP recommendation for everyone over the age of 6 months. The Oregon Health Authority (OHA) supports the ACIP recommendations and is advising against using the nasal spray. The nasal spray will NOT be supplied through the Vaccines For Children (VFC) population. Medicaid Fee-For-Service will not be paying for administration of the nasal spray for patients aged 2 through 18 years old. OHA has stated that the inactivated injectable form is preferred for all ages.[9] The 2016-17 Oregon immunization protocols can be accessed at the following web link:
https://public.health.oregon.gov/PreventionWellness/VaccinesImmunization/ImmunizationProviderResources/Documents/PharmIIV.pdf

Human Papillomavirus (HPV) Vaccine - New formulation added to adult schedule

Human papillomavirus is a common sexually transmitted infection and is associated with cervical cancer. HPV infection is also associated with oropharyngeal cancer and other anogenital cancers. There are 3 HPV vaccines in the United States. The newest vaccine, Gardasil-9® was recently added to the adult vaccination schedule. This nine valent vaccine targets five additional strains of the HPV virus that account for 15% of cervical cancers.[10] The differences between the 3 vaccines are outlined in Table 1. Of note the bivalent vaccine (Cervarix®) is only approved for use in women for prevention of cervical cancer and pre-cancers. The quadrivalent vaccine (Gardasil®) has additional approval for prevention of genital warts. The vaccines will not have a therapeutic effect on existing HPV infection, genital warts or cervical lesions. Three HPV vaccine doses are recommended starting at age 11 or 12. Vaccination is recommended through age 26 for all females, through age 21 for all males and through age 26 for immunocompromised males including those with HIV and men who have sex with men.[11]

Table 1 – HPV Vaccines licensed in the United States

Brand Name	HPV Types	Sex	Age Groups	Schedule
Cervarix®	16,18	Females	9-25 years	3 doses (0, 1, 6 mo.)
Gardasil®	6,11,16,18	Females and Males	9-26 years	3 doses (0, 2, 6 mo.)
Gardasil-9®	6,11,16,18,31, 33,42,52, 58	Females and Males	9-26 years	3 doses (0, 2, 6 mo.)

Adult Pneumococcal Vaccine – New scheduling recommendations

The US Food and Drug Administration (FDA) has approved two pneumococcal vaccines for adults: conjugate PCV13 (Prevnar®) and polysaccharide PPSV23 (Pneumovax®). The two pneumococcal vaccinations should not be given at the same time and should be administered in a specific order at specific intervals. ACIP recommends administering PCV-13 first to provide optimal immune response to the vaccine. For most healthy adults aged 19- 64 years, PPSV23 can be given one year after the initial PCV 13 dose.[12] However, for adults of all ages with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants PCV13 and PPSV23 should be administered at least 8 weeks apart.[11] PCV 13 is only recommended to be administered one time. Revaccination with PPSV23 five years after the first dose is recommended for: 1) children and adults younger than 65 of age who are at high risk for serious pneumococcal infection and 2) adults 65 years and older who have received their first PPSV23 dose for any reason when they were younger than 65 years old.[12] Adults who receive PPSV23 after the age of 65 only need a single dose. The risk of administering pneumococcal vaccines too soon is increased injection site swelling and pain.[13]

Meningococcal Vaccine - Additional meningitis vaccine added to adult schedule

The meningococci that can cause invasive meningitis are one of five bacterial serogroups: A, B, C, W or Y. Serogroup prevalence varies by geographic area. For example, epidemics of serogroup A meningococcal disease have frequently occurred in sub-Saharan Africa. The major causes of meningococcal disease in the United States are due to serogroups B, C and Y. Three meningitis vaccines are available that provide immunity to serogroups A, C, W and Y (MenACWY): Menactra®, Menveo® and Menomune®. These formulations have been available for several years. Until late 2014, there was no vaccine available for serogroup B. Due to recent outbreaks of serogroup B meningococcal disease on college campuses, the development of vaccines targeted towards Group B meningococcal vaccines was fast tracked by the FDA. The first serogroup B meningococcal vaccine, Trumenba® was introduced in late 2014. In early 2015 a second serogroup B meningococcal vaccine, Bexsero® received FDA approval. Trumenba® is a 3 dose vaccine while Bexsero® is a 2 dose series. Table 2 provides a comparison of all meningococcal vaccines available in the United States.

Table 2- Meningococcal Vaccines Licensed in the United States

Brand Name	Type of Vaccine	Serogroups	Year Licensed	Age Range
Menomune®	Polysaccharide	A,C,W,Y	1981	≥ 2 years
Menactra®	Conjugate	A,C,W,Y	2005	9 mo. - 55 yrs.
Menveo®	Conjugate	A,C,W,Y	2010	2 mo.– 55 yrs.
MenHibrix®	Conjugate	C,Y and H influenzae type B (Hib)	2012	6 wks. – 18 mo.
Trumenba®	Recombinant Protein	B	2014	10 – 25 yrs.
Bexsero®	Recombinant Protein	B	2015	10 – 25 yrs.

The recent ACIP recommendations provide guidance as to who should receive the meningococcal B (MenB) vaccines. The products are not interchangeable and the same product must be used to complete the two- or three-dose series. MenB vaccine series **should** be administered to persons aged ≥10 years who are at increased risk for serogroup B meningococcal disease. Patients with persistent genetic deficiencies, receiving eculizumab, or with anatomic asplenia are at risk for meningococcal disease and have a higher mortality rate (40-70%) then healthy people.[14] MenB vaccine series **may** be administered to adolescents and young adults aged 16 through 23 years (preferred age is 16 through 18 years) to provide protection against most strains of serogroup B meningococcal disease.[15] ACIP did not recommend all adolescents routinely receive the MenB vaccine because there is still limited data on the effectiveness and safety of these new vaccines. In addition, the increasing rarity of meningitis type B infections limited ACIP from making administration of MenB vaccine a universal recommendation. At-risk microbiologists (those who might be exposed through work) also need both types of meningococcal vaccinations. MenACWY vaccine may be administered at the same time as the MenB vaccine, but at a different anatomic site.

In conclusion, vaccines are one of the best defenses in preventing hospitalizations and complications from communicable diseases. Insuring the appropriate vaccine formulation is administered to target populations at recommended intervals are important components of effective immunization

strategies. Staying updated on ACIP guidelines can assist health care practitioners in providing their patients with reliable vaccine information.

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References

1. CDC Press Releases. CDC. http://www.cdc.gov/media/releases/2016/s0622-laiv-flu.html. Published January 1, 2016. Accessed August 10, 2016.
2. Influenza Vaccine Effectiveness, Including LAIV vs IIV in Children and Adolescents, US Flu VE Network, 2015-16 - influenza-05-flannery.pdf. http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2016-06/influenza-05-flannery.pdf. Accessed August 10, 2016.
3. LAIV vs IIV effectiveness Summary of evidence since 2009 - influenza-07-flannery.pdf. http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2016-06/influenza-07-flannery.pdf. Accessed August 10, 2016.
4. Chung JR, Flannery B, Thompson MG, et al. Seasonal Effectiveness of Live Attenuated and Inactivated Influenza Vaccine. *Pediatrics*. 2016;137(2):e20153279. doi:10.1542/peds.2015-3279.
5. Types of Influenza Viruses | Seasonal Influenza (Flu) | CDC. http://www.cdc.gov/flu/about/viruses/types.htm. Accessed August 22, 2016.
6. Caspard H, Gaglani M, Clipper L, et al. Effectiveness of live attenuated influenza vaccine and inactivated influenza vaccine in children 2-17 years of age in 2013-2014 in the United States. *Vaccine*. 2016;34(1):77-82. doi:10.1016/j.vaccine.2015.11.010.
7. Gaglani M, Pruszynski J, Murthy K, et al. Influenza Vaccine Effectiveness Against 2009 Pandemic Influenza A(H1N1) Virus Differed by Vaccine Type During 2013-2014 in the United States. *J Infect Dis*. 2016;213(10):1546-1556. doi:10.1093/infdis/jiv577.
8. Loeb M, Russell ML, Manning V, et al. Live Attenuated Versus Inactivated Influenza Vaccine in Hutterite ChildrenA Cluster Randomized Blinded TrialLive Attenuated Versus Inactivated Influenza Vaccine in Hutterite Children. *Ann Intern Med*. 2016;N/A(N/A):N/A-N/A. doi:10.7326/M16-0513.
9. PharmIIV.pdf. https://public.health.oregon.gov/PreventionWellness/VaccinesImmunization/ImmunizationProviderResources/Documents/PharmIIV.pdf. Accessed August 22, 2016.
10. Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6411a3.htm. Accessed August 10, 2016.
11. Adult Immunization Schedules and Tools for Providers | CDC. http://www.cdc.gov/vaccines/schedules/hcp/adult.html. Accessed August 10, 2016.
12. Intervals Between PCV13 and PPSV23 Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6434a4.htm. Accessed August 10, 2016.
13. Miernyk KM, Butler JC, Bulkow LR, et al. Immunogenicity and reactogenicity of pneumococcal polysaccharide and conjugate vaccines in alaska native adults 55-70 years of age. *Clin Infect Dis*. 2009;49(2):241-248. doi:10.1086/599824.
14. Use of Serogroup B Meningococcal Vaccines in Persons Aged ≥10 Years at Increased Risk for Serogroup B Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices, 2015. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6422a3.htm. Accessed August 10, 2016.
15. Use of Serogroup B Meningococcal Vaccines in Adolescents and Young Adults: Recommendations of the Advisory Committee on Immunization Practices, 2015. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6441a3.htm. Accessed August 10, 2016.

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Endocrine Therapy for Breast Cancer

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Breast cancer is the most common type of cancer in women. There is an estimated average lifetime risk of 12.5% for women without additional risk factors.[1] The risk is even higher in women with risk factors. Women with mutations in the *BRCA* tumor suppressor genes can have an estimated lifetime risk up to 85%,[1] and approximately 33% of patients with a history of ductal carcinoma in situ (DCIS; a non-invasive carcinoma contained within the duct) develop invasive disease within 20 years.[2] This article reviews risk factors and evaluates treatments for prevention of breast cancer. Typical therapy for primary chemoprevention consists of an aromatase inhibitor or selective estrogen receptor modulator (SERM). Endocrine therapy is also used as adjuvant treatment in women with a history of breast cancer after surgery, radiation or chemotherapy and for treatment of metastatic disease. Table 1 describes place in therapy for preventative breast cancer therapies.

Table 1. Preventative Breast Cancer Therapies[3-6]

Drug	Class	Place in Therapy
Anastrozole	Aromatase Inhibitors	- Adjuvant treatment of hormone receptor-positive or advanced breast cancer - Use in postmenopausal women - Off-label: primary chemoprevention and use in premenopausal women*
Exemestane		
Letrozole		- Adjuvant therapy for hormone receptor-positive, advanced or metastatic cancer - Use in postmenopausal women - Off-label: Use in premenopausal women*
Raloxifene	Selective Estrogen Receptor Modulators (SERMs)	- Primary chemoprevention - Treatment or prophylaxis of postmenopausal osteoporosis - Use in postmenopausal women
Tamoxifen		- Primary chemoprevention - Adjuvant treatment of DCIS and hormone receptor-positive, advanced, or metastatic breast cancer - Use in pre- and post-menopausal women
Toremifene		- Metastatic breast cancer in postmenopausal women

*Use of an aromatase inhibitor in premenopausal women requires concurrent ovarian suppression or ablation.

Breast Cancer Risk

National Comprehensive Care Network (NCCN) and American Society of Clinical Oncology guidelines recommend consideration of chemoprevention or surgical risk reduction in women at least 35 years of age with a life expectancy greater than 10 years who are at high risk of breast cancer and little risk of complications from therapy.[5] High risk is defined as women with a 5-year risk greater than 1.7%, exposure to thoracic radiation before the age of 30 years, or those with a history of lobular carcinoma in situ.[5] Risk can be estimated using the modified Gail model (http://www.cancer.gov/bcrisktool). This risk assessment tool accounts for multiple risk factors including age, ethnicity, reproductive history (including early menarche and older age at menopause or live birth), family history, and positive history of atypical hyperplasia.[7] The tool is typically not used for populations with prior history of carcinoma in situ or *BRCA* mutations as these factors are very strong predictors of invasive breast cancer.[7] Additional treatment options such as surgery or radiation should be considered in populations who have high risk for breast cancer.

Primary Chemoprevention

Both tamoxifen and raloxifene are FDA approved for primary prevention of breast cancer. Exemestane and anastrozole may be used off-label for chemoprevention, but are more commonly used as adjuvant treatment in women with a history of breast cancer. A systematic review conducted by the U.S. Preventative Services Task Force in 2013 compared tamoxifen and raloxifene for primary prevention of breast cancer in high-risk women.[8] Median duration of treatment ranged from 3-5 years with follow-up from 7-13 years.[8] In placebo-controlled trials, both tamoxifen (relative risk [RR] 0.70, 95% CI 0.59 to 0.82; 7 cases per 1000 over 5 years; number needed to treat [NNT] 143) and raloxifene (RR 0.44, 95% CI 0.27 to 0.71; 9 cases per 1000 over 5 years; NNT 111) reduced the incidence of invasive breast cancer but had no impact on non-invasive breast cancer or estrogen receptor-negative breast cancer.[8] Upon direct comparison in a randomized controlled trial (RCT; n=19,747), raloxifene had a higher incidence of invasive breast cancer (RR 1.24, 95% CI 1.05 to 1.47; 5 cases per 1000 over 5 years).[8] No difference was observed for either agent in all-cause mortality or mortality due to cancer. Though they are not approved by the FDA for primary prevention, therapy with either anastrozole or exemestane for 5 years has also shown to significantly reduce risk for breast cancer recurrence compared to placebo (RR 0.468, 95% CI 0.346 to 0.634; p<0.001; NNT 61).[9]

Secondary Prevention

After primary treatment with surgery, chemotherapy, or radiation, adjuvant treatment for 5 to 10 years with an aromatase inhibitors or tamoxifen can prevent recurrence and improve survival. Choice of therapy depends on type of cancer and menopause status at time of cancer diagnosis.

Following initial treatment of DCIS, both tamoxifen and anastrozole may be considered in pre- and post-menopausal women to reduce breast cancer recurrence.[5] In a systematic review including 2 RCTs (n=3,375), tamoxifen decreased recurrence of ipsilateral DCIS (RR 0.75 95% CI 0.61 to 0.92), contralateral DCIS (RR 0.50 95% CI 0.28 to 0.87), and contralateral invasive cancer (RR 0.57 95% CI 0.39 to 0.83).[10] A statistically significant reduction was not shown for invasive ipsilateral carcinoma (HR 0.79, 95% CI 0.62 to 1.01) or all-cause mortality.[10] One recent RCT of anastrozole (n=2,980) also demonstrated similar rates of breast cancer recurrence compared to tamoxifen (HR 0.89, 95% CI 0.64 to 1.23) with no difference in mortality.[11]

For treatment of invasive breast cancer, tamoxifen or an aromatase inhibitor may be considered in premenopausal women.[6] Aromatase inhibitors alone are unable to prevent production of estrogen from the ovaries, and use in premenopausal women requires concurrent ovarian suppression or ablation.[6] In postmenopausal women, NCCN recommends the following regimens:

- Tamoxifen for 5-10 years (if unable to use an aromatase inhibitor)[6] OR
- Aromatase inhibitor for 5 years[6] OR
- Sequential therapy with tamoxifen for 2-3 years followed by an aromatase inhibitor for up to 5 years[6] OR
- Sequential therapy with an aromatase inhibitor for 2-3 years followed by tamoxifen for 5 years total[6] OR
- Tamoxifen for 4.5-6 years followed by 5 years of an aromatase inhibitor[6]

One systematic review (n=31,920) compared efficacy of aromatase inhibitors versus tamoxifen for treatment of estrogen receptor-positive early breast cancer.[12] Compared to 5 years of tamoxifen, use of an aromatase inhibitor for 5 years was associated with reduced risk of breast cancer recurrence (10-year absolute risk reduction [ARR] 3.6%, 95% CI 1.7 to 5.4%; p<0.00001) and all-cause mortality (ARR 2.7%; RR 0.89, 95% CI 0.81 to 0.97; p=0.01).[12] Similarly, at 10 years, patients on tamoxifen for 2-3 years followed by an aromatase inhibitor for a total of 5 years had a lower risk of breast cancer recurrence (ARR 2.0%, 95% CI 0.2 to 3.8; p=0.0001), breast cancer mortality (ARR 1.5%, RR 0.84, 95% CI 0.72 to 0.96; p=0.01), and all-cause mortality (ARR 2.9%, RR 0.82, 95% CI 0.73 to 0.91; p=0.0002)

compared to 5 years of tamoxifen.[12] Because aromatase inhibitors improve survival and reduce disease recurrence, NCCN guidelines recommend tamoxifen monotherapy only in women who remain premenopausal for the duration of their treatment or those unable to tolerate aromatase inhibitors.[6]

Total treatment duration is typically 5 to 10 years following primary treatment. Evidence from 1 systematic review suggests that extending therapy to 10 years improves breast cancer survival (OR 0.87; 95% CI 0.81 to 0.95; p=0.001) and relapse-free survival (OR 0.79; 95% CI 0.68 to 0.92; p=0.002) compared to 5 years of therapy.[13] However, other systematic reviews have found no difference in all-cause mortality in patients receiving 10 or 5 years of therapy.[14,15] In addition, evidence for use of an aromatase inhibitor beyond 5 years is limited. One RCT (n=1,918) has examined letrozole versus placebo as extended therapy for 5 years following completion of an initial 4.5 to 6 years of an aromatase inhibitor. This trial demonstrated reduced rates of disease-free survival and breast cancer recurrence (HR 0.66, 95% CI 0.48 to 0.91).[16] Nonetheless, due to limited evidence, current standard of care for aromatase inhibitor use is a maximum of 5 years alone or in combination with tamoxifen.

Safety of Endocrine Therapy

Risks and benefits of treatment must be weighed carefully especially when used in the risk reduction setting (women with DCIS or at high risk of breast cancer). In women with a history of invasive cancer, benefits of therapy generally outweigh the risks. The results of several high quality systematic reviews examining the safety of these agents are summarized here.

Endometrial Cancer – Tamoxifen is consistently associated with a higher risk of endometrial cancer compared to other treatments. When compared directly to tamoxifen, raloxifene had 5 fewer cases of endometrial cancer per 1000 women (RR 0.55, 95% CI 0.36 to 0.83).[8] Aromatase inhibitors also demonstrated a significantly decreased risk compared to tamoxifen (10-year ARR 0.8%; RR 0.33, 95% CI 0.21 to 0.51; p<0.0001).[12] Risk of cancer in women taking tamoxifen also increases with age. Compared to placebo, women over 50 years of age had a significant increased risk for endometrial cancer (RR 3.32, 95% CI 1.95 to 5.67; p<0.0001), but no difference was seen in women less than 50 years of age (RR 1.19, 95% CI 0.53 to 2.65; p=0.60).[17]

Thromboembolic Events – Risk of venous thromboembolic events (VTE) is increased with both tamoxifen (RR 1.93, 95% CI 1.41 to 2.64; 4 cases in 1000 women) and raloxifene (RR 1.60, 95% CI 1.15 to 2.23; 7 cases in 1000 women) compared to placebo.[8] Upon direct comparison to tamoxifen, raloxifene had lower risk of VTE (RR 0.75, 95% CI 0.60 to 0.93; 4 cases in 1000 women).[8] Compared to placebo, rates of pulmonary embolism (PE) were significantly increased with tamoxifen (RR 2.69, 95% CI 1.12 to 6.47), but failed to reach statistical significance with raloxifene (RR 2.19, 95% CI 0.97–4.97).[8] Raloxifene was also associated with a higher stroke mortality compared to placebo (RR 1.49, 95% CI 1.00 to 2.24).[8] Compared to tamoxifen, aromatase inhibitors demonstrated decreased odds of VTE (ARR 1.3%; OR 0.55, 95% CI 0.46 to 0.64; p<0.001).[18]

Ocular Effects – In a systematic review of primary prevention trials, rate of cataracts was higher in tamoxifen users than in those taking raloxifene (RR 0.80, 95% CI 0.72 to 0.95; 15 cases per 1000 women).[8]

Fractures and Musculoskeletal Effects – Tamoxifen and raloxifene are typically associated with decreased rates of fractures. In postmenopausal women, these SERMs act as estrogen agonists in bone tissue and can help prevent osteoporosis. In a systematic review of primary prevention RCTs, rates of vertebral fractures were reduced with raloxifene (RR 0.61, 95% CI 0.54 to 0.69; 7 cases in 1000 women), non-vertebral fractures were reduced with tamoxifen (RR 0.66, 95% CI 0.45 to 0.98; 3 cases in 1000 women), and rates of vertebral fractures were similar with direct comparison of the agents.[8] Compared to tamoxifen, aromatase inhibitors were associated with a 2.7% increased risk of fractures at 5 years (RR 1.42 95% 1.28 to 1.57; p<0.0001), and risk remained elevated in the 5 years after treatment discontinuation (RR 1.29, 95% 1.09 to 1.53; p=0.003).[12] Other adverse effects commonly associated with aromatase inhibitors include arthralgias and myalgias.[3,4] Because adherence to endocrine therapy is often poor, with reported non-adherence rates of 10.8% to 85%,[19] these adverse effects must be considered carefully as they may be limiting factors to treatment.

Conclusions

As primary chemoprevention, use of endocrine therapy decreases incidence of breast cancer without any effect on mortality. Compared to raloxifene upon long-term follow up, tamoxifen was associated with lower rates of recurrent breast cancer. However, tamoxifen is also associated with increased rates of endometrial cancer, thrombotic events, and cataracts. When used as primary chemoprevention, the risks and benefits of therapy must be weighed carefully. As adjuvant treatment of invasive breast cancer, aromatase inhibitors have demonstrated reduced disease recurrence and mortality compared to tamoxifen. More information on these treatment options, along with other therapeutic reviews, can be found on the Oregon Health Plan fee-for-service searchable preferred drug list at http://www.orpdl.org/drugs/.

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References:

1. DynaMed [internet database]. Ipswich, MA: EBSCO Publishing. Updated July 25, 2016. Accessed August 24, 2016.
2. Staley H, McCallum I, Bruce J. Postoperative tamoxifen for ductal carcinoma in situ: Cochrane systematic review and meta-analysis. *Breast.* 2014;23(5):546-551.
3. Micromedex Healthcare Series [internet database]. Greenwood Village, CO: Truven Health Analytics, Inc. Updated Periodically. Accessed August 17, 2016.
4. Lexicomp [internet database]. Hudson, OH: Wolters Kluwer. Updated periodically. Accessed August 17, 2016.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Risk Reduction Version 1.2016. https://www.nccn.org/. Accessed September 03, 2016.
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Version 2.2016. https://www.nccn.org/. Accessed September 03, 2016.
7. Breast Cancer Risk Assessment Tool. National Cancer Institute. http://www.cancer.gov/bcrisktool. Updated May 16, 2011. Accessed August 31, 2016.
8. Nelson HD, Smith MEB, Griffin JC, Fu R. Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2013;158(8):604-614.
9. Mocellin S, Pilati P, Briarava M, Nitti D. Breast cancer chemoprevention: a network meta-analysis of randomized controlled trials. *J Natl Cancer Inst.* 2016;108(2).
10. Staley H, McCallum I, Bruce J. Postoperative tamoxifen for ductal carcinoma in situ. *Cochrane Database Syst Rev.* 2012;10:CD007847.
11. Forbes JF, Sestak I, Howell A, et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. *Lancet.* 2016;387(10021):866-873.
12. Early Breast Cancer Trialists' Collaborative Group. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet.* 2015;386(10001):1341-1352.
13. Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Lonati V, Barni S. Five or more years of adjuvant endocrine therapy in breast cancer: a meta-analysis of published randomised trials. *Breast Cancer Res Treat.* 2013;140(2):233-240.
14. Josefsson ML, Leinster SJ. Aromatase inhibitors versus tamoxifen as adjuvant hormonal therapy for oestrogen sensitive early breast cancer in post-menopausal women: meta-analyses of monotherapy, sequenced therapy and extended therapy. *Breast.* 2010;19(2):76-83.
15. Al-Mubarak M, Tibau A, Templeton AJ, et al. Extended adjuvant tamoxifen for early breast cancer: a meta-analysis. *PLoS One.* 2014;9(2):e88238.
16. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N Engl J Med.* 2016;375(3):209-219.
17. Iqbal J, Ginsburg OM, Wijeratne TD, et al. Endometrial cancer and venous thromboembolism in women under age 50 who take tamoxifen for prevention of breast cancer: a systematic review. *Cancer Treat Rev.* 2012;38(4):318-328.
18. Amir E, Seruga B, Niraula S, Carlsson L, Ocana A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *J Natl Cancer Inst.* 2011;103(17):1299-1309.

19. Banning M. Adherence to adjuvant therapy in post-menopausal breast cancer patients: a review. *Eur J Cancer Care (Engl).* 2012;21(1):10-19.

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RetroDUR - Dose Consolidation Program

Goals

1. Educate providers on the fiscal impacts of dose frequencies and tablet counts
2. Reduce pharmacy payments without adversely impacting access to medications

Program Description

Certain drugs products are priced such that lower dose products (e.g. 5mg) are more expensive per milligram than higher dose products (e.g. 10mg) Dose consolidation is the practice of replacing multiple tablets or capsules with a single tablet or capsule without altering the total daily dose or dose frequency. The Oregon Fee-For-Service (FFS) program has had multiple dose consolidation programs over the last two decades. This voluntary, education-based initiative is focused on carve out medications due the high volume, high per unit cost, and limited utilizations controls. This program does not promote either tablet splitting or changing formulations (i.e. extended vs. immediate release).

Drug products were selected based on both volume and cost reduction potential. Table 1 lists drugs which are recommended for once daily dosing. Table 2 lists drugs recommended for twice daily dosing. The first 5 columns contain data used to identify FFS claims which could be dose optimized. The GSN is a unique identifier for a particular drug, strength, and formulation. The column “Units Per Day (Claim)” indicates the number of units found on a particular paid claim. The Alternative GSN corresponds to the same generic drug and formulation and an alternative strength. When a FFS claim with a listed GSN and matching Units Per Day (Claim) is paid, a letter will be generated requesting the provider change the prescription to the optimized alternative strength and units per day. For example, a paid FFS claim for aripiprazole tablet 5mg, 2 tablets per day would generate a letter suggesting the prescriber change to aripiprazole tablet 10mg, 1 tablet per day. The letter format can be found in Appendix A. If all recommendations were accepted, the currently listed products and optimizations would produce a cost savings of over $1,500,000 annually.

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Table 1 Proposed Conversions and Associated Savings per day

Frequency	Drug	Current Daily Dose	Current Strength	Current Rate per Unit($)	Suggested Daily Dose	Suggested Strength	Suggested Rate per Unit($)	Estimated Savings Per Day ($)
QD	ABILIFY	2	10 mg	2.476870	1	20 mg	3.162490	1.791250
QD	ABILIFY	2	15 mg	2.647340	1	30 mg	3.416730	1.877950
QD	ABILIFY	2	2 mg	2.701450	1	5 mg	2.636910	2.765990
QD	ABILIFY	2	5 mg	2.636910	1	10 mg	2.476870	2.796950
QD	ABILIFY	3	10 mg	2.476870	1	30 mg	3.416730	4.013880
QD	ABILIFY	3	20 mg	3.162490	2	30 mg	3.416730	2.654010
QD	ABILIFY	3	5 mg	2.636910	1	15 mg	2.647340	5.263390
QD	ABILIFY	4	10 mg	2.476870	2	20 mg	3.162490	3.582500
QD	ABILIFY	4	15 mg	2.647340	2	30 mg	3.416730	3.755900
QD	ABILIFY	4	5 mg	2.636910	1	20 mg	3.162490	7.385150
QD	ABILIFY	5	2 mg	2.701450	1	10 mg	2.476870	11.030380
QD	ABILIFY	6	20 mg	3.162490	4	30 mg	3.416730	5.308020
QD	ABILIFY	6	5 mg	2.636910	1	30 mg	3.416730	12.404730
QD	ABILIFY	8	5 mg	2.636910	2	20 mg	3.162490	14.770300
QD	ARIPIPRAZOLE	2	10 mg	2.476870	1	20 mg	3.162490	1.791250
QD	ARIPIPRAZOLE	2	15 mg	2.647340	1	30 mg	3.416730	1.877950
QD	ARIPIPRAZOLE	2	2 mg	2.701450	1	5 mg	2.636910	2.765990
QD	ARIPIPRAZOLE	2	5 mg	2.636910	1	10 mg	2.476870	2.796950
QD	ARIPIPRAZOLE	3	10 mg	2.476870	1	30 mg	3.416730	4.013880
QD	ARIPIPRAZOLE	3	20 mg	3.162490	2	30 mg	3.416730	2.654010
QD	ARIPIPRAZOLE	3	5 mg	2.636910	1	15 mg	2.647340	5.263390
QD	ARIPIPRAZOLE	4	10 mg	2.476870	2	20 mg	3.162490	3.582500
QD	ARIPIPRAZOLE	4	15 mg	2.647340	2	30 mg	3.416730	3.755900
QD	ARIPIPRAZOLE	4	5 mg	2.636910	1	20 mg	3.162490	7.385150
QD	ARIPIPRAZOLE	5	2 mg	2.701450	1	10 mg	2.476870	11.030380

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Frequency	Drug	Current Daily Dose	Current Strength	Current Rate per Unit($)	Suggested Daily Dose	Suggested Strength	Suggested Rate per Unit($)	Estimated Savings Per Day ($)
QD	ARIPIPRAZOLE	6	20 mg	3.162490	4	30 mg	3.416730	5.308020
QD	ARIPIPRAZOLE	6	5 mg	2.636910	1	30 mg	3.416730	12.404730
QD	ARIPIPRAZOLE	8	5 mg	2.636910	2	20 mg	3.162490	14.770300
QD	ARIPIPRAZOLE ODT	3	10 mg	30.635000	2	15 mg	30.635000	30.635000
QD	ARIPIPRAZOLE ODT	6	10 mg	30.635000	4	15 mg	30.635000	61.270000
QD	FETZIMA	2	20 mg	9.859040	1	40 mg	9.742250	9.975830
QD	FETZIMA	2	40 mg	9.742250	1	80 mg	9.760490	9.724010
QD	FETZIMA	3	40 mg	9.742250	1	120 mg	9.672790	19.553960
QD	FETZIMA	3	80 mg	9.760490	2	120 mg	9.672790	9.935890
QD	FETZIMA	4	20 mg	9.859040	1	80 mg	9.760490	29.675670
QD	FETZIMA	4	40 mg	9.742250	2	80 mg	9.760490	19.448020
QD	FETZIMA	6	20 mg	9.859040	1	120 mg	9.672790	49.481450
QD	FETZIMA	6	40 mg	9.742250	2	120 mg	9.672790	39.107920
QD	FETZIMA	8	20 mg	9.859040	2	80 mg	9.760490	59.351340
QD	FETZIMA	12	20 mg	9.859040	2	120 mg	9.672790	98.962900
QD	INVEGA	2	1.5 mg	18.510730	1	3 mg	11.980280	25.041180
QD	INVEGA	2	3 mg	11.980280	1	6 mg	13.366500	10.594060
QD	INVEGA	3	3 mg	11.980280	1	9 mg	22.335900	13.604940
QD	INVEGA	4	1.5 mg	18.510730	1	6 mg	13.366500	60.676420
QD	INVEGA	4	3 mg	11.980280	2	6 mg	13.366500	21.188120
QD	INVEGA	6	1.5 mg	18.510730	1	9 mg	22.335900	88.728480
QD	INVEGA	6	3 mg	11.980280	2	9 mg	22.335900	27.209880
QD	INVEGA	8	1.5 mg	18.510730	2	6 mg	13.366500	121.352840
QD	INVEGA	12	1.5 mg	18.510730	2	9 mg	22.335900	177.456960
QD	LAMICTAL XR	2	100 mg	19.760670	1	200 mg	21.394900	18.126440
QD	LAMICTAL XR	2	50 mg	19.240250	1	100 mg	19.760670	18.719830
QD	LAMICTAL XR	3	100 mg	19.760670	1	300 mg	31.773580	27.508430
QD	LAMICTAL XR	3	200 mg	21.394900	2	300 mg	31.773580	0.637540
QD	LAMICTAL XR	4	100 mg	19.760670	2	200 mg	21.394900	36.252880
QD	LAMICTAL XR	4	25 mg	9.357080	1	100 mg	19.760670	17.667650
QD	LAMICTAL XR	4	50 mg	19.240250	1	200 mg	21.394900	55.566100

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Frequency	Drug	Current Daily Dose	Current Strength	Current Rate per Unit($)	Suggested Daily Dose	Suggested Strength	Suggested Rate per Unit($)	Estimated Savings Per Day ($)
QD	LAMICTAL XR	5	100 mg	19.760670	2	250 mg	29.673000	39.457350
QD	LAMICTAL XR	5	50 mg	19.240250	1	250 mg	29.673000	66.528250
QD	LAMICTAL XR	6	100 mg	19.760670	2	300 mg	31.773580	55.016860
QD	LAMICTAL XR	6	50 mg	19.240250	1	300 mg	31.773580	83.667920
QD	LAMICTAL XR	8	100 mg	19.760670	4	200 mg	21.394900	72.505760
QD	LAMICTAL XR	8	25 mg	9.357080	1	200 mg	21.394900	53.461740
QD	LAMICTAL XR	8	50 mg	19.240250	2	200 mg	21.394900	111.132200
QD	LAMICTAL XR	10	25 mg	9.357080	1	250 mg	29.673000	63.897800
QD	LAMICTAL XR	10	50 mg	19.240250	2	250 mg	29.673000	133.056500
QD	LAMICTAL XR	12	25 mg	9.357080	1	300 mg	31.773580	80.511380
QD	LAMICTAL XR	12	50 mg	19.240250	2	300 mg	31.773580	167.335840
QD	LAMICTAL XR	16	25 mg	9.357080	2	200 mg	21.394900	106.923480
QD	LAMICTAL XR	16	50 mg	19.240250	4	200 mg	21.394900	222.264400
QD	LAMOTRIGINE ER	2	100 mg	3.530390	1	200 mg	6.085840	0.974940
QD	LAMOTRIGINE ER	2	50 mg	6.442480	1	100 mg	3.530390	9.354570
QD	LAMOTRIGINE ER	4	100 mg	3.530390	2	200 mg	6.085840	1.949880
QD	LAMOTRIGINE ER	4	25 mg	1.816960	1	100 mg	3.530390	3.737450
QD	LAMOTRIGINE ER	4	50 mg	6.442480	1	200 mg	6.085840	19.684080
QD	LAMOTRIGINE ER	5	50 mg	6.442480	1	250 mg	10.088110	22.124290
QD	LAMOTRIGINE ER	6	50 mg	6.442480	1	300 mg	10.614170	28.040710
QD	LAMOTRIGINE ER	8	100 mg	3.530390	4	200 mg	6.085840	3.899760
QD	LAMOTRIGINE ER	8	25 mg	1.816960	1	200 mg	6.085840	8.449840
QD	LAMOTRIGINE ER	8	50 mg	6.442480	2	200 mg	6.085840	39.368160
QD	LAMOTRIGINE ER	10	25 mg	1.816960	1	250 mg	10.088110	8.081490
QD	LAMOTRIGINE ER	10	50 mg	6.442480	2	250 mg	10.088110	44.248580
QD	LAMOTRIGINE ER	12	25 mg	1.816960	1	300 mg	10.614170	11.189350
QD	LAMOTRIGINE ER	12	50 mg	6.442480	2	300 mg	10.614170	56.081420
QD	LAMOTRIGINE ER	16	25 mg	1.816960	2	200 mg	6.085840	16.899680
QD	LAMOTRIGINE ER	16	50 mg	6.442480	4	200 mg	6.085840	78.736320
QD	LATUDA	2	20 mg	29.883590	1	40 mg	29.809500	29.957680
QD	LATUDA	2	40 mg	29.809500	1	80 mg	29.976640	29.642360

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QD	LATUDA	3	20 mg	29.883590	1	60 mg	29.816990	59.833780
QD	LATUDA	3	40 mg	29.809500	1	120 mg	44.379800	45.048700
QD	LATUDA	3	80 mg	29.976640	2	120 mg	44.379800	1.170320
QD	LATUDA	4	20 mg	29.883590	1	80 mg	29.976640	89.557720
QD	LATUDA	4	40 mg	29.809500	2	80 mg	29.976640	59.284720
QD	LATUDA	4	60 mg	29.816990	2	120 mg	44.379800	30.508360
QD	LATUDA	6	20 mg	29.883590	1	120 mg	44.379800	134.921740
QD	LATUDA	6	40 mg	29.809500	2	120 mg	44.379800	90.097400
QD	LATUDA	8	20 mg	29.883590	2	80 mg	29.976640	179.115440
QD	PALIPERIDONE ER	2	1.5 mg	18.510730	1	3 mg	11.980280	25.041180
QD	PALIPERIDONE ER	2	3 mg	11.980280	1	6 mg	13.366500	10.594060
QD	PALIPERIDONE ER	3	3 mg	11.980280	1	9 mg	22.335900	13.604940
QD	PALIPERIDONE ER	4	1.5 mg	18.510730	1	6 mg	13.366500	60.676420
QD	PALIPERIDONE ER	4	3 mg	11.980280	2	6 mg	13.366500	21.188120
QD	PALIPERIDONE ER	6	1.5 mg	18.510730	1	9 mg	22.335900	88.728480
QD	PALIPERIDONE ER	6	3 mg	11.980280	2	9 mg	22.335900	27.209880
QD	PALIPERIDONE ER	8	1.5 mg	18.510730	2	6 mg	13.366500	121.352840
QD	PALIPERIDONE ER	12	1.5 mg	18.510730	2	9 mg	22.335900	177.456960
QD	PRISTIQ ER	2	25 mg	9.574570	1	50 mg	9.463290	9.685850
QD	PRISTIQ ER	2	50 mg	9.463290	1	100 mg	9.450920	9.475660
QD	PRISTIQ ER	4	25 mg	9.574570	1	100 mg	9.450920	28.847360
QD	PRISTIQ ER	4	50 mg	9.463290	2	100 mg	9.450920	18.951320
QD	PRISTIQ ER	6	25 mg	9.574570	3	50 mg	9.463290	29.057550
QD	PRISTIQ ER	6	50 mg	9.463290	3	100 mg	9.450920	28.426980
QD	PRISTIQ ER	8	25 mg	9.574570	2	100 mg	9.450920	57.694720
QD	PRISTIQ ER	12	25 mg	9.574570	3	100 mg	9.450920	86.542080
QD	REXULTI	2	0.25 mg	31.158000	1	0.5 mg	30.338540	31.977460
QD	REXULTI	2	0.5 mg	30.338540	1	1 mg	30.346240	30.330840
QD	REXULTI	2	1 mg	30.346240	1	2 mg	30.600570	30.091910
QD	REXULTI	2	2 mg	30.600570	1	4 mg	31.158000	30.043140
QD	REXULTI	3	1 mg	30.346240	1	3 mg	30.227330	60.811390

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QD	REXULTI	3	2 mg	30.600570	2	3 mg	30.227330	31.347050
QD	REXULTI	4	0.25 mg	31.158000	1	1 mg	30.346240	94.285760
QD	REXULTI	4	0.5 mg	30.338540	1	2 mg	30.600570	90.753590
QD	REXULTI	4	1 mg	30.346240	1	4 mg	31.158000	90.226960
QD	REXULTI	4	2 mg	30.600570	2	4 mg	31.158000	60.086280
QD	REXULTI	4	3 mg	30.227330	3	4 mg	31.158000	27.435320
QD	REXULTI	6	0.25 mg	31.158000	3	0.5 mg	30.338540	95.932380
QD	REXULTI	6	0.5 mg	30.338540	1	3 mg	30.227330	151.803910
QD	REXULTI	6	1 mg	30.346240	2	3 mg	30.227330	121.622780
QD	REXULTI	6	2 mg	30.600570	3	4 mg	31.158000	90.129420
QD	REXULTI	8	0.25 mg	31.158000	1	2 mg	30.600570	218.663430
QD	REXULTI	8	0.5 mg	30.338540	1	4 mg	31.158000	211.550320
QD	REXULTI	8	1 mg	30.346240	2	4 mg	31.158000	180.453920
QD	REXULTI	10	0.25 mg	31.158000	5	0.5 mg	30.338540	159.887300
QD	REXULTI	12	0.25 mg	31.158000	1	3 mg	30.227330	343.668670
QD	REXULTI	12	0.5 mg	30.338540	2	3 mg	30.227330	303.607820
QD	SEROQUEL XR	2	150 mg	14.365110	1	300 mg	20.734950	7.995270
QD	SEROQUEL XR	2	200 mg	15.769790	1	400 mg	24.244020	7.295560
QD	SEROQUEL XR	3	200 mg	15.769790	2	300 mg	20.734950	5.839470
QD	SEROQUEL XR	3	50 mg	7.981370	1	150 mg	14.365110	9.579000
QD	SEROQUEL XR	4	150 mg	14.365110	2	300 mg	20.734950	15.990540
QD	SEROQUEL XR	4	200 mg	15.769790	2	400 mg	24.244020	14.591120
QD	SEROQUEL XR	4	300 mg	20.734950	3	400 mg	24.244020	10.207740
QD	SEROQUEL XR	4	50 mg	7.981370	1	200 mg	15.769790	16.155690
QD	SEROQUEL XR	6	200 mg	15.769790	3	400 mg	24.244020	21.886680
QD	SEROQUEL XR	6	50 mg	7.981370	1	300 mg	20.734950	27.153270
QD	SEROQUEL XR	8	200 mg	15.769790	4	400 mg	24.244020	29.182240
QD	SEROQUEL XR	8	50 mg	7.981370	1	400 mg	24.244020	39.606940
BID	FANAPT	4	4 mg	9.616330	2	8 mg	18.838410	0.788500
BID	FANAPT	4	6 mg	18.703420	2	12 mg	30.406000	14.001680
BID	FANAPT	8	1 mg	15.430830	2	4 mg	9.616330	104.213980

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Frequency	Drug	Current Daily Dose	Current Strength	Current Rate per Unit($)	Suggested Daily Dose	Suggested Strength	Suggested Rate per Unit($)	Estimated Savings Per Day ($)
BID	FANAPT	8	4 mg	9.616330	4	8 mg	18.838410	1.577000
BID	FANAPT	12	1 mg	15.430830	2	6 mg	18.703420	147.763120
BID	FANAPT	16	1 mg	15.430830	2	8 mg	18.838410	209.216460
BID	FANAPT	20	1 mg	15.430830	2	10 mg	30.406000	247.804600
BID	FANAPT	24	1 mg	15.430830	2	12 mg	30.406000	309.527920
BID	SAPHRIS	4	2.5 mg	16.768000	2	5 mg	16.245900	34.580200
BID	SAPHRIS	4	5 mg	16.245900	2	10 mg	16.304600	32.374400
BID	SAPHRIS	8	2.5 mg	16.768000	2	10 mg	16.304600	101.534800
BID	SAPHRIS	8	5 mg	16.245900	4	10 mg	16.304600	64.748800
BID	SAPHRIS	12	2.5 mg	16.768000	6	5 mg	16.245900	103.740600
BID	SAPHRIS	16	2.5 mg	16.768000	4	10 mg	16.304600	203.069600

Note: Not all available strengths are listed, only products with savings based on current prices.

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Patient Selection Criteria

Include

A. Unit Measure IN ('CAP','TAB')

B. Benefit Package = BMH

C. Day Supply >=28

D. Potential Net Savings Per Month >=$84 (i.e. > $1000/year)

E. Quantity Dispensed / Day Supply >= 2

F. Other Coverage Code <> 02 or 04 (Payment Collected or Payment Applied to Deductible)

G. Associated PA Number is blank (null or '')

H. GSN listed in Table 1 or 2

I. Claims paid within 30 days

J. Same GSN (i.e. drug, strength, formulation), Quantity Dispensed and Day Supply for 6 consecutive paid claims

Exclude

A. Claims for the same member and the same GSN successfully sent a letter within the last 9 months.

B. Members with eligibility ending within 30 days.

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Safety Monitoring

A safety monitoring process will be created to prevent inadvertent interruptions in therapy. After a letter is sent, paid claims will be monitored. A report will be generated for all members with no paid claims for the targeted drug in any formulation within 45 days of the fax sent. A pharmacist will review the claims profile and collaborate with the prescribing clinician, pharmacy, and/or patient as necessary.

Reporting

Impact of the program will be tracked in the "Retro - DUR Intervention History by Quarter" report using the following format.

Program	Initiative	Metric	Value
Cost Savings	Dose Optimization	Total Claims Identified	#
		Total Faxes Successfully Sent	#
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	#
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	#
		Prescriptions Unchanged after 3 Months of Fax Sent	#
		Safety Monitoring Profiles Identified	#
		Safety Monitoring Interventions (call, fax, etc.)	#
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$

Cumulative Payment Reduction Calculation:

For members identified for which therapy was switched to the recommended strength and frequency, determine the difference between the amounts paid for the triggering claim and subsequent claims at the recommended strength and frequency with a paid date within 1 year of the date the fax was sent.

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Appendix A – Dose Consolidation Provider Letter

<Provider name>	MMM, dd, yyyy
Telephone: xxx-xxx-xxxx	
Fax: xxx-xxx-xxxx	

Re: <Drug Brand name> for <Member First name> <Member Last name> <Member ID> DOB: <DOB MM/DD/YYYY>

The accompanying forms are for patients filling a prescription linked to your NPI number and an OHP fee for service pharmacy claim. The most recent prescription indicated a daily dose of XX <Tablet/Capsule>s per day. Consolidating the dose (same drug, same formulation) to use fewer <Tablet/Capsule>s would result in a pharmacy **cost saving of $xxx,xxx annually**.

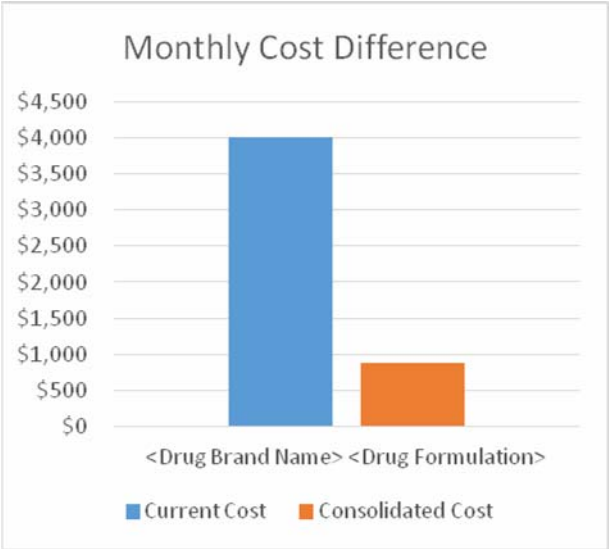
Please evaluate each patient for a **voluntary change** to a dose optimized regimen. Please take the time to review the forms and discuss them with your patient(s) as necessary.

Use the forms to communicate a change and fax it directly to the patient's identified pharmacy.

If you have any questions about this message, please contact the Division of Medical Assistance Programs at 503-945-6513.

Dose Consolidation:

- <Drug Brand Name> <Drug Formulation> is FDA approved for <Once/Twice> daily dosing and is compatible with the pharmacokinetic properties of the formulation.
- Dose consolidation encourages medication adherence.
- Using one higher dose tablet to equal the strength of two lower dose tablets can save up to one half of the original prescription cost.
- However, for some patients, especially those that have difficulty adjusting to medication changes, using divided doses may be preferable.



Pharmacy costs for <Drug Brand Name> <Formulation> <Drug Strength> when prescribed <Current Units per Day> per day vs. consolidated <Alternative Strength> prescribed <Alternative Units per day> per day.

TO: <Pharmacy name> **MMM DD, YYYY**

<Pharmacy Address>
<Pharmacy City>, <Pharmacy State> <Pharmacy Zip>
Phone:<Pharmacy Phone>
Fax: <Pharmacy Fax>

FROM: <Prescriber Name>
<Prescriber Address>
<Prescriber City>, < Prescriber State> < Prescriber Zip>
Phone:< Prescriber Phone>
Fax: < Prescriber Fax>

PATIENT: <Patient First Name> <Patient Last Name>
Date of Birth: <Patient DOB>
Medicaid Member ID: <Member ID>
Address: <Patient Address> < Patient City>, < Patient State> < Patient Zip>

Discontinue the following prescription:

<Drug Brand Name> <Formulation> <Drug Strength>

Qty: <Quantity Dispensed> for <Day Supply> Days

New Prescription:

<Drug Brand Name> <Drug Formulation> <Alternative Strength>

Directions: Take <Alternative Units Per Day> <Tablet/Capsule> by mouth <Once/Twice> daily.

Dispense Quantity: <Day Supply * Alternative Units Per Day>

Refills:____

Prescriber Signature:_____

Fax completed prescription to: <Pharmacy Fax>

Palivizumab (Synagis®)

Goal(s):

- Promote safe and effective use of palivizumab.

Length of Authorization:

- Based on individual factors; may extend up to 5 months (5 doses)

<table>
<tr><th colspan="3">Approval Criteria</th></tr>
<tr><td>1. What diagnosis is being treated?</td><td colspan="2">Record ICD10 code</td></tr>
<tr><td>2. Has the patient been receiving monthly palivizumab prophylaxis and been hospitalized for a breakthrough RSV infection?</td><td>Yes: Pass to RPh; deny for medical appropriateness.</td><td>No: Go to #3</td></tr>
<tr><td>3. Is the request for immunoprophylaxis between the months of November and March?</td><td>Yes: Go to #5</td><td>No: Go to #4</td></tr>
<tr><td>4. Is the request for immunoprophylaxis starting in October due to an early onset* of the RSV season in the region from which the patient resides (see below)?

* Onset is defined as 2 consecutive weeks where % positive is ≥10%, (data are provided by the Oregon's Weekly Respiratory Syncytial Virus Surveillance Report from the Oregon Public Health Division based on regions. Weekly updates are found at: https://public.health.oregon.gov/DiseasesConditions/DiseasesAZ/Pages/disease.aspx?did=40)

<table>
<tr><th>Region</th><th>Counties</th></tr>
<tr><td>NW Oregon- SW Washington</td><td>Benton, Clackamas, Clatsop, Columbia, Lane, Lincoln, Linn, Marion, Multnomah, Polk, Tillamook, Washington, Yamhill</td></tr>
<tr><td>Central Oregon</td><td>Crook, Deschutes, Grant, Harney, Jefferson, Wheeler</td></tr>
<tr><td>Columbia Gorge – NE Oregon</td><td>Baker, Gilliam, Hood River, Morrow, Sherman, Umatilla, Union, Wasco, Wallowa</td></tr>
<tr><td>Southern Oregon</td><td>Coos, Curry, Douglas, Jackson, Josephine, Klamath, Lake, Malheur</td></tr>
</table>
</td><td>Yes: Go to #5</td><td>No: Pass to RPh. Deny; medical appropriateness. Prophylaxis is indicated only during high viral activity.</td></tr>
<tr><td>5. Is the current age of the patient < 24 months at start of RSV season?</td><td>Yes: Go to #6</td><td>No: Pass to RPh. Deny; medical appropriateness. Not recommended for patients ≥24 months old.</td></tr>
</table>

Approval Criteria		
6. **GROUP A** Does the patient have the CLD (chronic lung disease) of prematurity ICD10 Q331through Q339 **and** in the past 6 months has required medical treatment with at least one of the following: a. diuretics b. chronic corticosteroid therapy c. supplemental oxygen therapy	**Yes:** Go to #18	**No:** Go to #7
7. **GROUP B** Has the patient received a cardiac transplant during the RSV season?	**Yes:** Go to #18	**No:** Go to #8
8. **GROUP C** Is the child profoundly immunocompromised during the RSV season (i.e. solid organ transplant or hematopoietic stem cell transplantation)?	**Yes:** Go to #18	**No:** Go to #9
9. **GROUP D** Does the infant have cystic fibrosis and manifestations of severe lung disease or weight or length less than the 10th percentile?	**Yes:** Go to #18	**No:** Go to #10
10. **GROUP E** Is the request for a second season of palivizumab prophylaxis for a child born <32 weeks, 0 days gestation who required at least 28 days of oxygen, chronic systemic corticosteroid therapy, or bronchodilator therapy within 6 months of start of second RSV season?	**Yes:** Go to #18	**No:** Go to #11
11. Will the patient be <12 months at start of RSV season?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. **GROUP F** Was the infant born before 29 weeks, 0 days gestation?	**Yes:** Go to #18	**No:** Go to #13
13. **GROUP G** Does the infant have pulmonary abnormalities of the airway or neuromuscular disease compromising handling of secretions?	**Yes:** Go to #18	**No:** Go to #14

Approval Criteria		
14. **GROUP H** Does the patient have hemodynamically significant congenital heart disease (CHD) ICD10: P293, Q209, Q220-Q223, Q225, Q229-Q234, Q238, Q240-Q246, Q248-Q249, Q250-Q256, Q278-Q279,Q282-Q283,Q288-Q289, Q2560-Q2565,Q2568-Q2569, Q2570-Q2572, Q2579,Q2731-Q2732 and at least one of the following: a. Acyanotic heart disease who are receiving treatment to control congestive heart failure and will require cardiac surgical procedures **or** b. Have moderate to severe pulmonary hypertension **or** c. History of lesions adequately corrected by surgery AND still requiring medication for congestive heart failure?	**Yes:** Go to #18	**No:** Go to #15
15. **GROUP I** Does the patient have chronic lung disease (CLD) of prematurity defined as gestational age <32 weeks, 0 days and requirement for >21% oxygen for at least the first 28 days after birth?	**Yes:** Go to #18	**No:** Go to #16
16. **GROUP J** Does the patient have cyanotic heart defects and immunoprophylaxis is recommended?	**Yes:** Go to #18	**No:** Go to #17
17. **GROUP K** Does the patient have cystic fibrosis with clinical evidence of CLD and/ or nutritional compromise?	**Yes:** Go to #18	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
18. Is the request for more than 5 doses within the same RSV season or for dosing <28 days apart?	**Yes:** Pass to RPh. Deny; medical appropriateness. Prophylaxis is indicated for 5 months maximum and doses should be administered ≥28 days apart. May approve for the following on a case-by-case basis: a. >5 doses; b. Prophylaxis for a second / subsequent RSV season	**No:** Go to #19
19. Has the patient had a weight taken within the last 30 days?	**Yes:** Document weight and date and go to #20 Weight:_____ Date:_____	**No:** Pass to RPh. Obtain recent weight so accurate dose can be calculated.
20. Approve palivizumab for a dose of 15 mg/kg. Document number of doses received in hospital and total number approved according to BIRTH DATE and GROUP based on start of RSV season: - Immunoprophylaxis between November - March refer to **Table 1** - Immunoprophylaxis starting in October based on above (#4) refer to **Table 2** Total number of doses approved for RSV season:_____ Number of doses received in the hospital:_____ Prior to each refill, the patient's parent/caregiver and prescriber must comply with all case management services, including obtaining current weight for accurate dosing purposes throughout the approved treatment period as required by the Oregon Health Authority.		

Table 1. Maximum Number of Doses for RSV Prophylaxis (based on criteria group from above) Beginning **NOVEMBER 1**

MONTH OF BIRTH	ALL GROUPS
November 1 – March 31	5
April	5
May	5
June	5
July	5
August	5
September	5
October	5
November	5
December	4
January	3
February	2
March	1

* Infant may require less doses than listed based on age at the time of discharge from the hospital. Subtract number of doses given in hospital from total number of approved doses.

Table 2. Maximum Number of Doses for RSV Prophylaxis (based on criteria group from above) Beginning **OCTOBER 1**

MONTH OF BIRTH	ALL GROUPS
November 1 – March 31	5
April	5
May	5
June	5
July	5
August	5
September	5
October	5
November	5
December	4
January	3
February	2
March	1

* Infant may require less doses than listed based on age at the time of discharge from the hospital. Subtract number of doses given in hospital from total number of approved doses.

Notes:

- Dose: 15 mg/kg via intramuscular injection once monthly throughout RSV season.
- The start date for Synagis® is November 1 each year (or sooner when the Oregon Public Health Division has determined that RSV season onset has occurred) for a total of up to 5 doses.
- Approval for more than 5 doses or additional doses after March 31 will be considered on a case-by-case basis. Results from clinical trials indicate that Synagis® trough concentrations greater than 30 days after the 5th dose are well above the protective concentration. Therefore, 5 doses will provide more than 20 weeks of protection.

P&T Review: *11/16 (DE); 9/14; 5/11; 5/12*
Implementation: *3/30/12*

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Prior Authorization Review: Cysteamine Delayed-release Capsule (PROCYSBI®)

Background:
Cysteamine is a medication used to deplete cystine from the cells of patients with nephropathic cystinosis. Cystinosis is a rare, autosomal recessive error in the metabolic transport of cystine out of lysosomes.[1] The accumulation of cystine and subsequent formation of crystals can damage various organs.[2] The kidneys are severely affected by cystine accumulation and cystinosis can lead to progressive renal failure by 10 years of age.[1] Infants with this syndrome present between 3 and 6 months of age with failure to thrive, vomiting, constipation, polyuria, excessive thirst, rickets, and dehydration.[1] The estimated incidence is 1 case per 100,000 to 200,000 live births with a prevalence of 1.6 cases per million people.[3] Diagnosis is confirmed by measuring cystine levels in white blood cells (WBC).[1] Patients with newly diagnosed cystinosis will have WBC cystine levels in the range of 3 to 20 nmol ½ cystine/mg protein.[1] The usual range for WBC cystine levels in patients without cystinosis is less than 0.2 nmol ½ cystine/mg protein.[1] The most frequent form of this disease is infantile nephropathic cystinosis; however, 2 other variations of cystine accumulation have also been described.[1] The intermediate form is usually diagnosed during childhood or adolescence and presents with less severe renal symptoms and ocular discomfort. In adults, a third form has been identified that is characterized by photophobia and cystine accumulation in the corneas. For ocular cystinosis, a topical eye drop product is available that must be administered every waking hour and, due to limited stability, should be discarded after one week.[4]

Lifelong oral cysteamine therapy is indicated for all patients with nephropathic cystinosis. Early treatment is imperative and can delay progression to end stage renal disease by 6 to 10 years.[1] Cysteamine is available as an immediate-release (IR) formulation (Cystagon®) and a delayed-release (DR) formulation (Procysbi®). The IR formulation must be administered every 6 hours around-the-clock to prevent cysteine accumulation. The DR formulation can be administered every 12 hours. The dose is titrated to a WBC cystine trough concentration of less than 1 nmol ½ cystine/mg protein. The most frequently reported adverse effect with both IR and DR formulations is gastrointestinal (GI) such as nausea, dyspepsia, and epigastric pain.[5,6] More GI adverse reactions have been reported with the DR formulation compared to the IR formulation.[6] Reducing the dose and gradually titrating back up to the target dose is recommended to minimize GI adverse effects. The DR formulation is approved in adults and children over 2 years of age. The IR formulation does not have any age restrictions so it can be administered to infants by opening the capsule and sprinkling the contents directly onto food.[5] The DR formulation should be swallowed whole, although the prescribing information has instructions for opening the capsule to disperse the DR granules into 4 ounces of applesauce or berry jam for patients that cannot swallow capsules.[6]

An 8-week crossover study demonstrated DR cysteamine was not inferior to IR cysteamine controlling WBC cystine levels in 43 patients with nephropathic cystinosis.[7] The mean WBC cystine level with IR cysteamine was 0.54 nmol ½ cystine/mg protein compared to a mean WBC level of 0.62 nmol ½ cystine/mg protein with DR cysteamine.[7] The difference between the two formulations was 0.08 nmol ½ cystine/mg protein (95.8 % Confidence Interval, 0-0.16).[7] There were 3-fold more adverse GI effects with the IR product than the DR product. The same investigators extended this first crossover study into a 24-month, open-label, single arm study to evaluate the long term efficacy of DR cysteamine as assessed by WBC cystine levels. [8] Other metrics evaluated in the study included kidney function, growth, and quality of life.[8] Forty of the 41 patients that completed the initial study participated in the 2-year extension trial. Laboratory assessments, physical examination, and BMI were obtained for the first six months of the study followed by quarterly visits. The average age of the participants

was 11.5 years. Over 24 months, administration of DR cysteamine maintained WBC cystine levels under optimal control which was defined as less than 1 nmol ½ cystine/mg protein.[8] The baseline WBC cystine level was 0.43 ± 0.15 nmol ½ cystine/mg protein and at 24 months the median WBC cystine level was 0.55 ± 0.34 nmol ½ cystine/mg protein (p = 0.38).[7] Changes in patient body mass index (BMI) did not change significantly over the study period (baseline BMI = 18.2 kg/m^2, compared to 24 month BMI = 18.3 kg/m^2 p=0.27).[8] Kidney function, as evaluated by the estimated glomerular filtration rate (eGFR), was preserved in 39 patients (baseline eGFR = 63±25 ml/min/1.73m^2, compared to 24 month eGFR of 57 ±25 ml/min/1.73m^2, p=0.32).[8] One patient proceeded to renal transplantation at 17 months and another patient was placed on maintenance dialysis at 21 months of the study. Emesis was experienced by 28 (70.0%) subjects, followed by headache in 14 (35.0%) subjects, upper respiratory tract symptoms in 9 (22.5%) subjects, and diarrhea in 8 (20.0%) subjects.[8] The authors concluded administration of DR cysteamine over 24 months did not significantly impact WBC cystine levels, kidney function, or patient growth; however, there were substantial GI adverse effects. This extension of the original non-inferiority study did not directly compare the 2 different formulations of cysteamine but it does provide some long-term safety and efficacy data for DR cysteamine.

Another exploratory study evaluated conversion from the IR to the DR product in 11 pediatric patients with an average age of 12 years.[9] The primary reason for switching products was difficulty adhering to the night time administration of the IR formulation. Eight patients successfully transitioned to the DR formulation without any complications or additional side effects. Three patients had difficulties switching from IR to DR cysteamine due to vomiting, weight loss, and difficulty swallowing the DR capsules. Median follow-up in this study was 14 months (range, 3 to 18 months). No significant changes in WBC cystine values were noted after the transition to DR therapy (median 1 nmol ½ cystine/mg protein before [range 0.2-5.7 nmol ½ cystine /mg protein] and 1 nmol ½ cystine/mg protein after [range 0-2.5 nmol ½ cystine /mg protein]; p = 0.64).[9]

Prior Authorization (PA) requests for the DR cysteamine product in the Oregon Health Plan Fee-for-Service population has averaged between 1-3 per month for the past year and all requests have been approved.

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

References:

1. Elmonem MA, Veys KR, Soliman NA, van Dyck M, van den Heuvel LP, Levtchenko E. Cystinosis: a review. *Orphanet J Rare Dis*. 2016;11. doi:10.1186/s13023-016-0426-y.

2. Wilmer MJ, Emma F, Levtchenko EN. The pathogenesis of cystinosis: mechanisms beyond cystine accumulation. *Am J Physiol Renal Physiol*. 2010;299(5):F905-916. doi:10.1152/ajprenal.00318.2010.

3. Gahl WA, Thoene JG, Schneider JA. Cystinosis. *N Engl J Med*. 2002;347(2):111-121. doi:10.1056/NEJMra020552.

4. Cysteamine Opthalmic Solution (Cystaran) Prescribing Information. Amityville, NY: Sigma-Tau Pharmaceuticals ; 10/2012.

5. Cysteamine bitartre (Cystagon) Prescribing Information. Morganton, WV: Mylan Pharmaceuticals, Inc.; July 2007.

Author: Moretz Date: November 2016

6. Cysteamine bitartrate (Proscybi) Prescribing Information. Novato, CA: Raptor Pharmaceuticals Inc.; 8/2015.

7. Langman CB, Greenbaum LA, Sarwal M, et al. A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety. *Clin J Am Soc Nephrol*. 2012;7(7):1112-1120. doi:10.2215/CJN.12321211.

8. Langman CB, Greenbaum LA, Grimm P, et al. Quality of Life is Improved and Kidney Function Preserved in Patients with Nephropathic Cystinosis Treated for 2 Years with Delayed-Release Cysteamine Bitartrate. *J Pediatr*. 2014;165(3):528-533.e1. doi:10.1016/j.jpeds.2014.05.013.

9. Ahlenstiel-Grunow T, Kanzelmeyer NK, Froede K, et al. Switching from immediate- to extended-release cysteamine in nephropathic cystinosis patients: a retrospective real-life single-center study. *Pediatr Nephrol*. June 2016. doi:10.1007/s00467-016-3438-x.

Cysteamine Delayed-release (PROCYSBI®)

Goal(s):

- To restrict use of costly agents to appropriate patient populations.

Length of Authorization:

Up to 6 months

Requires PA:

- Cysteamine delayed-release capsules (PROCYSBI)

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 nephropathic cystinosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the patient receiving medications through a gastrostomy tube?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Has the patient had an adequate trial of cysteamine immediate-release capsules (CYSTAGON) AND Is the prescriber experienced in managing metabolic diseases such as nephropathic cystinosis AND has documentation of justified patient non-adherence to cysteamine IR that prevents the patient from achieving WBC cysteine levels (<1 nmol ½ cysteine per mg protein)?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *11/16 (DM); 3/14 (MH)*
Implementation: *5/1/14*

Author: Moretz Date: November 2016

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Prior Authorization Review: repository corticotropin injection (HP Acthar Gel for Injection)

Background:
Adrenocorticotropin hormone (ACTH) is secreted by the pituitary gland and stimulates the adrenal cortex to secrete cortisol, aldosterone and other hormones. Repository corticotropin injection, an ACTH analog, is available as an injectable gel that must be administered via intramuscular or subcutaneous routes. Corticotropin injection is indicated as monotherapy for the treatment of infantile spasms (West Syndrome) in infants and children under the age of 2 years.[1] It is also indicated for the treatment of multiple sclerosis exacerbations in adults.[1] Other FDA-approved indications include treatment of rheumatic, collagen, dermatologic, allergic, ophthalmic, respiratory, and edematous disorders.[1] The adverse effects of corticotropin are related to its steroidogenic effects and are similar to those of corticosteroids.[1] Corticotropin is contraindicated for patients with porcine protein hypersensitivity, scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history or presence of a peptic ulcer, congestive heart failure, adrenocortical hypofunction, and uncontrolled hypertension.[1]

Corticotropin injection was previously reviewed by the P and T committee in March 2013. Conclusions from that review were as follows:

- There remains very low to insufficient evidence for the treatment of infantile spasms. Most trials are open label or retrospective analysis.
- There is low quality evidence that ACTH may be effective and that vigabatrin is possibly effective for the short term treatment of infantile spasms; however, there remains insufficient evidence if treatment will result in better long-term developmental outcomes.
- There is insufficient evidence to support the use of repository corticotropin injection in the use of aiding in the diagnosis of adrenocortical insufficiency and this indication was removed from the product label in 2010.
- There is insufficient evidence comparing repository corticotropin injection in corticosteroid responsive disorders and no evidence proving superior efficacy or safety to systemic corticosteroids. Available evidence is based on retrospective analyses and case series.
- There is low quality evidence that ACTH is beneficial compared to placebo in improving the symptoms of MS acute exacerbations and insufficient evidence that treatment with ACTH prevents new exacerbations or reduces long term disability.
- There is insufficient evidence demonstrating a difference in rate of recovery between high dose glucocorticoids and ACTH in the treatment of MS exacerbations. ACTH may be an option in those patients who cannot tolerate steroids.
- There is insufficient evidence to support the use of repository corticotropin injection in conditions not responsive to corticosteroid therapy (tobacco cessation, acute gout, childhood epilepsy)

Infantile Spasms (West Syndrome):
West syndrome is form of infant epilepsy characterized by spasms, hypsarrhythima detected on EEG, and psychomotor delay.[2] Approximately two thirds of infants with West syndrome will have an underlying neurologic abnormality.[2] The incidence of infantile spasms is estimated as 2-3 infants per 10,000 live births.[2] Effective treatments have been difficult to identify due to adverse reactions, incomplete response rates, and variable availability of treatments in different countries.[3] Three therapies are presently utilized to manage infantile spasms: ACTH, vigabatrin, and oral corticosteroids. [4] The mechanism of action of ACTH in treating infantile spasms is not known.[1]

The Cochrane Collaboration updated a review in 2013 of pharmacotherapeutic agents for treatment of infantile spasms.[3] The analysis included 18 RCTs in 858 patients treated with 12 different medications.[3] Drugs assessed in the RCTs included: ACTH (9 different treatment regimens and preparations), hydrocortisone, prednisone, prednisolone, vigabatrin, magnesium sulfate, nitrazepam, valproate, sulthiame, flunarizine, ganaxolone methysergide, and alpha-methylparatyrosine. Outcome measures included: cessation of spasms, quantitative reduction of spasms, resolution of EEG abnormality, relapse rates, long-term psychomotor development, subsequent epilepsy rates, adverse effects and mortality.[3] Interventions varied by choice of medication, dose, frequency, route of administration and length of treatment. The authors rated the overall quality of the studies as poor due to a small numbers of participants, inadequate power, and unclear methods of randomization, inadequate concealment of allocation, unclear blinding techniques, and loss to follow-up. The authors concluded that ACTH, prednisolone, and tetracosactide depot resolve spasms faster than vigabatrin, but it is not clear if this improves long-term outcomes. The optimum dose of ACTH (150 units/m^2/day vs. 20-30 units/day) is not clear. The FDA approved recommended dose is 150 units/m^2 divided into twice daily intramuscular injections of 75 u/m^2 for 2 weeks.[1] After 2 weeks the dose should be gradually tapered and discontinued over a 2 week period.[1] More research is needed with robust methodology and detailed reporting to clarify optimal pharmacotherapy for management of infantile spasms.

A task force for the Commission of Pediatrics developed consensus recommendations for management of infantile seizures in 2015. Child neurologists were recruited from the International League Against Epilepsy (ILAE). [5] The task force found that evidence was limited due to inconsistency amongst studies, poor study design, and small study sizes. Treatment recommendations were based on low quality evidence and were often based on expert opinion:[5]

- ACTH is preferable in the short-term control of spasms (level B evidence)*
- Oral corticosteroids are probably effective for short-term control of spasms (level C evidence)*
- Data are insufficient to comment on the optimal preparation, dosage, and duration of treatment of corticosteroids (level U evidence)*
- Low-dose ACTH (20-30 IU) may be considered as an alternative to high-dose ACTH (150 IU/m^2) for treatment of epileptic spasms (level B evidence)*
- Vigabatrin is possibly effective in the short-term control of spasms (level C evidence), especially in the case of tuberous sclerosis complex (level C evidence)*

  **American Academy of Neurology Practice parameters: Strength of the practice recommendation based on the reviewed literature*[6]
  - *Level A Established as effective, ineffective, or harmful, or as useful/predictive or not useful/predictive*
  - *Level B Probably effective, ineffective, or harmful, or as useful/predictive or not useful/predictive*
  - *Level C Possibly effective, ineffective, or harmful, or as useful/predictive or not useful/predictive*
  - *Level U Data are inadequate or conflicting; treatment, test or predictor unproven*

Multiple Sclerosis:
No new evidence regarding the use of corticotropin in multiple sclerosis has been published since the last review in 2013.

Other Indications:
No new evidence regarding the use of corticotropin in rheumatic, collagen, dermatologic, or ophthalmic diseases has been published since the last review in 2013.

There were no claims for corticotropin in the Oregon Health Plan Fee-for-Service population during 2015.

Recommendations:
No changes to the current Prior Authorization (PA) criteria are recommended.

References:

1. Acthar Gel (repository corticotropin injection). Hazelwood, MO: Mallinckrodt Pharmaceuticals. January 2015.

2. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. *Epilepsia*. 2010; 51(10):2175-2189. doi:10.1111/j.1528-1167.2010.02657.x.

3. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. [Review][Update of Cochrane Database Syst Rev. 2008 ;(4):CD001770; PMID: 18843624]. *Cochrane Database of Systematic Reviews*. 2013. doi:10.1002/14651858.CD001770.pub3.

4. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2012; 78(24):1974-1980. doi:10.1212/WNL.0b013e318259e2cf.

5. Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. *Epilepsia*. 2015; 56(8):1185-1197. doi:10.1111/epi.13057.

6. Edlund, W, et.al, American Academy of Neurology, 2004 AAN Process Manual.pdf. ww.aan.com/uploadedFiles/Website_Library_Assets/Documents/2.Clinical_Guidelines/4.About_Guidelines/1.How_Guidelines_Are_Developed/.pdf. Accessed June 9, 2016.

Repository Corticotropin Injection

Goal(s):

- To restrict use to patient populations in which corticotropin has been shown to be effective and safe.

Length of Authorization:

4 weeks

Requires PA:

- Repository Corticotropin Injection

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 monotherapy for infantile spasms in infants and children under 2 years of age?	**Yes:** Approve up to 4 weeks (2 weeks of treatment and 2-week taper)	**No:** Go to #3
3. Is the diagnosis for acute exacerbation or relapse of multiple sclerosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient tried and been unable to tolerate intravenous methylprednisolone or high-dose oral methylprednisolone?	**Yes:** Approve up to 5 weeks (3 weeks of treatment, followed by 2-week taper).	**No:** Go to #5

Approval Criteria		
5. Is the prescription for adjunctive therapy for short-term administration in corticosteroid-responsive conditions, including: • The following rheumatic disorders: psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis or ankylosing spondylitis; **OR** • The following collagen diseases: systemic lupus erythematosus or systemic dermatomyositis; **OR** • Dermatologic diseases such as erythema multiforme or Stevens-Johnson syndrome; **OR** • Ophthalmic diseases such as keratitis, iritis, uveitis, optic neuritis, or chorioretinitis; **OR** • For the treatment of respiratory diseases, including symptomatic sarcoidosis or for treatment of an edematous state?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is there a contraindication, intolerance, or therapeutic failure with at least one intravenous corticosteroid?	**Yes:** Approve for 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

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

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Class Update: Oral Cystic Fibrosis Modulators

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

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

Purpose for Class Update:
The purpose of this class update is to evaluate new evidence for the safety and effectiveness of oral Cystic Fibrosis (CF) modulators in reducing respiratory symptoms or pulmonary exacerbations associated with CF and improving quality of life. Additionally, the purpose is to identify who will benefit from oral CF modulators and to better define a clinical response to treatment.

Research Questions:
1. What is the comparative evidence for oral CF modulators (ivacaftor and lumacaftor/ivacaftor) in improving clinically important outcomes such as respiratory symptoms, pulmonary exacerbations, and quality of life in children and adults with CF? If comparative evidence remains insufficient, does any new evidence change previous conclusions regarding the effectiveness or efficacy of ivacaftor or lumacaftor/ivacaftor?
2. What are the comparative harms of oral CF modulators in patients being treated for CF? If comparative evidence remains insufficient, does any new evidence change previous conclusions regarding the safety of ivacaftor or lumacaftor/ivacaftor?
3. Are there subpopulations of patients with CF based on a specific gene mutation, disease severity, race, age, or sex, for which one of the oral CF modulators are more effective or associated with greater harm than other populations?

Conclusions:
- Evidence remains insufficient to compare the efficacy/effectiveness or safety of ivacaftor and lumacaftor/ivacaftor for the treatment of children or adults with CF.
- Evidence remains insufficient to determine the long term effects of ivacaftor and lumacaftor/ivacaftor on long term disease progression.
- Evidence remains insufficient to determine appropriate criteria for stopping ivacaftor or lumacaftor/ivacaftor for lack of effectiveness.
- Evidence remains insufficient to know if lumacaftor/ivacaftor is effective in patients with very severe CF ($ppFEV_1$ <40%) or very mild CF ($ppFEV_1$ >90%).
- Evidence remains insufficient to support clinically important changes in $ppFEV_1$ with lumacaftor/ivacaftor; in addition, there is insufficient long-term evidence to support any improvement in clinically meaningful outcomes with lumacaftor/ivacaftor (i.e., mortality, frequency of pulmonary exacerbations, quality of life and respiratory symptoms).
- Evidence remains insufficient to suggest ivacaftor reduces pulmonary exacerbations or significantly improves lung function in patients with the *R117H* mutation

- Evidence remains insufficient to support improvements in clinically meaningful outcomes with ivacaftor in the FDA approved gating mutations other than G551D (G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D). Evidence of benefit is limited to a modest improvement in FEV_1 compared to placebo and an improvement in sweat chloride concentrations. However, there is no evidence that sweat chloride is correlated with meaningful clinical benefits.
- There is insufficient evidence that lumacaftor/ivacaftor is effective or safe and well tolerated over 24 weeks in children ages 6 to 11 years homozygous for the *F508del* mutation in the CFTR mutation. These data remain unpublished so it is not possible to assess evidence for internal validity or applicability. The FDA approved this expanded indication based on pharmacokinetic data and safety data from an open-label phase 3 safety study (n=58) including only short-term $ppFEV_1$ results.

Recommendations:
- No changes recommended to the PDL.
- Continue to require prior authorization policy (Appendix 3) for the approval in appropriate patients and amend criteria to accommodate FDA approval for use of lumacaftor/ivacaftor in children ages 6 to 11 years.

Previous Conclusions:
- Treatment with LUM/IVA is approved for patients with CF homozygous for the F508del mutation in the CFTR gene. Lifelong therapy is used to slow lung function decline. Treatment has not been demonstrated to be curative.
- There is moderate quality evidence from two randomized controlled trials (RCTs) that short-term use of LUM/IVA 400/250 mg twice daily improves percent-predicted FEV1 compared to placebo over 24 weeks (mean difference 2.8% to 3.3% with LUM 400 mg/IVA twice daily and LUM 600 mg/IVA twice daily, respectively) in CF patients homozygous for the F508del mutation in the CFTR gene; however, the clinical significance of this improvement is unknown. The magnitude of effect (2.8%) was considerably less than that produced by IVA alone versus placebo in patients with G115D mutation (11%) at 24 weeks, and similar to that for IVA alone in the F508del mutation for which IVA was decided to be not efficacious. There is insufficient and inconsistent evidence that LUM/IVA improves body mass index (BMI). Changes in the quality of life questionnaire (CFQ-R respiratory domain) and pulmonary exacerbations were not statistically significant compared to placebo due to hierarchal design, but there was a nominal decrease in pulmonary exacerbations (LUM 400 mg RR 0.61; 95% CI 0.49 to 0.76 for and LUM 600 mg RR 0.70; 95% CI 0.56 to 0.87), and was confounded by other concomitant pre-modulation therapies.
- An area of clinical uncertainty remains whether the combination of LUM/IVA provides more benefit than IVA monotherapy which was found to be deleterious in F508del homozygotes adults in previous clinical trials. With phase 2 trials demonstrating a dose dependent decrease in $PPFEV_1$ with LUM alone, LUM/IVA treatment effect similar to IVA monotherapy, and LUM monotherapy not included as a comparator in confirmatory studies, the clinical significance of the combination agent remains uncertain.
- It is unclear from existing data whether the LUM/IVA combination is superior to IVA alone; evidence so far is insufficient to support use of IVA monotherapy in patients homozygous for the F508del mutation as the drug did not significantly improve percent-predicted FEV1. Although statistically significant, the small FEV1 effect seen with LUM/IVA in CF patients homozygous for the F508del mutation was similar to that for IVA alone (2-3%). The individual components of the drug were not included in phase 3 studies, so it is unknown to what degree each medication contributes to its efficacy.
- There is low quality evidence that LUM/IVA produces a numerical decrease in sweat chloride of about 10 mmol/L, which is a much smaller decrease compared to that observed with IVA alone in patients with the G551D and R117H mutations (50 and 24 mmol/L, respectively). However, change in sweat chloride is not known to be clinically relevant to decline in respiratory function.

- Minor and reversible elevations of transaminases were seen across all groups and significant elevations occurred only in 5.1% of placebo patients and 5.2% of LUM/IVA patients. Serious adverse events related to abnormal liver function were not observed in the placebo group and were reported for seven patients in the LUM/IVA groups. Due to hepatic and respiratory related safety concerns, transaminases and pulmonary function should be monitored throughout therapy; this is particularly important in pediatric patients receiving therapy who will be potentially receiving therapy for years to come.
- LUM/IVA did not demonstrate a significant effect in patients who were heterozygous for the F508del mutation and therapy should not be used in patient populations outside of those homozygous for the F508del mutation.
- More data are needed to determine the long-term effects of LUM/IVA on survival and quality of life as well as the applicability of LUM/IVA in real-world settings, including criteria that define treatment success and time to response after initiation.

Previous Recommendations:

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

Background:

Cystic Fibrosis (CF) is a genetic disease that can affect multiple organs, of which progressive lung disease is responsible for approximately 85% of mortality observed in this population.[1] Most available treatments for CF focus on symptom management and treatment of chronic infection, including antibiotics, dornase alfa, hypertonic saline, inhaled corticosteroids, oral nonsteroidal anti-inflammatory drugs, and inhaled bronchodilators.[2] CF is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, found on the surface of cells in a variety of tissues where it functions as a regulator of the chloride ion channel.[3] Over 1900 mutations have been identified in the CFTR gene, with different protein defects resulting from the mutation.[4] The F508del mutation results in misprocessing of CFTR resulting in failure of CFTR to travel to the cell surface, while the G551D and other gating mutations result in failure of CFTR to open channels at the cell surface. Lastly, the R117H mutation affects chloride conductance in the pore region of the channel leading to poor conductance of chloride ions.[4] There are three common alleles at the poly-T locus of the *R117H* gene (5T, 7T, 9T), with the 5T variant associated with greater severity of CF.[5] Of the various clinical symptoms of CF, only pancreatic function has been shown to correlate well with CFTR genotype. The most common CFTR mutation is the *F508del*, which accounts for approximately two thirds of the recognized mutations, and carries the most severe prognosis.[6]

Clinically meaningful outcomes of CF treatment include mortality, frequency of pulmonary exacerbations, quality of life and respiratory symptoms. Forced expiratory volume in one second (FEV_1) is a commonly used surrogate outcome in clinical trials. A minimal clinically important difference for FEV_1 has not been defined because of the heterogeneous nature of the condition.[7] Changing the FEV_1 rate of decline would be the most meaningful effect, but would require a long study duration. In CF patients, FEV_1 decreases on average by 1-3% per year but varies based on age and baseline lung function.[8] The Cystic Fibrosis Questionnaire-revised (CFQ-R) is a validated patient-reported outcome questionnaire specific to CF which focuses on health perception, quality of life, and clinically relevant respiratory symptoms. A minimally clinically important difference of 4 points was established for the respiratory symptom domain.[9] Weight is also a commonly measured secondary outcome in trials of CF children, as studies have shown that lower than average birth weights and poor growth are correlated with poorer lung function, and increased morbidity and mortality.[9] The nutritional status of patients with CF is strongly associated with pulmonary function, respiratory status and survival. Sweat chloride level is the gold standard for a diagnosis of CF. Normal individuals typically have levels <40 mmol/L but patients with CF have elevated levels >60 mmol/L.[10] More recently, endpoints such as sweat chloride, nasal potential difference, and the intestinal current measurement are proposed surrogate markers of CFTR function, as these reflect sodium absorption and chloride secretion dependent on CFTR function.[4] Sweat chloride has been used as a biomarker for evaluation of change in CFTR activity in clinical trials of ivacaftor.[11] Although initial studies showed a reduction in the sweat chloride levels to values below the diagnostic threshold for CF (60 mmol/L), there is no evidence that sweat chloride is correlated with meaningful clinical

benefits and it has not shown to correlate with improvement in FEV_1. [10] Clinical severity of CF is dependent on other factors in addition to CFTR function, and what aspect of CFTR function is affected depends on the specific combination of mutations in the individual.

Ivacaftor (Kalydeco®) and lumacaftor/ivacaftor (Orkambi®) are oral agents intended to enhance mutant CFTR protein function.[12] Both of these agents are specific to CFTR mutation dysfunction. Ivacaftor is a CFTR potentiator indicated for the management of CF in patients in patients 2 years of age and older who have one of the following gating mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H.*[13] The most common gating mutations, G551D and R117H, represent approximately 7% of the U.S. CF population.[12] In trials of patients with the G115D mutation, ivacaftor increased FEV1 by an absolute value of 10.6% compared to placebo within 2 weeks of treatment; a 26% absolute decrease in respiratory exacerbations, a reduction in sweat chloride values by 50-60 mmol/L and a weight gain of 2.7 kg was also found.[14] However, the 2-week endpoint was noted in a post-hoc analysis but the study was designed to look at outcomes at 24 weeks. Ivacaftor is proposed to treat the underlying cause of CF by influencing the basic gene defect which can normalize airway surface liquid and help re-establish mucociliary clearance.[15,16] Ivacaftor is designed to increase the time that activated CFTR channels at the cell surface remain open. [15,16]

Lumacaftor/ivacaftor is a combination drug that contains the molecular entity lumacaftor. The exact mechanism of lumacaftor is unknown, but it may promote more functional folding of the defective F508del CFTR protein, allowing it to get to the cell surface. Previous studies of ivacaftor did not demonstrate a clinical improvement in lung function in patients with an F508del mutation.[6] However, the combination was approved after phase 3 trials demonstrated its efficacy for the management of CF in patients 12 years of age and older homozygous for the F508del mutation in the CFTR gene.[17] Phase 2 trials demonstrated lack of improvement in patients heterozygous for the F508del CFTR mutation.[18] It is currently FDA-approved for those age 12 years and older who are homozygous for the F508del mutation in the CFTR gene.[19] This patient group includes approximately 34% of the U.S. CF population.[12] Studies of lumacaftor/ivacaftor did not demonstrate clinically significant results on meaningful outcomes. It was associated with only a absolute 2.8% improvement in FEV1 (estimated by averaging the absolute change at weeks 16 and 24) and nominal decrease in pulmonary exacerbations compared to placebo (RR 0.61; 95% CI 0.49 to 0.76). However, this outcome was actually reported as the number of events per 48 weeks which is unreliable since the trial only went through 24 weeks. There is insufficient evidence to make the assumption that a reduction in pulmonary exacerbations is maintained as long as people stayed on treatment. It remains unclear if the combination provides more benefit than ivacaftor alone which was found to be deleterious in F508del homozygous adults in previous trials.

Methods:

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

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

New Systematic Reviews:

A Cochrane Collaboration systematic review evaluated the effects of CFTR potentiators on clinically important outcomes in children and adults with CF.[20] Four RCTs were identified and included in the review (n=378) comparing ivacaftor to placebo. No trials including lumacaftor/ivacaftor were included in this analysis. Risk of bias in included trials was moderate. Participant blinding was not clear and participant data were excluded from the analysis in 3 trials. Overall, in the adult phase 3 trial, there was an improvement in relative change from baseline in FEV_1 at 24 weeks (mean difference 16.9%; 95% CI 13.6 to 20.2%) and 48 weeks (mean difference 16.80%; 95% CI 13.50 to 20.10%). In the pediatric trial, there was an improvement also seen at 24 weeks (mean difference 17.4%).[20] Results are not available out to 48 weeks in children and only interim data was available from a conference abstract. Significantly higher quality of life scores in the respiratory domain were reported in the adult trials, but not in the pediatric trials. No improvements in quality of life or lung function were reported in the F508del participants. In the phase 3 G551D trials, fewer participants developed pulmonary exacerbations when on ivacaftor than placebo (OR 0.54; 95% CI 0.29 to 1.01). Data reviewed were limited only to those with the G551D mutation. The authors concluded that in this population, phase 3 trials demonstrated a clinically relevant impact of ivacaftor on outcomes. [20]

New Guidelines:

1. Guidance from the National Institute for Health and Clinical Excellence (NICE) published recommendations for lumacaftor-ivacaftor for treating cystic fibrosis homozygous for the F508del mutation.[7] The following recommendation was included:
    - *Lumacaftor/ivacaftor is not recommended for treating CF in people 12 years and older who are homozygous for the F508del mutation in the CFTR gene.*

This recommendation came from a systematic review of the literature which identified 2 studies evaluating clinical effectiveness and safety of lumacaftor/ivacaftor. The panel concluded that the two trials were generally of good quality and included people with mild to moderate CF and therefore the clinical evidence may not be generalizable to people with severe CF ($ppFEV_1$ <40%) or with very mild CF ($ppFEV_1$ >90%). In addition, the absolute change in $ppFEV_1$ was less than 5% which would be considered clinically important and there was insufficient long-term evidence to support the assumptions that a reduction in pulmonary exacerbations is maintained as long as people stay on treatment.

2. The CF Foundation developed clinical care guidelines for preschool-aged children with CF.[21] The guideline committee consisted of 16 CF pediatric experts and parents; however, non-specialists or experts in methodology were not included on the guideline committee. Overall, there are very little data in children ages 2 to 5 years old and therefore the recommendations included in the guideline are based on expert opinion and are likely to change based on additional research.

New Safety Alerts:

None identified.

New Formulations or Indications:

In September 2016, the FDA approved lumacaftor/ivacaftor for use in an expanded population of patients, children ages 6 to 11 years, who are homozygous for the F508del mutation.[19] This is expected to cover approximately 2,400 additional patients in the U.S. Dosing in children ages 6 to 11 years is 2 lumacaftor 100 mg/ivacaftor 125 mg tablets every 12 hours. The efficacy in this group was extrapolated from previous studies in patients' aged 12 years and older with additional pharmacokinetic analyses showing similar drug exposure levels.[19]

The decision by the FDA to expand the indication was also based on data from an open-label phase 3 safety study (n=58) that remains unpublished.[19] A baseline ppFEV$_1$> 40% was required for inclusion. The within group mean absolute change from baseline in ppFEV$_1$ at week 24 was 2.5 percentage points. Patients were recruited from 6 sites within the US. This trial remains unpublished. In addition, study results have not been posted by the drug sponsor on clinicaltrials.gov. Therefore, it is not possible to assess the internal validity (i.e., risk of bias) or applicability of the clinical trial. In addition, it is not possible to grade the evidence based on other domains such as consistency or precision of study results.

Randomized Controlled Trials:

A total of 20 citations were manually reviewed from the literature search. After manual review, all 20 trials were excluded because of wrong study design (observational), outcome studied (non-clinical), wrong therapy (topical), or were published prior to November 2015.

References:

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

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

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

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

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

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

7. National Institute for Health and Care Excellence (NICE). Lumacaftor-ivacaftor for treating cystic fibrosis homozygoux for the F508del mutation. Technology appraisal guidance. Published: July 27 2016. Available at: www.nice.org.uk/guidance/ta398.

8. Liou TG, Elkin EP, Pasta DJ, et al. Year-to-year changes in lung function in individuals with cystic fibrosis. *J Cyst Fibros*. 2010;9(4):250-256. doi:10.1016/j.jcf.2010.04.002.

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

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

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

12. Mayer-Hamblett N, Boyle M, VanDevanter D. Advancing clinical development pathways for new CFTR modulators in cystic fibrosis. [Review]. *Thorax*. 2016;71(5):454-461. doi:10.1136/thoraxjnl-2015-208123.

13. Vertex Pharmaceuticals. Kalydeco (ivacaftor) Prescribing Information. March 2015. http://pi.vrtx.com/files/uspi_ivacaftor.pdf. Accessed April 28, 2014.

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

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

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

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

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

19. Orkambi Prescribing Information. Prescribing Information. Vertex Pharmaceuticals. Boston, MA 02210. September 2016. http://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf.

20. Patel S, Sinha IP, Dwan K, Echevarria C, Schechter M, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. [Review]. *Cochrane Database of Systematic Reviews*. 2015. doi:10.1002/14651858.CD009841.pub2.

21. Lahiri T, Hempstead SE, Brady C, et al. Clinical Practice Guidelines From the Cystic Fibrosis Foundation for Preschoolers With Cystic Fibrosis. *Pediatrics*. 2016;137(4). doi:10.1542/peds.2015-1784.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	GRAN PACK	KALYDECO	IVACAFTOR	N
ORAL	TABLET	KALYDECO	IVACAFTOR	N
ORAL	TABLET	ORKAMBI	LUMACAFTOR/IVACAFTOR	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to September Week 2, 2016
1 ivacaftor.mp. 212
2 lumacaftor.mp. 72
3 kalydeco.mp. 12
4. Cystic Fibrosis Trtansmembrane Conductance Regulator/ 6727
5 orkambi.mp. 2
6. 1 or 2 or 3 or 4 or 5
7. cystic fibrosis.mp or Cystic Fibrosis/ 26187
8 6 and 7
9 limit 8 to (English language and humans and yr="2015-Current" and (clinical trial or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews)) 20

Oral Cystic Fibrosis Modulators

Goals:

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

Length of Authorization:

- 90 days to 6 months

Requires PA:

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

Preferred Alternatives:

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

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program (patient already on ivacaftor or lumacaftor/ivacaftor)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Is the request from a practitioner at an accredited Cystic Fibrosis Center or a pulmonologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. How many exacerbations and/or hospitalizations in the past 12 months has the patient had?	Prescriber must provide documentation before approval. Document baseline value. Go to #5	

Approval Criteria		
5. Is the request for ivacaftor?	**Yes:** Go to #6	**No:** Go to #10
6. What is the patient's baseline sweat chloride level?	Prescriber must provide documentation before approval. Document baseline value. Go to #7	
7. Does the patient have a diagnosis of cystic fibrosis and is 2 years of age or older?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have a documented G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene detected by an FDA-cleared CF mutation test?	**Yes:** Go to #14	**No:** Go to #9 If unknown, there needs to be a FDA-approved CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).
9. Does the patient have a documented R117H mutation in the CFTR gene detected by an FDA-cleared CF mutation test?	**Yes:** Pass to RPh. Refer request to Medical Director for manual review and assessment of clinical severity of disease for approval.	**No:** Pass to RPh. Deny; medical appropriateness. If unknown, there needs to be a FDA-approved CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).

Approval Criteria		
10. Is the request for lumacaftor/ivacaftor?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Does the patient have a diagnosis of cystic fibrosis and is ~~12~~ 6 years of age or older?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Does the patient have a documented homozygous Phe508del mutation in the CFTR gene detected by an FDA-approved CF mutation test?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness If unknown, there needs to be a FDA-approved CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including those who are heterozygous for the F508del mutation)
13. Is a baseline FEV1 is provided and is between ≥40% and ≤90% of predicted normal for age, sex and height for those ≥ 12 years of age and at least 40% for children 6-11 years?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness If no baseline, request a baseline value before approving therapy.
14. Is the patient on ALL the following drugs, or has had an adequate trial of each drug, unless contraindicated or not appropriate based on age <6 years and normal lung function: • Dornase alfa; AND • Hypertonic saline; AND • Inhaled or oral antibiotics (if appropriate)?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
15. Is the patient on concomitant therapy with a strong CYP3A4 inducer (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #16
16. What are the baseline liver function (AST/ALT) and bilirubin levels (within previous 3 months)?	Document labs. Go to #17	
17. Is medication dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for 90 days Note: Approve for 90 days to allow time for patient to have a sweat chloride test done after 30 days of treatment if on ivacaftor (see **Renewal Criteria**)	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is this the first time the patient is requesting a renewal (after 90 days of initial approval)?	**Yes:** Go to #2	**No:** Go to #4
2. If prescription is for ivacaftor: Does the patient have a documented physiological response to therapy and evidence of adherence after 30 days of treatment, as defined by a sweat chloride test that has decreased by at least 20 mmol/L from baseline?	**Yes:** Go to #7	**No:** Go to #3 Consider patient's adherence to therapy and repeat test in 2 weeks to 45 days to allow for variability in test. If sodium chloride has still not decreased by 20 mmol/L, deny therapy for medical appropriateness

Renewal Criteria		
3. If the prescription is for lumacaftor/ivacaftor: Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?	**Yes:** Go to #7	**No:** Pass to RPh; Deny (medical appropriateness)
4. Does the patient have documented response to therapy as defined as below : For patients age ≥6 years: • An improvement or lack of decline in lung function as measured by the FEV1 when the patient is clinically stable; OR • A reduction in the incidence of pulmonary exacerbations; OR • A significant improvement in BMI by 10% from baseline? For patients age 2-5 years (cannot complete lung function tests) • Significant improvement in BMI by 10% from baseline; OR • Improvement in exacerbation frequency or severity; OR • Sweat chloride test has decreased from baseline by 20 mmol/L from baseline?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient been compliant with therapy, as determined by refill claims history?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
6. Have liver function tests been appropriately monitored? What are the most recent liver function tests (AST, ALT, and bilirubin)? Note: Monitoring LFTs is recommended every 3 months for the first year, followed by once a year.	Document. Go to #7 Note: Therapy should be interrupted in patients with AST or ALT >5x the upper limit of normal (ULN), or ALT or AST >3x ULN with bilirubin >2x ULN.	
7. Is the CFTR modulator dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for additional 4 months (total of 6 months since start of therapy)	**No:** Pass to RPh. Deny; medical appropriateness

Dosage and Administration:

<u>Ivacaftor:</u>

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

Table 1. Examples of CYP3A4 inhibitors and inducers.

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

Lumacaftor/ivacaftor:

- Adults and pediatrics age ≥12 years: 2 tablets (lumacaftor 200 mg/ivacaftor 125 mg) every 12 hours
- Pediatric patients age 6 through 11 years: 2 tablets (lumacaftor 100mg/ivacaftor 125 mg) every 12 hours
- Hepatic impairment
  - Moderate impairment (Child-Pugh class B):
    - 2 tablets in the morning and 1 tablet in the evening
  - Severe impairment (Child-Pugh class C): Use with caution at a dose of 1 tablet twice daily, or less, after weighing the risks and benefits of treatment.
- Dose adjustment with concomitant medications:
  - When initiating therapy in patients taking strong CYP3A inhibitors (see table above), reduce dose to 1 tablet daily for the first week of treatment. Following this period, continue with the recommended daily dose.

P&T Review: *11/16 (MH);11/15; 7/15; 5/15; 5/14; 6/12*
Implementation: *TBD; 1/1/16; 8/25/15; 8/12*

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Class Update: Opioid Analgesics

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

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

Purpose for Class Update:
The purpose of this update is to propose new drug policies for short- and long-acting opioid analgesics that align with guidance from the U.S. Centers for Disease Control and Prevention (CDC) and the prioritized list of health services established by the Oregon Health Plan (OHP) Health Evidence Review Commission (HERC). The focus of the review will be on evidence for short-acting opioids (SAO) published since this class was last presented to the Oregon Drug Use Review / Pharmacy and Therapeutics (P&T) Committee in May 2015. The long-acting opioid class was recently reviewed by the P&T Committee in May 2016;[1] however, new approvals by the U.S. Food and Drug Administration (FDA) of long-acting opioid products since May 2016 will also be reviewed.

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

Conclusions:
- Updated evidence for SAO comes from one systematic review of opioids for chronic low back pain,[2] one systematic review that compared NSAIDs to opioids for acute soft tissue injuries,[3] one systematic review of hydromorphone for neuropathic pain,[4] and 2 systematic reviews that studied tramadol with or without acetaminophen.[5,6] In general, systematic reviews that specifically limited their research to SAO analgesics were not found. Two randomized controlled clinical trials assessed SAO agents in the Emergency Department (ED) setting.[7,8]
- There is insufficient comparative evidence to know if SAOs differ in their analgesic effect for acute or chronic non-cancer pain when given at equivalent doses. Increasing the dose of an opioid, or combining an opioid with a simple analgesic such as acetaminophen, modestly improves analgesia in chronic pain but it is unclear if these improvements are clinically important.
- There is low quality but consistent evidence of no difference in functional improvement or pain relief from acute soft tissue injuries between NSAID therapy and opioid therapy with or without acetaminophen.

- There is insufficient comparative evidence to know if SAOs differ in harms, such risk for abuse, diversion, addiction, or respiratory depression when administered at equipotent doses, regardless of whether the formulation has abuse-deterrent properties or not.
- There is insufficient evidence to know if specific subpopulations may benefit more from one SAO over another.
- Evidence for use of a new extended-release capsule formulation of oxycodone and naltrexone (Troxyca ER) is based on one short-term, placebo-controlled trial in patients with chronic low back pain that showed modest pain reduction of unclear clinical importance.[9]

Recommendations:

- No further review or research needed at this time. Review comparative SAO costs in the executive session to inform PDL status.
- Maintain non-preferred status for Troxyca ER (oxycodone/naltrexone) extended-release capsules.
- Approve the proposed clinical prior authorization (PA) criteria for short- and long-acting opioid analgesics in **Appendix 4**. Current prior authorization criteria for opioid analgesics approved by the P&T Committee in May 2016 are in **Appendix 5**.
    - Patients with a terminal diagnosis or cancer diagnosis are exempt from PA.
    - All non-preferred SAO products and preferred SAO products prescribed for more than 7 days are subject to clinical PA criteria.
    - All long-acting opioid analgesics are subject to clinical PA criteria.
    - Update quantity limits for new drug approvals.
- Oregon Health Authority to work with the Pharmacy Benefits Manager (HPE) on timing of implementation of new drug policies.

Previous Conclusions and Recommendations:

- Update current prior authorization criteria for excessive dose limits on opioid/non-narcotic combination products.
- Propoxyphene products and combination products containing 500 mg of acetaminophen were removed, and the maximum recommended daily aspirin dose was decreased from 8 g/day to 4 g/day.

Background:

More than 30% of persons within the U.S. have some form of acute or chronic pain.[10] An estimated 20% of patients who present to physician offices with non-cancer pain symptoms or pain-related diagnoses (acute or chronic) receive an opioid prescription.[11] Opioid analgesics are now the most commonly prescribed class of medications in the U.S.[10] Per capita prescriptions for opioid analgesics increased 7.3% from 2007 to 2012, with the largest increases occurring in family practice, general practice and internal medicine compared to other specialties.[11] About 65% of opioid prescriptions dispensed from retail pharmacies are for short-term (<3 weeks) therapy.[10] However, approximately 3-4% of the U.S. adult population receives long-term opioid therapy, which accounts for an estimated 9.6-11.5 million adults.[11] There is a clear lack of consensus among prescribers, however, as stark differences in opioid prescribing patterns exist between states that cannot be explained by underlying health status.[11]

Prevention, assessment, and treatment of chronic pain are challenging for clinicians. Pain might go unrecognized, and patients of racial and ethnic minority groups, women, elderly, persons with cognitive impairment, patients with cancer, and patients at the end of life, can be at risk for inadequate pain treatment.[11] There are clinical, psychological and social consequences associated with chronic pain. For example, pain can limit the ability to perform certain activities, and can result in decreased work productivity, reduced quality of life, and stigma. However, there are also serious harms associated with opioid use. Opioid analgesics are widely diverted and improperly used, which has resulted in a national epidemic of opioid-related deaths.[10] From 1999 to 2014, more than 165,000 people died from overdose related to opioids in the U.S, and increasing rates of overdose deaths during that time correlated with increasing rates of opioid

prescribing.[11] In addition, more than 420,000 ED visits were related to misuse or abuse of opioids in 2011, the last year with available data for ED visits.[11] Increased diagnoses of opioid use disorder, which is distinct from opioid dependence or tolerance which inevitably results with repeated administration of an opioid, has shown that opioid misuse and abuse causes significant impairment and distress in an increasing number of opioid users in the U.S.

The major source of diverted opioids is from physician prescriptions.[10] Such consequences emphasize the importance of appropriate and compassionate care with careful consideration of the benefits and risks of treatment options.[11] Many clinicians, however, admit that they are not confident about how to prescribe opioids safely, how to detect emerging addiction, or even how discuss these issues with their patients.[10] Addiction to opioids is unpredictable and is not limited to a few high-risk individuals even when risk mitigation strategies are used.[12] The CDC issued guidance in 2016 for prescribing opioids for chronic pain to help address some of these issues.[11] The guidance is based on a systematic review of studies over the past 20 years, expert opinion and stakeholder review in order to inform recommendations for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care.[11] Pain management involves a full range of therapeutic options. However, it is difficult to estimate the number of patients who could potentially benefit from long-term opioid therapy. Evidence supports short-term efficacy (less than 12 weeks) of opioids for relieving pain and improving function in non-cancer nociceptive and neuropathic pain,[11] although the effects in some pain conditions such as low back pain are modest and may not be clinically meaningful for most patients.[2] Evidence for long-term efficacy of opioids, however, is lacking despite well documented risks for long-term opioid therapy.[11]

In 2016, the Oregon Health Plan (OHP) Health Evidence Review Commission (HERC) established Guideline Note 60 in the Prioritized List of Health Services based on evidence for low back pain.[13] Low back pain is the leading cause of disability worldwide and is the leading reason for prescribing opioids in the primary care setting.[12] Low back pain can be managed with several nonpharmacological measures which can be supplemented with analgesics like acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs).[2] However, many patients with chronic low back pain are prescribed opioid analgesics despite their lack of long-term efficacy, their well-documented harms, and modest, if clinically insignificant, short-term pain relief.[2] The HERC clinical guideline note establishes restrictions for opioid prescribing for conditions of the back and spine in OHP patients:[13]

For <u>acute</u> injury, acute flare of chronic pain, or after surgery:

1) *During the first 6 weeks after the acute injury, flare or surgery, opioid treatment is included on these lines ONLY*
    a. *When each prescription is limited to 7 days of treatment, AND*
    b. *For short acting opioids only, AND*
    c. *When one or more alternative first line pharmacologic therapies such as NSAIDs, acetaminophen, and muscle relaxers have been tried and found not effective or are contraindicated, AND*
    d. *When prescribed with a plan to keep active (home or prescribed exercise regime) and with consideration of additional therapies such as spinal manipulation, physical therapy, yoga, or acupuncture, AND*
    e. *There is documented lack of current or prior opioid misuse or abuse.*
2) *Treatment with opioids after 6 weeks, up to 90 days, requires the following:*
    a. *Documented evidence of improvement of function of at least thirty percent as compared to baseline based on a validated tools (e.g. Oswestry, Neck Disability Index, SF-MPQ, and MSPQ);*
    b. *Must be prescribed in conjunction with therapies such as spinal manipulation, physical therapy, yoga, or acupuncture;*
    c. *Verification that the patient is not high risk for opioid misuse or abuse. Such verification may involve:*
        i. *Documented verification from the state's prescription monitoring program database that the controlled substance history is consistent with the prescribing record*
        ii. *Use of a validated screening instrument to verify the absence of a current substance use disorder (excluding nicotine) or a history of prior opioid misuse or abuse*

iii. Administration of a baseline urine drug test to verify the absence of illicit drugs and non-prescribed opioids;

d. Each prescription must be limited to 7 days of treatment and for short acting opioids only.

3) Further opioid treatment after 90 days may be considered ONLY when there is a significant change in status, such as a clinically significant verifiable new injury or surgery. In such cases, use of opioids is limited to a maximum of an additional 7 days. In exceptional cases, use up to 28 days may be covered, subject to the criteria in #2 above.

For patients with chronic pain from diagnoses on these lines currently treated with long term opioid therapy, opioids must be tapered off using an individual treatment plan developed by January 1, 2017 with a quit date no later than January 1, 2018. Taper plans must include nonpharmacological treatment strategies for managing the patient's pain based on Guideline Note 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE. If a patient has developed dependence and/or addiction related to their opioids, treatment is available on Line 4 SUBSTANCE USE DISORDER.[13]

There is no simple or single change in prescribing that can alleviate risk for opioid diversion, overdose and addiction since these risks are largely independent and governed by different factors.[10] The contributing factors associated with overdose can be divided into those associated with the opioid itself (potency, dose, duration of action) and factors specific to the patient (e.g., older age, adolescence, depression, substance use disorder, history of overdose). However, several common strategies can mitigate these risks: 1) use of screening tools to identify patients with a substance-use disorder (e.g., Opioid Risk Tool; the Screener and Opioid Assessment for Patients with Pain [SOAPP], version 1.0; SOAPP-Revised; or the Brief Risk Interview); 2) use of data from the Prescription Drug Monitoring Program (PDMP); 3) use of urine drug screening; and 4) doctor-patient agreement on opioid adherence.[10]

Routine use of opioid analgesia for pain management should be practiced only with the awareness of opioid abuse and the role that prescription opioids have in contributing to opioid abuse.[12] Information on potential misuse and abuse of prescription opioid analgesics can help prescribers such as primary care physicians and dentists strike a balance between alleviating pain for patients and ensuring safe prescribing.[14] Prescription drug monitoring programs (PDMP) are statewide databases that accrue information from pharmacies on dispensed prescriptions of controlled substances. All states except Missouri have implemented the PDMP as a tool to curb high-risk prescribing behaviors (i.e., multiple prescriptions from multiple prescribers) and abuse of controlled substances like opioid analgesics.[15] Prescribers, pharmacists, law enforcement agencies, and medical licensure boards may access their state PDMP for information on controlled substance prescribing.[14] National data over a 10-year period have shown that implementation of a PDMP has been associated with a sustained reduction of more than 30% in rates of opioid prescribing and a slight increase in prescribing of non-opioid analgesics.[14] The PDMPs have also been associated with an average reduction of 1.12 opioid-related overdose deaths per 100,000 population in their first year after implementation, with more robust programs associated with greater reductions in opioid-related overdose deaths.[15]

Pain research is needed to improve the practice of opioid prescribing.[10] Areas of uncertainty include how to differentiate the unique properties of acute and chronic pain and how to describe the process by which acute pain transitions into chronic pain.[10] In addition, research is needed to identify new, potent non-opioid analgesics and other pain treatment strategies.[10] In general, opioids have shown modest efficacy in pain reduction. Pain intensity measurements used in the trials included the visual analog scale (VAS; scale, 0-100 or 0-10) and numerical rating scale (NRS; scale, 0-10).[2] The NRS and VAS are highly correlated and can be interpreted equally.[2] For acute pain, the minimum clinically important difference (MCID) in the 11-point VAS is 1.4 (95% CI, 1.2 to 1.6).[16] Similar MCID values have been shown with 100-point scales.[17] The proposed MCID thresholds for chronic pain and low back pain are about 2.0 points on the 0 to 10-point scale or 20 points on the 0 to 100-point scale.[2] The impact of opioids on disability is also frequently studied in clinical trials of low back pain. Measurements commonly used include the Oswestry Disability Index scores (range, 0-100) and the Roland-Morris Disability Questionnaire (RMDQ) scores (range, 0-24).[2] The Oswestry Disability Index and RMDQ tools are also highly correlated and share similar properties.[2] Similarly, a 10-point difference in 0-100 scales for chronic disability is considered a "minimal" difference and 20-point differences are considered to be "clinically important".[2]

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 U.S. Food and Drug Administration (FDA) website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

All FDA approvals identified since the long-acting opioid class update was reviewed and presented to the DUR/P&T Committee in May 2016 will also be included under "New Formulations or Indications".

New Systematic Reviews:
Opioids for Low Back Pain
A recently published systematic review with meta-analysis assessed the association between use of opioid analgesics and clinical efficacy, tolerability, and dose-dependent effects in patients with chronic low back pain.[2] Eligible studies included RCTs that studied single ingredient or combination opioid analgesics in patients with nonspecific acute or chronic low back pain (i.e., low back pain where a cause had not been identified).[2] Studies were included if they reported pain, disability or adverse event (AE) outcomes.[2] Both placebo-controlled RCTs and RCTs that compared 2 opioids or different doses of the same drug were eligible for inclusion.[2] Pain and disability outcomes were converted to a common 0 to 100 scale (0 = no pain or disability; 100 = worst possible pain or disability).[2] Pain intensity measurements used in the trials included the VAS and NRS.[2] The NRS was converted to the same 0-100 scale as in the VAS because of the high correlation between the tools.[2] The disability measurements used to calculate pooled effects were Oswestry Disability Index scores (range, 0-100) and Roland-Morris Disability Questionnaire (RMDQ) scores (range, 0-24).[2] The RMDQ was also converted to the same 0-100 scale as in the Oswestry Disability Index because of the high correlation between the tools and the fact that they share similar properties.[2] Results were presented in mean differences (MD).[2] A 10-point difference in 0-100 scales for pain and disability was considered a "minimal" difference and a 20-point difference was considered to be "clinically important" which is consistent with thresholds for MCIDs for chronic pain and low back pain literature.[2] The investigators considered differences less than 10 points (out of 100) on the pain or disability scales to be unnoticeable by most patients.[2] Short-term pain relief (follow-up <3 months) was the primary outcome.[2] Intermediate-term (≥3 months to <12 months) and long-term (≥12 months) pain relief was also evaluated if data were available.[2] Grading of recommendations assessment, development, and evaluation (GRADE) criteria were used to evaluate the evidence.

A total of 20 RCTs were included (n=7295 patients); 17 trials compared an opioid analgesic to placebo and 3 trials compared 2 opioid analgesics.[2] All but one trial evaluated patients with chronic low back pain and one head-to-head trial evaluated patients with subacute low back pain.[2] Subjects enrolled in 7 of the 13 trials were ineligible to be randomized in their respective studies unless they responded favorably to the study opioid and tolerated the drug in the initial run-in phase of the trial.[2] There was moderate-quality evidence from 13 studies of chronic low back pain (n=3419) for short-term efficacy of questionable clinical importance

for single-ingredient opioid analgesics on pain relief (MD -10.1; 95% CI, -12.8 to -7.4).[2] There was high-quality evidence from 6 studies (n=2605) for intermediate-term efficacy for single-ingredient opioid analgesics on pain relief (MD -8.1; 95% CI, -10.2 to -6.0).[2] Combination opioid analgesics (e.g., with acetaminophen) had moderate-quality evidence for intermediate-term efficacy on pain relief (MD -11.9; 95% CI, -19.3 to -4.4).[2] The effects of single-ingredient and combination opioids were minimal at approximately half the 20-point threshold for clinical importance, and in no case did the confidence intervals cross the 20-point clinically important threshold.[2] There were limited data on disability outcomes. Very low quality evidence from 2 short-term trials showed modest improvements by 4-6 points that were not clinically significant.[2]

The morphine milligram equivalent (MME) daily dose in these 13 studies ranged from 40.0 to 242.7 mg per day. A meta-regression model of these trials showed significant effects of the opioid dose on treatment effects, with a 12.0-point greater pain relief for every 10 MME per day increase in dose (p=0.046).[2] However, none of the doses recommended in the guidelines (40-120 MME/day) achieved clinical important pain relief in these trials.[2] In half of the trials, 50% of the patients enrolled withdrew early from the studies because of lack of pain relief.[2] Even in 7 trials where subjects were enrolled only if they tolerated and responded to medication in the run-in phase, early withdrawal ranged from 31.4% to 61.9% due to AEs and 3.3% to 29.6% withdrew early due to lack of efficacy.[2] Overall, the median rates of AEs were 49.1% for placebo (interquartile range [IQR] 44.0-55.0%) and 68.9% (IQR 55.0-85.0%) (risk ratio [RR] 1.3; p<0.01).[2] The most common AE reported were related to the central nervous system (headache, somnolence, dizziness), the gastrointestinal tract (constipation, nausea, vomiting) and autonomic events such as dry mouth.[2]

NSAIDs vs. Opioid Analgesics

The Cochrane Collaboration conducted a recent systematic review to assess the benefits and harms of NSAIDs with other oral analgesics, including opioid analgesics, for treatment of acute soft tissue injuries.[3] Sixteen RCTs that compared oral NSAID therapy to acetaminophen, or an opioid with or without acetaminophen in subjects with acute soft tissue injury that occurred within 48 hours of injury were included in the review.[3] Soft tissue injuries could be a sprain, strain or contusion of a joint, ligament, tendon or muscle.[3] Studies were excluded if they focused on back pain, cervical spine injury, repetitive strain injuries, delayed onset muscle soreness or primary inflammatory injuries (i.e., tendonitis or arthritis).[3] No restrictions were placed on age of subjects.[3] The primary outcome was pain which was assessed using categorical or VAS.[3] Secondary outcomes included swelling, function and AEs.[3] Quality of evidence was assessed using GRADE criteria.[3] Sixteen trials were included, 4 trials (n=958) of which compared NSAIDs with opioid therapy and 4 trials (n=240) that compared NSAIDs with opioid plus acetaminophen therapy.[3]

Most of the evidence that compared NSAID therapy to opioid therapy (without acetaminophen) focused on valdecoxib which was subsequently withdrawn from the market.[3] Pooled data from the remaining trials provided low quality evidence of no clinically important difference between NSAID therapy versus opioid therapy for acute soft tissue injuries when pain was measured using a VAS (0 to 100 mm) within 24 hours of therapy (MD 0.10 mm; 95% CI, -3.55 to 3.74 mm), at days 4 to 6 (MD -2.9 mm; 95% CI, -6.06 to 0.26 mm), and at day 7 (-6.50 mm; 95% CI, -9.31 to -3.69).[3] Little difference was found between the two groups in the number of patients with swelling at day 10 in one study (15/44 vs. 12/40; RR 1.14; 95% CI, 0.61 to 2.13).[3] However, return to function at or after day 7 was superior with NSAID therapy versus opioid therapy in pooled analysis (366/484 vs. 176/265, respectively; RR 1.13; 95% CI, 1.03 to 1.25; p=0.01) based on low quality evidence.[3] There were fewer gastrointestinal (GI) AEs with Cox-2 selective NSAID therapy versus opioid therapy (50/468 vs. 60/238, respectively; RR 0.42; 95% CI, 0.30 to 0.60) but no difference was seen with non-selective NSAID therapy versus opioid therapy (9/31 vs. 5/32, respectively; RR 1.86; 95% CI, 0.70 to 4.93; p=0.21) based on very low quality evidence with significant heterogeneity (I^2=87.3%).[3]

Most of the evidence that compared NSAID therapy to opioid plus acetaminophen therapy used propoxyphene combination drugs that are no longer available.[3] Overall, very low quality evidence suggests no difference in relief of pain (little to no pain) between NSAID therapy versus opioid plus acetaminophen therapy at

day 1 (1/26 vs. 0/25, respectively; RR 2.89; 95% CI, 0.12 to 67.75; p=0.51), day 3 (12/75 vs. 8/74, respectively; RR 1.49; 95% CI, 0.65 to 3.40; p=0.34) or day 7 (49/68 vs. 47/70, respectively; RR 1.05; 95% CI, 0.88 to 1.25; p=0.41).[3] For assessment of function, little difference was found between the groups in the number of cured patients by day 7 (30/45 vs. 23/44; RR 1.28; 95% CI, 0.90 to 1.81; p=0.17).[3] In addition, there was no difference in GI AEs (0/70 vs. 4/71; RR 0.21; 95% CI, 0.03 to 1.74) based on low quality evidence.[3] The authors concluded that there is low quality but consistent evidence of no difference between NSAID therapy and opioid therapy with or without acetaminophen for pain associated with acute soft tissue injuries and return to normal function.[3]

Hydromorphone for Neuropathic Pain

The Cochrane Collaboration also conducted a systematic review to assess the efficacy of hydromorphone at reducing chronic neuropathic pain in adults, as well as the AEs associated with its use in this population.[4] Trials eligible for inclusion were double-blind RCTs of at least 2 weeks' duration that compared hydromorphone (any dose and formulation) with placebo or an active treatment for chronic neuropathic pain.[4] However, only 4 studies were identified and 3 of them were excluded leaving only one post-hoc analysis that assessed reduction in chronic neuropathic pain.[4] Thus, insufficient evidence is available for this population to support or refute the use of hydromorphone for chronic neuropathic pain.[4]

Tramadol and Tramadol/Acetaminophen

The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted an updated abbreviated review for tramadol[5] and tramadol plus acetaminophen fixed-dose combination drugs[5,6] for the management of chronic and acute pain in adult patients. Tramadol has a relatively lower affinity for the mu-opioid receptor than other opioid analgesics.[5] Tramadol and its active metabolite bind to the mu-opioid receptors in the central nervous system and inhibit the ascending pain pathways, as well as inhibit the reuptake of norepinephrine and serotonin involved in the descending inhibitory pain pathway.[5] However, place in therapy for tramadol for management of pain is unclear. The first review assessed systematic reviews and RCTs published since 2012 that compared tramadol or tramadol combination products with placebo or active comparators.[5] The second review assessed RCTs published since 2014 that compared tramadol/acetaminophen fixed-dose combination products with active comparators for management of pain in adults.[5]

Four systematic reviews were identified as relevant to the fist review.[5] Three systematic reviews showed greater pain reduction with tramadol or tramadol combination when compared to placebo; however differences were statistically significant in only one systematic review that evaluated chronic low back pain (MD -0.55; 95% CI, -0.66 to -0.44). One systematic review for chronic low back pain did not find a statistically significant difference (MD -1.72; 95% CI, -3.45 to 0.01) and the third systematic review, which evaluated painful diabetic neuropathy, did not report statistical analyses (≥30% pain reduction: 56.2% vs. 37.9% for tramadol combination vs. placebo, respectively).[5] These systematic reviews found AEs to be more common with tramadol than placebo (RR 1.74; 95% CI, 1.20 to 2.52) and with tramadol/acetaminophen than placebo (nausea: 11.9% vs. 3.3%, dizziness: 6.3% vs. 1.3%, and somnolence: 6.3% vs. 1.3%).[5]

For active comparisons, one systematic review included an RCT which compared tramadol with celecoxib and found that improvement in pain intensity was numerically greater with tramadol compared with celecoxib (63.2% vs. 49.9%) but AEs were numerically greater with tramadol compared with celecoxib (30.4% vs. 14.4%).[5] One systematic review of 2 head-to-head RCTs that assessed pain intensity showed tramadol statistically significantly reduced pain versus celecoxib (RR 0.82; 95% CI, 0.76 to 0.90).[5]

Four RCTs compared tramadol plus acetaminophen fixed-dose combination therapy with placebo.[5] These reviews reported on pain assessment (mostly chronic low back pain) using a variety of tools and formats.[5] Tools included global pain change, pain relief success rate, VAS scores, total pain relief scores (TOTPAR), and sum of pain intensity difference (SPID).[5] There were generally greater improvements with the tramadol combination groups compared with placebo but the results were not always statistically significant.[5] Adverse events were higher in the tramadol combination groups compared to placebo groups.[5]

Three RCTs were identified that assessed the clinical effectiveness of tramadol plus acetaminophen fixed-dose combinations against active controls for the management of pain in adult patients.[5,6] One RCT identified compared tramadol plus acetaminophen and an NSAID as maintenance therapy in patients with knee osteoarthritis pain inadequately controlled by the NSAID.[5] All patients were treated with 4 weeks of add-on tramadol/acetaminophen and then randomized to tramadol/acetaminophen or NSAID.[5] Pain as assessed by NRS was not statistically significantly different between tramadol/acetaminophen versus NSAID (4.55 vs. 3.89, respectively; p=NS (p-values not provided)).[5] Prevalence and types of AEs were not significantly different between tramadol/acetaminophen vs. NSAID (nausea: 8.5% vs. 12.0%, dizziness: 8.5% vs. 8.0%, and constipation: 4.3% vs. 2.0%, respectively).[5] Another RCT found tramadol plus acetaminophen to be equally effective as paracetamol and codeine plus meprobamate at relieving pain after third molar extraction.[6] The third RCT investigated the use of tramadol and acetaminophen versus NSAID therapy in patients with low back pain and depression.[6] This study found that patients in the tramadol/acetaminophen group reported statistically significant less depression and lower pain scores on the NRS, but no statistically significant difference in scores in the Oswestry Disability Index, Pain Disability Assessment Scale, or Pain Catastrophizing Scale when compared to the NSAID group.[6] There was no significant difference in treatment-related AEs between the 2 groups.[6]

New Guidelines:
The Centers for Disease Control and Prevention (CDC) guideline for prescribing opioids for chronic non-cancer pain was published in 2016[11] and was previously reviewed in our class update for long-acting opioid analgesics.[1,11] The CDC systematically gathered 2 decades of the best scientific evidence combined with expert opinion and stakeholder review and found no evidence to support long-term use of opioid analgesics for chronic pain. The CDC systematic review and guideline is available in different formats.[11,18] Tools to help prescribers implement the guideline are also available at http://www.cdc.gov/drugoverdose/prescribing/resources.html.

New Safety Alerts:
The FDA issued a safety alert in August 2016 on the growing combined use of opioid analgesics with benzodiazepines or other drugs that suppress the central nervous system (CNS) which has resulted in numerous cases of respiratory depression and death.[19] In an effort to decrease the concurrent use of opioids and benzodiazepines, the FDA has added Boxed Warnings to the drug labeling of prescription opioid pain and cough medicines, and benzodiazepines.[19] Providers should limit prescribing opioid analgesics with benzodiazepines or other CNS depressants to patients for whom alternative treatment options are inadequate.[19] If these drugs must be prescribed concurrently, the dose and duration of each drug should be limited to the minimum possible.[19] Prescribing of prescription opioid cough medicines for patients on benzodiazepines or other CNS depressants, including alcohol, should be avoided.[19]

The FDA issued a safety alert in March 2016 regarding new safety warnings for opioid analgesics.[20] Specific warnings in labeling refer to opioid interactions with antidepressants and migraine medications that can increase the risk for serotonin syndrome. Warnings for increased risk of rare, but serious cases of adrenal gland cortisol suppression with opioid use and decreased sex hormone levels associated with long-term opioid use have also been added to drug labeling.[20]

New Formulations or Indications:
Troxyca ER (oxycodone/naltrexone extended-release [ER] capsule) was approved by the FDA in August 2016 for the management of chronic pain by healthcare providers knowledgeable in use of potent opioids.[21] Approval of oxycodone/naltrexone ER is based on one 12-week, double-blind RCT in opioid-naïve (n=162) and opioid-tolerant (n=119) patients with moderate-to-severe chronic low back pain.[9] Prior to the trial, there was an open-label phase where all enrolled patients were titrated to 20 to 160 mg of oxycodone/naltrexone every 12 hours.[9] Only patients with controlled pain (NRS ≤4) were eligible to be randomized to continue on oxycodone/naltrexone ER or to placebo after tapering off oxycodone/naltrexone.[9] A total of 281 of the 410 originally enrolled patients were eligible for randomization to oxycodone/naltrexone ER (n=147) or placebo (n=134).[9] Ninety-three patients did not complete the 12-week trial: 27% of patients withdrew early from the oxycodone/naltrexone group and 40% of patients withdrew early from the placebo group.[9] The primary end point of this study was defined as the mean change in weekly average 11-point NRS pain scores (based on patient diary entries) from baseline at randomization to the weeks 11 and 12.[9] The mean weekly NRS pain score at randomization baseline was 3.1 for placebo patients and 3.0 for oxycodone/naltrexone ER patients.[9] There was a statistically significant difference in mean change in the weekly average pain intensity NRS scores at weeks 11 and 12 from baseline between patients treated with oxycodone/naltrexone ER (least squares mean [LSM] +0.60; 95% CI, 0.27 to 0.93) compared to placebo (LSM +1.23; 95% CI, 0.87 to 1.58) (LSM Difference -0.62; 95% CI, -1.11 to -0.14; p=0.0114).[9] The differences observed are below accepted thresholds for clinical importance.

Randomized Controlled Trials:
A total of 41 citations were manually reviewed from the literature search. After manual review, 39 citations 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 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Friedman, et al.[7] DB, SC, RCT	1. Naproxen 500 mg BID + Placebo 1-2 tablets Q8h (10-day supply) 2. Naproxen 500 mg BID + cyclobenzaprine 5 mg 1-2 tablets Q8h (10-day supply) 3. Naproxen 500 mg BID + oxycodone/APAP 5/325 mg 1-2 tablets Q8h (10-day supply)	Adults age 21-64 years w/ ED visit for LBP	Improvement on the RMDQ (scale 0-24) between ED discharge and the 7-day telephone follow-up (5-point improvement considered clinically significant).	1. naproxen + placebo: +9.8 (98.3% CI, 7.9 to 11.17) 2. naproxen + cyclobenzaprine: +10.1 (98.3% CI, 7.9 to 12.3) 3. naproxen + oxycodone/APAP: +11.1 (98.3% CI, 9.0 to 13.2) Mean Between Group Differences: - Cyclobenzaprine vs. placebo: 0.3 (98.3% CI, -2.6 to 3.2; p=0.77) - Oxycodone/APAP vs. placebo: 1.3 (98.3% CI, -1.5 to 4.1; p=0.28) - Oxycodone/APAP vs. cyclobenzaprine: 0.9 (98.3% CI, -2.1 to 3.9; p=0.45)
Chang, et al.[8] DB, SC, RCT n=120	1. oxycodone/APAP 5/325 mg 1 tablet Q4h PRN pain (3-day supply) 2. hydrocodone/APAP 5/325 mg 1 tablet Q4h PRN pain (3-day supply)	Adults age 21-64 years w/ ED visit for acute musculoskeletal extremity pain (including hip or shoulder joints)	Difference in improvement in mean NRS pain scores* at approximately 24 hours post-discharge, measured at 2 hours following the most recent ingestion of the study drug relative to the time of phone contact. *Difference of 1.4 points considered to be clinically significant	Mean change NRS scores from baseline: Oxycodone/APAP: 4.4 NRS units Hydrocodone/APAP: 4.0 NRS units Mean Between Group Difference: - 0.4 NRS units (95% CI, -0.2 to 1.1)

Abbreviations: APAP = acetaminophen; BID = twice daily; CI = confidence interval; DB = double-blind; ED = emergency department; LBP = lower back pain; mg = milligrams; NRS = numerical rating scale; Q4h = every 4 hours; Q8h = every 8 hours; RCT = randomized clinical trial; RMDQ = Roland-Morris Disability Questionnaire (functional impairment questionnaire designed for LBP); SC = single-center

References:

1. Long-acting Opioid Class Update, May 2016. Drug Use Research and Management, Oregon State University College of Pharmacy. http://www.orpdl.org/durm/meetings/meetingdocs/2016_05_26/archives/2016_05_26_LAOClassUpdate.pdf. Accessed September 22, 2016.

2. Abdel Shaheed C, Maher CG, Williams KA, Day R, McLachlan AJ. Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain: A Systematic Review and Meta-analysis. *JAMA Intern Med*. 2016;176(7):958-968. doi:10.1001/jamainternmed.2016.1251.

3. Jones P, Dalziel SR, Lamdin R, Miles-Chan JL, Frampton C. Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury. *Cochrane Database Syst Rev*. 2015;(7):CD007789. doi:10.1002/14651858.CD007789.pub2.

4. Stannard C, Gaskell H, Derry S, et al. Hydromorphone for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2016;(5):CD011604. doi:10.1002/14651858.CD011604.pub2.

5. Tramadol for the Management of Pain in Adult Patients: A Review of the Clinical Effectiveness. Canadian Agency for Drugs and Technologies in Health (CADTH), February 2015. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0085775/pdf/PubMedHealth_PMH0085775.pdf. Accessed September 9, 2016.

6. Tramadol Plus Acetaminophen for the Management of Pain in Adult Patients: Clinical Effectiveness. Canadian Agency for Drugs and Technologies in Health (CADTH), November 2015. https://www.cadth.ca/sites/default/files/pdf/htis/nov-2015/RB0927%20Tramacet%20for%20Geriatric%20Patients%20Final.pdf. Accessed September 12, 2016.

7. Friedman BW, Dym AA, Davitt M, et al. Naproxen With Cyclobenzaprine, Oxycodone/Acetaminophen, or Placebo for Treating Acute Low Back Pain: A Randomized Clinical Trial. *JAMA*. 2015;314(15):1572-1580. doi:10.1001/jama.2015.13043.

8. Chang AK, Bijur PE, Holden L, Gallagher EJ. Comparative Analgesic Efficacy of Oxycodone/Acetaminophen Versus Hydrocodone/Acetaminophen for Short-term Pain Management in Adults Following ED Discharge. *Acad Emerg Med*. 2015;22(11):1254-1260. doi:10.1111/acem.12813.

9. Rauck RL, Hale ME, Bass A, et al. A randomized double-blind, placebo-controlled efficacy and safety study of ALO-02 (extended-release oxycodone surrounding sequestered naltrexone) for moderate-to-severe chronic low back pain treatment. *Pain*. 2015;156(9):1660-1669. doi:10.1097/j.pain.0000000000000230.

10. Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain--Misconceptions and Mitigation Strategies. *N Engl J Med*. 2016;374(13):1253-1263. doi:10.1056/NEJMra1507771.

11. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep 2016;65(No. RR-1):1–49. DOI: http://dx.doi.org/10.15585/mmwr.rr6501e1.

12. Ballantyne JC. Avoiding Opioid Analgesics for Treatment of Chronic Low Back Pain. *JAMA*. 2016;315(22):2459-2460. doi:10.1001/jama.2016.6753.

13. Prioritized List of Health Services, Health Evidence Review Commission, Oregon Health Plan; July 2016.pdf. http://www.oregon.gov/oha/herc/PrioritizedList/7-1-2016%20Prioritized%20List%20of%20Health%20Services.pdf. Accessed September 16, 2016.

14. Bao Y, Pan Y, Taylor A, et al. Prescription Drug Monitoring Programs Are Associated With Sustained Reductions In Opioid Prescribing By Physicians. *Health Aff (Millwood)*. 2016;35(6):1045-1051. doi:10.1377/hlthaff.2015.1673.

15. Patrick SW, Fry CE, Jones TF, Buntin MB. Implementation Of Prescription Drug Monitoring Programs Associated With Reductions In Opioid-Related Death Rates. *Health Aff (Millwood)*. 2016;35(7):1324-1332. doi:10.1377/hlthaff.2015.1496.

16. Holdgate A, Asha S, Craig J, Thompson J. Comparison of a verbal numeric rating scale with the visual analogue scale for the measurement of acute pain. *Emerg Med (Fremantle)*. 2003;15(5-6):441-446.

17. Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. *Ann Emerg Med*. 1996;27(4):485-489.

18. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. *JAMA*. 2016;315(15):1624-1645. doi:10.1001/jama.2016.1464.

19. FDA Drug Safety Communication [8/31/16], U.S. Food and Drug Administration. FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. http://www.fda.gov/Drugs/DrugSafety/ucm518473.htm. Accessed September 2, 2016.

20. FDA Drug Safety Communication [3/22/16], U.S. Food and Drug Administration. FDA warns about several safety issues with opioid pain medicines; requires label changes. http://www.fda.gov/Drugs/DrugSafety/ucm489676.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. Accessed September 2, 2016.

21. TROXYCA ER (oxycodone/naltrexone extended-release capsules) [Prescribing Information]. New York, NY; Pfizer Inc., August 2016.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
NASAL	SPRAY	BUTORPHANOL TARTRATE	BUTORPHANOL TARTRATE	Y
ORAL	ORAL SUSP	CAPITAL W-CODEINE	ACETAMINOPHEN WITH CODEINE	Y
ORAL	SOLUTION	ACETAMINOPHEN-CODEINE	ACETAMINOPHEN WITH CODEINE	Y
ORAL	SOLUTION	HYCET	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	SOLUTION	HYDROCODONE-ACETAMINOPHEN	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	SOLUTION	LORTAB	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	SOLUTION	MORPHINE SULFATE	MORPHINE SULFATE	Y
ORAL	SOLUTION	OXYCODONE HCL	OXYCODONE HCL	Y
ORAL	TABLET	ACETAMINOPHEN-CODEINE	ACETAMINOPHEN WITH CODEINE	Y
ORAL	TABLET	CODEINE SULFATE	CODEINE SULFATE	Y
ORAL	TABLET	DILAUDID	HYDROMORPHONE HCL	Y
ORAL	TABLET	ENDOCET	OXYCODONE HCL/ACETAMINOPHEN	Y
ORAL	TABLET	HYDROCODONE-ACETAMINOPHEN	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	HYDROMORPHONE HCL	HYDROMORPHONE HCL	Y
ORAL	TABLET	LORCET	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	LORCET HD	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	LORCET PLUS	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	LORTAB	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	MORPHINE SULFATE	MORPHINE SULFATE	Y
ORAL	TABLET	NORCO	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	OXYCODONE HCL	OXYCODONE HCL	Y
ORAL	TABLET	OXYCODONE-ACETAMINOPHEN	OXYCODONE HCL/ACETAMINOPHEN	Y
ORAL	TABLET	PERCOCET	OXYCODONE HCL/ACETAMINOPHEN	Y
ORAL	TABLET	ROXICODONE	OXYCODONE HCL	Y
ORAL	TABLET	TRAMADOL HCL	TRAMADOL HCL	Y
ORAL	TABLET	TYLENOL-CODEINE NO.3	ACETAMINOPHEN WITH CODEINE	Y
ORAL	TABLET	TYLENOL-CODEINE NO.4	ACETAMINOPHEN WITH CODEINE	Y
ORAL	TABLET	ULTRAM	TRAMADOL HCL	Y
RECTAL	SUPP.RECT	BELLADONNA-OPIUM	OPIUM/BELLADONNA ALKALOIDS	Y
RECTAL	SUPP.RECT	HYDROMORPHONE HCL	HYDROMORPHONE HCL	Y
RECTAL	SUPP.RECT	MORPHINE SULFATE	MORPHINE SULFATE	Y
BUCCAL	LOZENGE HD	ACTIQ	FENTANYL CITRATE	N
BUCCAL	LOZENGE HD	FENTANYL CITRATE	FENTANYL CITRATE	N
BUCCAL	TABLET EFF	FENTORA	FENTANYL CITRATE	N
NASAL	SPRAY/PUMP	LAZANDA	FENTANYL CITRATE	N

ORAL	CAPSULE	ASA-BUTALB-CAFFEINE-CODEINE	CODEINE/BUTALBITAL/ASA/CAFFEIN	N
ORAL	CAPSULE	ASCOMP WITH CODEINE	CODEINE/BUTALBITAL/ASA/CAFFEIN	N
ORAL	CAPSULE	BUTALB-ACETAMINOPH-CAFF-CODEIN	BUTALBIT/ACETAMIN/CAFF/CODEINE	N
ORAL	CAPSULE	BUTALB-CAFF-ACETAMINOPH-CODEIN	BUTALBIT/ACETAMIN/CAFF/CODEINE	N
ORAL	CAPSULE	BUTALBITAL COMPOUND-CODEINE	CODEINE/BUTALBITAL/ASA/CAFFEIN	N
ORAL	CAPSULE	FIORICET WITH CODEINE	BUTALBIT/ACETAMIN/CAFF/CODEINE	N
ORAL	CAPSULE	FIORINAL WITH CODEINE #3	CODEINE/BUTALBITAL/ASA/CAFFEIN	N
ORAL	CAPSULE	OXYCODONE HCL	OXYCODONE HCL	N
ORAL	LIQUID	DILAUDID	HYDROMORPHONE HCL	N
ORAL	LIQUID	HYDROMORPHONE HCL	HYDROMORPHONE HCL	N
ORAL	ORAL CONC	OXYCODONE HCL	OXYCODONE HCL	N
ORAL	SOLUTION	MEPERIDINE HCL	MEPERIDINE HCL	N
ORAL	SOLUTION	OXYCODONE-ACETAMINOPHEN	OXYCODONE HCL/ACETAMINOPHEN	N
ORAL	SOLUTION	ZAMICET	HYDROCODONE/ACETAMINOPHEN	N
ORAL	SYRINGE	MORPHINE SULFATE	MORPHINE SULFATE	N
ORAL	TABLET	HYDROCODONE-ACETAMINOPHEN	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	MEPERIDINE HCL	MEPERIDINE HCL	N
ORAL	TABLET	NUCYNTA	TAPENTADOL HCL	N
ORAL	TABLET	OPANA	OXYMORPHONE HCL	N
ORAL	TABLET	OXYMORPHONE HCL	OXYMORPHONE HCL	N
ORAL	TABLET	PENTAZOCINE-NALOXONE HCL	PENTAZOCINE HCL/NALOXONE HCL	N
ORAL	TABLET	PRIMLEV	OXYCODONE HCL/ACETAMINOPHEN	N
ORAL	TABLET	TRAMADOL HCL-ACETAMINOPHEN	TRAMADOL HCL/ACETAMINOPHEN	N
ORAL	TABLET	ULTRACET	TRAMADOL HCL/ACETAMINOPHEN	N
ORAL	TABLET	VICODIN	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	VICODIN ES	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	VICODIN HP	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	XODOL 10-300	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	XODOL 5-300	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	XODOL 7.5-300	HYDROCODONE/ACETAMINOPHEN	N
SUBLINGUAL	SPRAY	SUBSYS	FENTANYL	N
SUBLINGUAL	TAB SUBL	ABSTRAL	FENTANYL CITRATE	N
ORAL	TABLET	HYDROCODONE-ACETAMINOPHEN	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	HYDROCODONE-IBUPROFEN	HYDROCODONE/IBUPROFEN	N
ORAL	TABLET	IBUDONE	HYDROCODONE/IBUPROFEN	N
ORAL	TABLET	OXYCODONE HCL-IBUPROFEN	IBUPROFEN/OXYCODONE HCL	N
ORAL	TABLET	REPREXAIN	HYDROCODONE/IBUPROFEN	N
ORAL	TABLET	XYLON 10	HYDROCODONE/IBUPROFEN	N

Appendix 2: Abstracts of Clinical Trials

Benjamin Friedman, et al.
Naproxen With Cyclobenzaprine, Oxycodone/Acetaminophen, or Placebo for Treating Acute Low Back Pain: A Randomized Clinical Trial. *JAMA* 2015.

Importance: Low back pain (LBP) is responsible for more than 2.5 million visits to US emergency departments (EDs) annually. These patients are usually treated with nonsteroidal anti-inflammatory drugs, acetaminophen, opioids, or skeletal muscle relaxants, often in combination.
Objective: To compare functional outcomes and pain at 1 week and 3 months after an ED visit for acute LBP among patients randomized to a 10-day course of (1) naproxen + placebo; (2) naproxen + cyclobenzaprine; or (3) naproxen + oxycodone/acetaminophen.
Design, Setting, And Participants: This randomized, double-blind, 3-group study was conducted at one urban ED in the Bronx, New York City. Patients who presented with nontraumatic, nonradicular LBP of 2 weeks' duration or less were eligible for enrollment upon ED discharge if they had a score greater than 5 on the Roland-Morris Disability Questionnaire (RMDQ). The RMDQ is a 24-item questionnaire commonly used to measure LBP and related functional impairment on which 0 indicates no functional impairment and 24 indicates maximum impairment. Beginning in April 2012, a total of 2588 patients were approached for enrollment. Of the 323 deemed eligible for participation, 107 were randomized to receive placebo and 108 each to cyclobenzaprine and to oxycodone/acetaminophen. Follow-up was completed in December 2014.
Interventions: All participants were given 20 tablets of naproxen, 500 mg, to be taken twice a day. They were randomized to receive either 60 tablets of placebo; cyclobenzaprine, 5 mg; or oxycodone, 5 mg/acetaminophen, 325 mg. Participants were instructed to take 1 or 2 of these tablets every 8 hours, as needed for LBP. They also received a standardized 10-minute LBP educational session prior to discharge.
Main Outcomes and Measures: The primary outcome was improvement in RMDQ between ED discharge and 1 week later.
Results: Demographic characteristics were comparable among the 3 groups. At baseline, median RMDQ score in the placebo group was 20 (interquartile range [IQR], 17-21), in the cyclobenzaprine group 19 (IQR, 17-21), and in the oxycodone/acetaminophen group 20(IQR, 17-22).At 1-week follow-up, the mean RMDQ improvement was 9.8 in the placebo group, 10.1 in the cyclobenzaprine group, and 11.1 in the oxycodone/acetaminophen group. Between-group difference in mean RMDQ improvement for cyclobenzaprine vs placebo was 0.3 (98.3%CI, -2.6 to 3.2; p=0.77), for oxycodone/acetaminophen vs placebo, 1.3 (98.3%CI, -1.5 to 4.1; p=0.28), and for oxycodone/acetaminophen vs cyclobenzaprine, 0.9 (98.3% CI, -2.1 to 3.9; p=0.45).
Conclusions and Relevance: Among patients with acute, nontraumatic, nonradicular LBP presenting to the ED, adding cyclobenzaprine or oxycodone/acetaminophen to naproxen alone did not improve functional outcomes or pain at 1-week follow-up. These findings do not support use of these additional medications in this setting.

Andrew Chang, et al.
Comparative Analgesic Efficacy of Oxycodone/Acetaminophen Versus Hydrocodone/Acetaminophen for Short-term Pain Management in Adults Following ED Discharge. *Academic Emergency Medicine* 2015.

Objectives: The objective was to test the hypothesis that oxycodone/acetaminophen provides superior analgesia to hydrocodone/acetaminophen for the treatment of acute extremity pain following emergency department (ED) discharge.
Methods: This was a prospective, randomized, double-blind clinical trial of nonelderly adult ED patients with acute musculoskeletal extremity pain, randomly allocated at discharge to receive oxycodone/acetaminophen (5 mg/325 mg) or hydrocodone/acetaminophen (5 mg/325 mg). The primary outcome was the between-group difference in improvement in numerical rating scale (NRS) pain scores over a 2-hour period following the most recent ingestion of study drug, obtained during telephone contact 24 hours after ED discharge. Secondary outcomes included proportionate decrease in pain, comparative side-effect

profiles, and patient satisfaction.
Results: A total of 240 patients were enrolled. The final sample consisted of 220 patients, 107 randomly allocated to oxycodone/acetaminophen and 113 to hydrocodone/acetaminophen. At 24 hours after ED discharge, the mean NRS pain scores prior to the most recent dose of outpatient pain medication were 7.8 and 7.9 in the oxycodone/acetaminophen and hydrocodone/acetaminophen groups, respectively. The mean decreases in pain scores over 2 hours were 4.4 NRS units in the oxycodone/acetaminophen group versus 4.0 NRS units in the hydrocodone/acetaminophen group, for a difference of 0.4 NRS units (95% confidence interval = 0.2 to 1.1 NRS units). Satisfaction with the analgesics was similar.
Conclusions: This study design could not detect a clinically or statistically significant difference in analgesic efficacy between oxycodone/acetaminophen (5 mg/325 mg) and hydrocodone/acetaminophen (5 mg/325 mg) for treatment of acute musculoskeletal extremity pain in adults following ED discharge. Both opioids reduced pain scores by approximately 50%.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to August Week 5 2016

1 buprenorphine/ or butorphanol/ or codeine/ or fentanyl/ or hydrocodone/ or hydromorphone/ or meperidine/ or morphine/ or opium/ or oxycodone/ or oxymorphone/ or pentazocine/ or tramadol/ 30188

2 acute pain.mp. or exp Acute Pain/ 4959

3 short-acting.mp. 4274

4 immediate-release.mp. 2414

5 2 or 3 or 4 11541

6 1 and 5 914

7 limit 6 to (english language and humans and yr="2015 -Current" 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 randomized controlled trial or systematic reviews)) 41

Short-acting Opioid Analgesics

Goals:

- Restrict use of short-acting opioid analgesics for acute conditions funded by the OHP.
- Promote use of preferred short-acting opioid analgesics.

Length of Authorization:

7 to 30 days (except 12 months for end-of-life or cancer-related pain)

Covered Alternatives:

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

Requires a PA:

- Non-preferred short-acting opioids and opioid combination products.
- All short-acting products prescribed for more than 7 days.

Note:

- Patients on palliative care with a terminal diagnosis or with cancer-related pain (ICD10 C6900-C799; C800-C802) are exempt from this PA.
- This PA does not apply to pediatric use of codeine products, which is subject to separate clinical PA criteria.

Table 1. Daily Dose Threshold (90 morphine milligram equivalents per day (MME/day) of Oral Opioid Products.

Opioid	90 MME/day Dose Threshold
Codeine	600 mg (note: not recommended for pediatric use; codeine is a prodrug of morphine and is subject to different rates of metabolism placing certain populations at risk for overdose)
Hydrocodone	90 mg
Hydromorphone	22.5 mg
Meperidine	900 mg (note: not recommended for management of chronic pain due to potential accumulation of toxic metabolites)
Morphine	90 mg
Oxycodone	60 mg
Oxymorphone	30 mg
Tapentadol	225 mg
Tramadol	400 mg (note: 400 mg/day is max dose and is not equivalent to 90 MME/day)

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD10	
2. Is the diagnosis funded by the OHP? Note: conditions such as fibromyalgia, TMJ, pelvic pain syndrome and tension headache are not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP. Note: Management of opioid dependence is funded by the OHP.
3. Is the requested medication a preferred agent?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #5
5. Is the patient being treated for cancer-related pain (ICD10 G89.3) or under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months.	**No:** Go to #6
6. Is the prescription for a short-acting fentanyl product? Note: Short-acting transmucosal fentanyl products are designed for breakthrough cancer pain only. This PA does not apply to transdermal fentanyl patches.	**Yes:** Pass to RPh. Deny; medical appropriateness Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #7
7. Is the opioid prescribed for pain related to migraine or other type of headache? Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8

8. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 3 months that the patient has been prescribed opioid analgesics by only a single prescribing practice or prescriber?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Did the patient's pain originate from acute injury, flare, or surgery that occurred in the last 6 weeks?	**Yes:** Go to #10	**No:** Go to #15
10. Has at least one non-opioid analgesic (e.g., NSAID, acetaminophen, and/or muscle relaxant) been tried and found to be ineffective or are contraindicated?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the opioid prescription for pain associated with a back or spine condition?	**Yes:** Go to #12	**No:** Approve for up to 30 days
12. Has the prescriber also developed a plan with the patient to stay active (home or prescribed exercise regimen) and with consideration of additional therapies such as spinal manipulation, physical therapy, yoga, or acupuncture?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is this the first opioid prescription the patient has received for this pain condition?	**Yes:** Approve for up to 7 days	**No:** Go to #14
14. Can the prescriber provide documentation of sustained improvement in function of at least 30% compared to baseline with prior use of opioid analgesics (e.g., validated tools to assess function include: Oswestry, Neck Disability Index, SF-MPQ, and MSPQ)?	**Yes:** Approve for up to 7 days	**No:** Pass to RPh. Deny; medical appropriateness.
15. Has the patient been prescribed opioid analgesics for more than 6 weeks?	**Yes:** Go to #16	**No:** Go to #10

16. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale.*	**Yes:** Document tool used to measure pain and/or function. Go to #17	**No:** Pass to RPh. May approve for up to 30 days one time. For future claims without documentation: deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.
17. Has the patient had a urinary drug screen (UDS) within the past year to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Go to #18	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.
18. Is the opioid prescription for pain associated with a back or spine condition?	**Yes:** Go to #19	**No:** Go to #20
19. Have any of the following therapies also been prescribed and utilized by the patient: spinal manipulation, physical therapy, yoga or acupuncture?	**Yes:** Document additional therapy. Approve for up to 7 days. <u>Note</u>: Risks outweigh benefits for back and spine conditions. OHP will not fund chronic use of opioids for back or spine conditions beginning 1/1/2018. Prescriber must develop a taper plan with the patient with a quit date before 1/1/2018. OHP funds treatment for patients who have become dependent or addicted to opioid analgesics.	**No:** Pass to RPh. Deny; medical appropriateness.

20. Does the total daily opioid dose exceed 90 MME (Table 1)?	**Yes:** Pass to RPh. May approve one time. For future claims: deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.	**No:** Approve for up to 30 days.

*The PEG is freely available to the public http://www.agencymeddirectors.wa.gov/Files/AssessmentTools/1-PEG%203%20item%20pain%20scale.pdf.
Citation of the original publication:
Krebs EE, Lorenz KA, Bair MJ, Damush TA, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a 3-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*. 2009 Jun;24:733-738

Clinical Notes:

How to Discontinue Opioids.
Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Selecting the optimal timing and approach to tapering depends on multiple factors. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

1. Consider sequential tapers for patients who are on chronic benzodiazepines and opioids. Coordinate care with other prescribers (e.g. psychiatrist) as necessary. In general, taper off opioids first, then the benzodiazepines.
2. Do not use ultra-rapid detoxification or antagonist-induced withdrawal under heavy sedation or anesthesia (e.g. naloxone or naltrexone with propofol, methohexital, ketamine or midazolam).
3. Establish the rate of taper based on safety considerations:
    a. Immediate discontinuation if there is diversion or non-medical use,
    b. Rapid taper (over a 2 to 3 week period) if the patient has had a severe adverse outcome such as overdose or substance use disorder, or
    c. Slow taper for patients with no acute safety concerns. Start with a taper of ≤10% of the original dose per week and assess the patient's functional and pain status at each visit.
4. Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. emergence of opioid withdrawal symptoms (see Table below)).
5. Watch for signs of unmasked mental health disorders (e.g. depression, PTSD, panic disorder) during taper, especially in patients on prolonged or high dose opioids. Consult with specialists to facilitate a safe and effective taper. Use validated tools to assess conditions.
6. Consider the following factors when making a decision to continue, pause or discontinue the taper plan:
    a. Assess the patient behaviors that may be suggestive of a substance use disorder
    b. Address increased pain with use of non-opioid options.
    c. Evaluate patient for mental health disorders.
    d. If the dose was tapered due to safety risk, once the dose has been lowered to an acceptable level of risk with no addiction behavior(s) present, consider maintaining at the established lower dose if there is a clinically meaningful improvement in function, reduced pain and no serious adverse outcomes.
7. Do not reverse the taper; it must be unidirectional. The rate may be slowed or paused while monitoring for and managing withdrawal symptoms.

8. Increase the taper rate when opioid doses reach a low level (e.g. <15 mg/day MED), since formulations of opioids may not be available to allow smaller decreases.
9. Use non-benzodiazepine adjunctive agents to treat opioid abstinence syndrome (withdrawal) if needed. Unlike benzodiazepine withdrawal, opioid withdrawal symptoms are rarely medically serious, although they may be extremely unpleasant. Symptoms of mild opioid withdrawal may persist for 6 months after opioids have been discontinued (see Table below).
10. Refer to a crisis intervention system if a patient expresses serious suicidal ideation with plan or intent, or transfer to an emergency room where the patient can be closely monitored.
11. Do not start or resume opioids or benzodiazepines once they have been discontinued, as they may trigger drug cravings and a return to use.
12. Consider inpatient withdrawal management if the taper is poorly tolerated.

Symptoms and Treatment of Opioid Withdrawal.

Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Restlessness, sweating or tremors	Clonidine 0.1-0.2 mg orally every 6 hours or transdermal patch 0.1-0.2 mg weekly (If using the patch, oral medication may be needed for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects.
Nausea	Anti-emetics such as ondansetron or prochlorperazine
Vomiting	Loperamide or anti-spasmodics such as dicyclomine
Muscle pain, neuropathic pain or myoclonus	NSAIDs, gabapentin or muscle relaxants such as cyclobenzaprine, tizanidine or methocarbamol
Insomnia	Sedating antidepressants (e.g. nortriptyline 25 mg at bedtime or mirtazapine 15 mg at bedtime or trazodone 50 mg at bedtime). Do not use benzodiazepines or sedative-hypnotics.

P&T Review: *11/16 (AG)*
Implementation: *TBD*

Long-acting Opioid Analgesics

Goals:

- Restrict use of long-acting opioid analgesics to OHP-funded conditions with documented sustained improvement in pain and function and with routine monitoring for opioid misuse and abuse.
- Restrict use of long-acting opioid analgesics for conditions of the back and/or spine due to evidence of increased risk vs. benefit.
- Promote the safe use of long-acting opioid analgesics by restricting use of high doses that have not demonstrated improved benefit and are associated with greater risk for accidental opioid overdose and death.

Length of Authorization:

90 days (except 12 months for end-of-life or cancer-related pain)

Covered Alternatives:

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

Requires a PA:

- All long-acting opioids and opioid combination products.

Note:

- Patients on palliative care with a terminal diagnosis or with cancer-related pain (ICD10 C6900-C799; C800-C802) are exempt from this PA.
- This PA does not apply to pediatric use of codeine products, which is subject to separate clinical PA criteria.

Table 1. Daily Dose Threshold (90 MME/day) of Opioid Products.

Opioid	90 MME/day Threshold
Codeine	600 mg (Note: not recommended for pediatric use; codeine is a prodrug of morphine and is subject to different rates of metabolism placing certain populations at risk for overdose.)
Fentanyl (transdermal patch)	37.5 mcg/hr (Note: use only in opioid-tolerant patients who have been taking ≥60 MME daily for a ≥1 week. Deaths due to a fatal overdose of fentanyl have occurred when pets, children and adults were accidentally exposed to fentanyl transdermal patch. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure.)
Hydrocodone	90 mg
Hyrdomorphone	22.5 mg
Methadone	20 mg (Note: do not use unless very familiar with the complex pharmacokinetic and pharmacodynamics properties of methadone. Methadone exhibits a non-linear relationship due to its long half-life and accumulates with chronic dosing. Methadone also has complex interactions with several other drugs. The dose should not be increased more frequently than once every 7 days. Methadone is associated with an increased incidence of prolonged QTc interval, torsades de pointe and sudden cardiac death.)
Morphine	90 mg
Oxycodone	60 mg
Oxymorphone	30 mg
Tapentadol	225 mg
Tramadol	300 mg (Note: 300 mg/day is max dose and is not equivalent to 90 MME/day.)

Table 2. Specific Long-acting Opioid Products Subject to Quantity Limits per FDA-approved Labeling.

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

Drug Product	Quantity Limit
HYSINGLA ER	2 doses/day
KADIAN	2 doses/day
MORPHABOND	2 doses/day
NUCYNTA ER	2 doses/day
OPANA ER	2 doses/day
OXYCONTIN	2 doses/day
TROXYCA ER	2 doses/day

Drug Product	Quantity Limit
XARTEMIS XR	4 doses/day
XTAMPZA ER	2 doses/day
ZOHYDRO ER	2 doses/day

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD10 code	
2. Is the diagnosis funded by the OHP? Note: Management of pain associated with *back or spine conditions with long-acting opioids* is not funded by the OHP*. Other conditions, such as fibromyalgia, TMJ, tension headache and pelvic pain syndrome are also not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP. Note: Management of opioid dependence is funded by the OHP.
3. Is the requested medication a preferred agent?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #5
5. Is the patient being treated for cancer-related pain (ICD10 G89.3) or under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months	**No:** Go to #6
6. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 3 months that the patient has been prescribed opioid analgesics by only a single prescribing practice or prescriber?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the prescription for pain associated with migraine or other type of headache? Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8

8. Does the total daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #9
9. Is the patient concurrently on other short- or long-acting opioids (patients may receive a maximum of one opioid product regardless of formulation)? Note: There is insufficient evidence for use of concurrent opioid products (e.g., long-acting opioid with short-acting opioid).	**Yes:** Pass to RPh. Deny; medical appropriateness Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #10
10. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale.**	**Yes:** Go to #12 Document tool used and score vs. baseline: _____	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.
12. Has the patient had a urinary drug screen (UDS) within the past 1 year to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Approve for up to 90 days.	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.

*See Guideline Note 60 within the Prioritized List of Health Services for conditions of coverage for pain associated with back or spine conditions: http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx

**The PEG is freely available to the public http://www.agencymeddirectors.wa.gov/Files/AssessmentTools/1-PEG%203%20item%20pain%20scale.pdf.

Citation of the original publication:

Krebs EE, Lorenz KA, Bair MJ, Damush TA, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a 3-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*. 2009 Jun;24:733-738.

Clinical Notes:

How to Discontinue Opioids.

Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Selecting the optimal timing and approach to tapering depends on multiple factors. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

13. Consider sequential tapers for patients who are on chronic benzodiazepines and opioids. Coordinate care with other prescribers (e.g. psychiatrist) as necessary. In general, taper off opioids first, then the benzodiazepines.
14. Do not use ultra-rapid detoxification or antagonist-induced withdrawal under heavy sedation or anesthesia (e.g. naloxone or naltrexone with propofol, methohexital, ketamine or midazolam).
15. Establish the rate of taper based on safety considerations:
    a. Immediate discontinuation if there is diversion or non-medical use,
    b. Rapid taper (over a 2 to 3 week period) if the patient has had a severe adverse outcome such as overdose or substance use disorder, or
    c. Slow taper for patients with no acute safety concerns. Start with a taper of ≤10% of the original dose per week and assess the patient's functional and pain status at each visit.
16. Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. emergence of opioid withdrawal symptoms (see Table below)).
17. Watch for signs of unmasked mental health disorders (e.g. depression, PTSD, panic disorder) during taper, especially in patients on prolonged or high dose opioids. Consult with specialists to facilitate a safe and effective taper. Use validated tools to assess conditions.
18. Consider the following factors when making a decision to continue, pause or discontinue the taper plan:
    a. Assess the patient behaviors that may be suggestive of a substance use disorder
    b. Address increased pain with use of non-opioid options.
    c. Evaluate patient for mental health disorders.
    d. If the dose was tapered due to safety risk, once the dose has been lowered to an acceptable level of risk with no addiction behavior(s) present, consider maintaining at the established lower dose if there is a clinically meaningful improvement in function, reduced pain and no serious adverse outcomes.
19. Do not reverse the taper; it must be unidirectional. The rate may be slowed or paused while monitoring for and managing withdrawal symptoms.
20. Increase the taper rate when opioid doses reach a low level (e.g. <15 mg/day MED), since formulations of opioids may not be available to allow smaller decreases.
21. Use non-benzodiazepine adjunctive agents to treat opioid abstinence syndrome (withdrawal) if needed. Unlike benzodiazepine withdrawal, opioid withdrawal symptoms are rarely medically serious, although they may be extremely unpleasant. Symptoms of mild opioid withdrawal may persist for 6 months after opioids have been discontinued (see Table below).
22. Refer to a crisis intervention system if a patient expresses serious suicidal ideation with plan or intent, or transfer to an emergency room where the patient can be closely monitored.
23. Do not start or resume opioids or benzodiazepines once they have been discontinued, as they may trigger drug cravings and a return to use.
24. Consider inpatient withdrawal management if the taper is poorly tolerated.

Symptoms and Treatment of Opioid Withdrawal. Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)	
Restlessness, sweating or tremors	Clonidine 0.1-0.2 mg orally every 6 hours or transdermal patch 0.1-0.2 mg weekly (If using the patch, oral medication may be needed for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects.
Nausea	Anti-emetics such as ondansetron or prochlorperazine
Vomiting	Loperamide or anti-spasmodics such as dicyclomine
Muscle pain, neuropathic pain or myoclonus	NSAIDs, gabapentin or muscle relaxants such as cyclobenzaprine, tizanidine or methocarbamol
Insomnia	Sedating antidepressants (e.g. nortriptyline 25 mg at bedtime or mirtazapine 15 mg at bedtime or trazodone 50 mg at bedtime). Do not use benzodiazepines or sedative-hypnotics.

P&T Review: *11/16 (AG); 05/16*
Implementation: *TBD*

Opioid Analgesics

Goals:

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

Length of Authorization:

3 to 12 months (criteria-specific)

Covered Alternatives:

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

Requires a PA:

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

Note:

- Preferred opioid products that do not exceed 90 MME per day are exempt from this PA.
- Patients on palliative care with a terminal diagnosis or with cancer-related pain (ICD10 C6900-C799; C800-C802) are exempt from this PA.
- This PA does not apply to pediatric use of codeine products, which is subject to separate clinical PA criteria.

Table 1. Daily Dose Threshold (90 MME/day) of Opioid Products.

Opioid	Dose Threshold (90 MME/day)	Recommended starting dose for opioid-naïve patients	Considerations
Note: Any opioid exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing an opioid and monitor all patients regularly for the development of these behaviors or conditions.			
Codeine	600 mg/24 hours	30 mg q 4-6 hours	Codeine is a prodrug of morphine. Metabolism and conversion to morphine is subject so multiple polymorphisms in different populations. Subsequently, persons may be hypersensitive to the analgesic and respiratory effects of codeine or may be resistant to the effects of codeine. Dosing limits based on combinations (e.g., acetaminophen) may further limit the maximum daily dose.
Fentanyl (transdermal patch)	37.5 mcg/hour (q 72 hr)	12.5 mcg/hour q 72 hours	Use only in opioid-tolerant patients who have been taking ≥60 MME daily for a ≥1 week. Deaths due to a fatal overdose of fentanyl have occurred when pets, children and adults were accidentally exposed to fentanyl transdermal patch. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure.
Hydrocodone	90 mg/24 hours	IR: 5-10 mg q 4-6 hours ER: 10 mg q 12 hours	Dosing limits based on combinations (e.g., acetaminophen) may further limit the maximum daily dose. Use the ER formulation with extreme caution due to potentially fatal interaction with alcohol or medications containing alcohol. Accidental consumption of even 1 dose of the ER formulation, especially by children, can result in a fatal overdose.
Hydromorphone	22.5 mg/24 hours	IR: 2 mg q 4–6 hours ER 8 mg q 24 hours	Hydromorphone is a potent opioid. Accidental ingestion of even one dose of hydromorphone ER, especially by children, can result in a fatal overdose of hydromorphone.
Methadone	20 mg/24 hours	2.5-5 mg BID or TID	Methadone is a very effective and inexpensive opioid but should be reserved to prescribers very familiar with the complex pharmacokinetic and pharmacodynamics variability of this drug. Methadone exhibits a non-linear relationship due to its long half-life and accumulates with chronic dosing. Methadone also has complex interactions with several other drugs. The dose should not be increased more frequently than once every 7 days.
Morphine	90 mg/24 hours	IR 10 mg q 4 hours ER 15 mg q 12 hours	Co-ingestion of alcohol with morphine ER may result in increased plasma levels and a potentially fatal overdose of morphine. Accidental ingestion of even one dose of morphine, especially by children, can result in a fatal overdose of morphine.

Oxycodone	60 mg/24 hours	IR: 5 mg q 4-6 hours ER: 10 mg q12 hours	Accidental ingestion of even one dose of oxycodone ER, especially by children, can result in a fatal overdose of oxycodone. The concomitant use of oxycodone ER with all cytochrome P450 (CYP-450) 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used CYP3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving oxycodone ER and any CYP3A4 inhibitor or inducer. Avoid concurrent use of any products containing acetaminophen (maximum combined APAP dose = 4000 mg/day for <10 days or 2500 mg/day for ≥10 days)
Oxymorphone	30 mg/24 hours	IR: 5–10 mg q 4-6 hours ER: 10 mg q 12 hours	Accidental ingestion of even 1 dose of oxymorphone ER, especially by children, can result in a fatal overdose of oxymorphone. Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while taking oxymorphone ER. Co-ingestion of alcohol with oxymorphone ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.
Tapentadol	225 mg/24 hours	IR: 50 mg q 4-6 hours ER: 50 mg q 12 hours	Accidental ingestion of even one dose of tapentadol ER, especially by children, can result in a fatal overdose of tapentadol. Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while taking tapentadol ER. Co-ingestion of alcohol with tapentadol ER may result in increased plasma tapentadol levels and a potentially fatal overdose of tapentadol. Tramadol also possesses SSRI-like properties and interacts with multiple drugs. Use with caution with other drugs that may increase risk of serotonin syndrome or decrease seizure threshold.
Tramadol	400 mg/24 hours (IR) 300 mg/24 hours (ER)	IR: 50 mg q 4-6 hours ER: 100 mg per 24 hours	The threshold is based on maximum daily dosing for the IR and ER formulations. The threshold is not equivalent to 90 MME per day. Tramadol also possesses SSRI-like properties and interacts with multiple drugs. Use with caution with other drugs that may increase risk of serotonin syndrome or decrease seizure threshold.

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

Table 2. Specific Opioid Products Subject to Quantity Limits per FDA-approved Labeling.

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

Drug Product	Quantity Limit
HYSINGLA ER	2 doses/day
KADIAN	2 doses/day
MORPHABOND	2 doses/day
NUCYNTA ER	2 doses/day
OPANA ER	2 doses/day
OXYCONTIN	2 doses/day
XARTEMIS XR	4 doses/day

Drug Product	Quantity Limit
XTAMPZA ER	2 doses/day
ZOHYDRO ER	2 doses/day

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD10	
2. Is the request for renewal of current therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the requested medication a preferred agent?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy. Both oral and transdermal options are available.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #5
5. Is the patient being treated for cancer-related pain (ICD10 G89.3) or under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months	**No:** Go to #6
6. Is the diagnosis funded by the OHP?	**Yes:** Go to #7	**No:** Pass to RPh. Go to #15
7. Is the opioid prescription for pain associated with a back or spine condition or for migraine headache?	**Yes:** Pass to RPh. Go to #15	**No:** Go to #8
8. Will the prescriber change to a preferred product, not to exceed 90 MME per day and not to exceed quantity limits in Table 2? Note: Preferred products that do not exceed 90 MME per day and do not exceed quantity limits in Table 2 do not require prior authorization.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #9
9. Does the total daily opioid dose exceed 90 MME?	**Yes:** Pass to RPh. Go to #15	**No:** Go to #10

10. Is the patient concurrently on other short- or long-acting opioids (patients are permitted to be on only one opioid product total at a time)?	**Yes:** Pass to RPh. Go to #15	**No:** Go to #11
11. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Go to #15	**No:** Go to #12
12. Can the prescriber provide documentation of sustained improvement of both pain and function in the past 3 months compared to baseline (e.g., validated tools to assess function include: Oswestry, Neck Disability Index, SF-MPQ, and MSPQ)?	**Yes:** Go to #13	**No:** Pass to RPh. Go to #15
13. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (PDMP) and has the prescriber verified at least once in the past 3 months that the patient has been prescribed analgesics by only a single prescribing practice or prescriber and has received those analgesics by only a single pharmacy?	**Yes:** Go to #14	**No:** Pass to RPh. Go to #15
14. Has the patient had a urinary drug screen (UDS) within the past 1 year to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Approve for up to 3 months. Subsequent approvals will require: • Verification of patient's opioid claims history in the Oregon PDMP at least every 3 months • Documentation of sustained improvement in both baseline pain and function at least every 3 months • Documented UDS at least every 12 months	**No:** Pass to RPh. Go to #15

15. Is the request to initiate new opioid therapy or to increase the total daily MME dose?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Pass to RPh. Approve for 3 months. Note: Documentation of progress towards meeting all criteria in this PA will be required for approval of subsequent claims. All future opioid claims are subject to **Renewal Criteria** 3 months from this index claim.

Renewal Criteria		
1. Has the patient had a urinary drug screen (UDS) within the past 1 year to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (PDMP) and has the prescriber verified at least once in the past 3 months that the patient has been prescribed analgesics by only a single prescribing practice or prescriber and has received those analgesics by only a single pharmacy?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Can the prescriber provide documentation of sustained improvement of both pain and function in the past 3 months compared to baseline (e.g., validated tools to assess function include: Oswestry, Neck Disability Index, SF-MPQ, and MSPQ)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
4. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Approve for up to 3 months if there is documentation of an individualized taper plan with progress to meet the quantity limits applied in Table 2.	**No:** Go to #5 if not applicable. Without documentation, pass to RPh. Deny; medical appropriateness.
5. Is the patient concurrently on other short- or long-acting opioids (patients are permitted to be on only one opioid product total at a time)?	**Yes:** Approve for up to 3 months if there is documentation of an individualized taper plan with progress to be managed on one short- or long-acting opioid only.	**No:** Go to #6 if not applicable. Without documentation, pass to RPh. Deny; medical appropriateness.
6. Does the total daily opioid dose exceed 90 MME?	**Yes:** Approve for up to 3 months if there is documentation of an individualized taper plan with progress toward meeting ≤90 MME per day.	**No:** Go to #7 if not applicable. Without documentation, pass to RPh. Deny; medical appropriateness.
7. Is the diagnosis funded by the OHP?	**Yes:** Approve for up to 3 months. Subsequent approvals will require: • Verification of patient's opioid claims history in the Oregon PDMP at least every 3 months • Documentation of sustained improvement in both baseline pain and function at least every 3 months • Documented UDS at least every 12 months	**No:** Approve for up to 3 months if there is documentation of an individualized taper plan with progress toward tapering off opioid. Without documentation, pass to RPh. Deny; medical appropriateness.

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Drug Effectiveness Review Project Summary Report – Disease-modifying Drugs for Multiple Sclerosis

Date of Review: November 2016

Date of Last Review: September 2015 (orals only)
Literature Search: Up to January 2016

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

Research Questions:
1. What is the comparative effectiveness and safety of disease-modifying treatments for multiple sclerosis?
2. Does the relationship between neutralizing antibodies and outcomes differ by treatment?
3. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?
4. Do disease-modifying treatments for multiple sclerosis or a clinically isolated syndrome differ in harms?
5. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?

Conclusions:
- There is low strength evidence from one small RCT that relapse rates were increased with teriflunomide 7 mg orally once daily but not 14 mg orally once daily compared to interferon beta-1a 44 mcg subcutaneously (SC)three times a week (relative risk [RR] 2.74, 95% confidence interval [CI] 1.66 to 4.53 and RR 1.52, 95% CI 0.87 to 2.67, respectively).
- An indirect comparison by network meta-analysis (NMA) showed treatment with fingolimod 0.5 mg once daily resulted in lower risk of relapse than treatment with interferon beta-1a 30 mcg intramuscularly (IM) once a week (RR 0.58, 95% CI 0.45 to 0.75). Definitive conclusions cannot be made regarding relative efficacy from indirect comparative evidence.
- From NMA data, alemtuzumab 12 mg infused once a day for 5 days followed by 12 mg infused once day for 3 days one year later is associated with the lowest risk of relapse (17.3%) and the lowest probability of study withdrawals due to adverse events (70.5%) compared with the other FDA approved MS drugs. However, since this is an indirect comparison, definitive conclusions cannot be made regarding relative efficacy.
- Ocrelizumab and daclizumab may be promising additions to current MS treatment, but additional comparative research is needed to draw definitive conclusions regarding benefits and harms. Specifically, low strength evidence from one randomized controlled trial (RCT) showed that treatment with daclizumab 150 mg SC once a month resulted in lower risk of relapse at week 144 (HR 0.59, 95% CI 0.50 to 0.69) and less disability progression at 24 weeks (HR 0.73, 95% CI 0.55 to 0.98) compared with interferon beta-1a 30 mcg IM once a week. Ocrelizumab is not yet approved by the U.S. Food and Drug Administration (FDA).
- Interferon beta-1a 30 mcg IM once a week (Avonex) appeared to have the lowest immunogenicity compared to the other interferons (interferon beta-1a 22 or 44 mcg SC and interferon beta-1b 250 mcg SC), with incidence of developing neutralizing antibodies ranging from 0% to 14% starting around 9 months

after initiation of treatment. With interferon beta-1a SC (Rebif®), antibodies also appeared around 9 months, with rates of immunogenicity ranging from 11% to 46%. With interferon beta-1b SC (Betaseron), neutralizing antibodies appeared as early as 3 months into treatment in 15% to 45% of patients. No differences in relapse were seen for any of the interferons within 2 years or less. There is insufficient evidence to determine what kind of impact the development of neutralizing antibodies has on disease progression.

- For patients with clinically isolated syndrome (CIS), there were no head-to-head trials of the drugs included in the DERP review to evaluate safety.
- Compared to interferon beta-1a (Avonex), withdrawals due to adverse events were more likely with teriflunomide 7 mg, glatiramer or interferon beta-1b (Betaseron), and less likely with teriflunomide 14 mg than with glatiramer.
- There was low strength evidence that treatment with daclizumab 150 mg SC once a month was associated with higher withdrawals due to adverse events (RR 1.57, 95% CI 1.21 to 2.03) compared with interferon beta-1a 30 mcg IM once a week, although there was similar risk of experiencing any adverse event or serious adverse event.
- One RCT provided low strength evidence of fewer early withdrawal due to adverse events with teriflunomide compared with interferon beta-1a 44 mcg (RR 0.44, 95% CI 0.25 to 0.76), although there were no differences in risk of experiencing any adverse event or serious adverse event.
- Fingolimod exposure in utero may be associated with increased risk of poor fetal outcomes.

Recommendations:

- Based on the DERP evidence review, no changes are recommended to the PDL at this time.
- Revise PA criteria to include assessment of lymphocyte count before initiating therapy with dimethyl fumarate.
- Evaluate comparative drug costs in the executive session.

Previous Conclusions:

- There is insufficient comparative evidence between oral disease modifying drugs for multiple sclerosis (MS) and other oral or injectable disease-modifying therapies.
- Moderate-quality evidence demonstrates the proportion of patients who experience at least one relapse over 2 years is reduced with use of dimethyl fumarate compared to placebo (relative risk [RR] 0.58; 95% CI, 0.50 to 0.67, p<0.00001) but not when compared to glatiramer acetate (RR 0.91; 95% CI, 0.72 to 1.13); however, the quality of the evidence to support benefit of dimethyl fumarate to slow worsening disability versus placebo is low (RR 0.66; 95% CI, 0.53 to 0.81).
- According to the National Institute for Health and Clinical Excellence (NICE), there is low quality evidence fampridine (i.e., dalfampridine), which is not a disease-modifying drug, may be more effective than placebo in response outcomes to different walking ability parameters are assessed; however, there is low quality evidence that there is no difference in efficacy between fampridine and placebo in time to walk 8 meters and there is insufficient evidence to determine if fampridine improves gait speed versus placebo. In addition, there is low quality evidence that there is no difference in the MS walking scale (MSWS-12) scores with fampridine compared to placebo. The NICE recommends against the use of dalfampridine due to poor cost effectiveness.
- There is low-quality evidence, based on one phase 3 trial, that a daily dose of 7 mg and 14 mg of teriflunomide may reduce time to first relapse in patients with a first clinical episode suggestive of MS (14 mg vs. placebo: hazard ratio [HR] 0.574 [95% CI, 0.379-0.869; p=0.0087] and 7 mg vs. placebo: HR 0.628 [95% CI, 0.416-0.949; p=0.0271]. It is currently FDA-approved to treat relapsing-remitting forms of multiple sclerosis (RRMS).
- A follow-up phase 3 trial of fingolimod confirms results from previous phase 3 trials, and provides moderate-quality evidence the drug significantly reduces relapse rates versus placebo in patients with RRMS (fingolimod 0.5 mg: rate ratio [RR] 0.52 (95% CI, 0.40-0.66; p<0.0001). It is currently FDA-approved to treat RRMS, to reduce the frequency of clinical exacerbations, and to delay the accumulation of physical disability in these patients.

Previous Recommendations:

- Update clinical prior authorization criteria for oral MS drugs to reflect Guideline Note 95 that restricts coverage to RRMS only.
- No change to the current PDL recommended at this time.

Methods:

The May 2016 Drug Class Review on Disease-modifying Drugs for Multiple Sclerosis 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. [1]

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.

The focus of the DERP update report is on disease-modifying drugs (DMDs), which are not designed to manage acute symptoms of MS but are designed to prevent relapses and slow the natural course of the disease over time. The DMDs that have been evaluated in the treatment of MS are outlined in **Table 1**. Of note, ocrelizumab received breakthrough therapy designation by the U.S. Food and Drug Administration (FDA) for treatment of PPMS in February 2016 and is included in the DERP update although it is not yet available in U.S. markets. Genentech, the manufacturer of ocrelizumab, announced in June 2016 that the FDA accepted the company's Biologic License Application (BLA) for the treatment of RRMS and PPMS. The targeted action date for FDA review is December 28, 2016.

Table 1: Disease-Modifying Drugs used to treat MS

Generic Name	Brand Name	Dose/Route/Frequency	FDA Indication
Oral Agents			
Fingolimod	Gilenya	0.5mg PO once daily	RRMS
Teriflunomide	Aubagio	7 mg or 14 mg PO once daily	RRMS
Dimethyl Fumarate	Tecfidera	240 mg PO twice a day	RRMS
Injectable Agents			
Glatiramer Acetate	Copaxone, Glatopa	20 mg SC once daily; OR 40 mg SC three times a week at least 48 hours apart	RRMS
Interferons			
Interferon beta-1a	Avonex	30 mcg IM once weekly	RRMS
Interferon beta-1a	Rebif	22 or 44 mcg SC three times a week	RRMS
Interferon beta-1b	Betaseron, Extavia	250 mcg SC every other day	RRMS

Peginterferon beta-1a	Plegridy	125 mcg SC every 14 days	RRMS
Monoclonal Antibodies			
Alemtuzumab	Lemtrada	Intravenous infusion for 2 treatment courses. (Total duration of therapy: 24 months) First course: 12 mg once a day for 5 days (total 60 mg). Second course: 12 mg once a day for 3 days (total 36 mg). Begin 12 months after the first treatment course.	RRMS Because of its safety profile, use should be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.
Daclizumab High Yield Process (HYP)	Zinbryta	150 mg SC once a month	RRMS Because of its safety profile, use should be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS
Ocrelizumab	NA	Intravenous infusion	Not FDA approved. Phase 3 trials are underway in RRMS and PPMS.

Abbreviations: FDA = U.S. Food and Drug Administration; IM = Intramuscular; MS = multiple sclerosis; NA = not applicable; PO = Oral; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SC= Subcutaneous

The DERP drug class review on DMDs for MS was the third update of the original report which was published in July 2007. The literature search was conducted through January 2016. The DERP literature search identified a total of 5,906 citations from searching electronic databases, reviews of reference lists, pharmaceutical manufacturer dossier submissions, and peer review comments. Thirty-nine head-to-head trials, 6 observational studies and 4 systematic reviews were included in the update. Most of the studies evaluated adult patients with RRMS, although patients with the other 3 forms of MS were included in the updated report. Adult patients with a clinical isolated syndrome (CIS) also known as 'first demyelinating event', 'first clinical attack suggestive of MS', or mono-symptomatic presentation were also included. The Oregon Health Evidence Review Commission (HERC) has stipulated via Guideline Note 95 that once a diagnosis of primary progressive or secondary progressive multiple sclerosis is reached, immune modifying therapies are not funded.[2] This summary report of the DERP findings will only focus on RRMS and CIS those are the only HERC funded forms of MS.

Effectiveness outcomes analyzed in the DERP update were: disability, clinical exacerbations/relapse, quality of life, functional outcomes (e.g. wheel chair use, time lost from work), and persistence (discontinuation rates). The effectiveness assessment of CIS outcomes included the same parameters for MS but added an additional outcome of progression to MS. Harms were assessed by evaluating the following: overall rate of adverse effects, withdrawals due to adverse effects or drug discontinuations due to adverse effects, serious adverse events, and specific adverse events (cardiovascular, hepatotoxicity, progressive multifocal leukoencephalopathy, secondary cancers, etc.). Comparative observational studies with 2 concurrent arms of at least 100 patients each and duration greater than 1 year were included to evaluate DMD harms.

For this third update, DERP conducted a NMA of RCTs in patients with RRMS and a NMA in patients with CIS. The authors compared their findings to a Cochrane NMA and pointed out when the DERP findings were not consistent with the Cochrane analysis. NMA is a procedure that permits inferences into the comparative effectiveness of interventions that may or may not have been evaluated directly against each other.[3] Estimates of treatment effects from NMAs should be interpreted with caution as treatment rankings or probabilities can be misleading.[3] The DERP authors note that in the absence of head-to-head evidence, the strength of evidence generated from NMA is low for indirect comparisons.

Summary Findings

1. What is the comparative effectiveness of disease modifying treatments for multiple sclerosis?

Two systematic reviews conducted a NMA to assess the effectiveness of drugs used to treat MS. One NMA limited comparisons of interferons to other injectable medications. The other NMA included all therapies except for ocrelizumab. A third NMA by the DERP reviewers included ocrelizumab at approved doses and dosing schedules for treatment durations up to 36 months. All drug formulations were evaluated in the dosing regimens outlined in **Table 1**. Thirty two studies including 18,576 subjects were included in the DERP NMA to assess risk of relapse in RRMS patients.

Daclizumab vs. Interferon beta-1a (Avonex)

- A randomized controlled trial (RCT) conducted in 1,841 patients with RRMS found low strength evidence that treatment with daclizumab 150 mg SC every 4 weeks resulted in a lower estimated risk of relapse at week 144 than treatment with interferon beta-1a 30 mcg (33% vs 49%, HR 0.59, 95% CI 0.50 to 0.69) and less estimated confirmed disability progression at 24 weeks (13% vs 18%, HR 0.73, 95% 0.55 to 0.98), but there were no statistically significantly differences in 12 week sustained disability progression. Annualized relapse rates were also lower with daclizumab (0.22 vs. 0.39, p<0.001). However, disability progression at week 144 was not significantly different between daclizumab and interferon beta-1a 30 mcg (16% vs. 20%, HR 0.84, 95% CI 0.66 to 1.07).

Alemtuzumab vs. Interferon beta-1a (Rebif)

- Treatment with interferon beta-1a 44 mcg SC results in higher risk of relapse when compared to alemtuzumab 12 mg (RR 1.67; 95% CI 1.37 to 2.04) in the DERP NMA. Similar results were noted with the lower 22 mcg dose of interferon beta-1a (RR 2.03; 95% CI 1.51 to 2.74). These conclusions are based on low strength evidence.

Glatiramer vs Dimethyl fumarate

- In the DERP NMA, no differences were found in the risk of relapse between glatiramer 20 mg or 40 mg SC compared to oral dimethyl fumarate 240 mg twice daily (RR 1.15; 95% CI 0.89 to 1.48, and RR 0.99; 95% CI 0.68 to 1.43, respectively). In addition, no significant differences were noted in annualized relapse rates between glatiramer and dimethyl fumarate in the Cochrane NMA. These conclusions are based on low strength evidence.

Glatiramer vs Interferon beta-1a (Avonex) and Interferon beta-1b (Betaseron)

- In the DERP NMA, no differences in relapse rates were noted between treatment with glatiramer 20 mg, glatiramer 40 mg, interferon beta-1a 22 mcg, interferon beta-1a 44 mcg, or interferon beta-1b 250 mcg. Results for annualized relapse rate from the Cochrane NMA were consistent with the DERP in relation to risk of relapse. This is based on low strength evidence.

Teriflunomide vs. Interferon beta-1a (Rebif)

- One RCT (N=324) compared a minimum of 48 weeks treatment (maximum 115 weeks) with teriflunomide 7 mg, teriflunomide 14 mg, and interferon beta-1a 44 mcg SC and found no differences between treatments in time to failure, defined as confirmed relapse or permanent treatment discontinuation (36% vs 33% vs 37%, respectively) at 48 weeks. There was a higher risk of relapse with lower dose teriflunomide compared with higher dose (42% vs 23%, RR 1.80, 95% CI 1.21 to 2.69) and low strength evidence of increased relapse risk with teriflunomide 7 mg versus interferon beta-1a 44ug SC (42% vs 16%, RR 2.74, 95% CI 1.66 to 4.53). There was low strength evidence no difference in risk of relapse between higher dose teriflunomide

and interferon beta-1a (RR 1.52, 95% CI 0.87 to 2.67). Adjusted annualized relapse rates were also higher with teriflunomide 7 mg compared with interferon beta-1a (0.41 vs 0.22, RR 1.90, 95% CI 1.05 to 3.43).

- In the DERP NMA, no differences in risk of relapse between treatments with teriflunomide 7 mg, teriflunomide 14 mg, and interferon beta-1a 22 mcg SC were noted (RR 0.82 to 1.10) based on low strength evidence. However, treatment with teriflunomide 7 mg was associated with increased risk of relapse compared with interferon beta-1a 44 mcg (RR 1.32; 95% CI 1.01 to 1.72). The Cochrane NMA showed no difference between teriflunomide and interferon beta-1a in annualized relapse rates, but teriflunomide doses were combined in that analysis.

Fingolimod vs Interferon beta-1a (Avonex)

- The DERP NMA included treatment with oral fingolimod 0.5 mg once daily resulted in lower risk of relapse than treatment with interferon beta-1a 30 mcg IM (RR 0.60; 95% CI 0.47 to 0.76). Fingolimod was associated with reduced annualized relapse rate compared with interferon beta-1a at 24 months but not at 12 months based on low strength evidence.

Pegylated interferon beta-1a vs. Placebo

- In one placebo-controlled RCT, 1512 RRMS patients were treated with pegylated interferon beta-1a 125 mcg SC administered every 2 or 4 weeks. There was moderate strength of evidence that risk of relapse was reduced with peginterferon compared with placebo (18% vs. 29%; HR 0.61; 95% CI 0.47 to 0.80: 22% vs. 29%; RR 0.74; 95% CI 0.59 to 0.92, respectively). Annualized relapse rates were 0.26 and 0.29 for peginterferon compared with 0.40 for placebo ($p<0.05$). Disability progression also favored peginterferon versus placebo (7% vs. 11%, HR 0.62, 95% CI 0.40 to 0.97) for both treatment regimens.

Interferons

- The DERP NMA showed that interferon beta-1a 44 mcg SC (Rebif) and interferon beta-1b 250 mcg SC (Betaseron) are associated with a relative lower risk of relapse compared with interferon beta-1a 30 mcg (Avonex) by 19% and 29% (RR 0.81; 95% CI 0.68 to 0.96, and RR 0.71; 95% CI 0.59 to 0.86, respectively). Pegylated interferon beta-1a is also associated with lower relapse risk versus interferon beta-1a 30 mcg (RR 0.67; 95% CI 0.47 to 0.95). Other treatment comparisons between interferons were not significantly different. The Cochrane NMA showed no differences in annualized relapse rates between interferons at 12 or 24 months, although point estimates favored interferon beta-1a 44 mcg SC (at 12 and 24 months) and beta-1b 250 mcg SC (at 24 months) over interferon beta-1a 30 mcg IM. An additional systematic review compared pegylated interferon beta-1a with the other interferons, and although peginterferon was numerically superior to the other interferons in annualized relapse rates, no comparison achieved statistical significance.

Ocrelizumab compared to interferon beta-1a (Avonex and Rebif)

- One published RCT compared ocrelizumab with interferon beta-1a 30 mcg and placebo. The trial included 220 patients from North America, east-central Europe and Asia, western Europe, and Latin America, although most patients were white (96%), female (65%), and had 2 or 3 relapses in the past 3 years (83%). There were 32 patients who experienced relapses within 24 weeks of treatment. Compared to interferon beta-1a 30 mcg IM, treatment with ocrelizumab 600 mg and 2000 mg resulted in a similar risk of relapse (5% vs. 17%, RR 0.33, 95% CI 0.09 to 1.14; 7% vs. 17%, RR 0.44, 95% CI 0.14 to 1.33, respectively), although annualized relapse rates versus interferon beta-1a 30 mcg were significantly lower for ocrelizumab 600 mg (0.13 vs. 0.36, p=0.03). When the two doses of ocrelizumab were combined (the relapse rate for ocrelizumab 2000 mg was higher than the rate for 600 mg), there was low strength evidence that ocrelizumab was associated with lower relapse rates than interferon beta-

1a, 6% vs 17%, RR 0.38, 95% CI 0.15 to 0.97. Annualized relapse rates by week 24 were 0.13 to 0.17 with ocrelizumab, 0.36 with interferon, and 0.64 for placebo.

- In the DERP NMA, treatment with ocrelizumab 600 mg IV is associated with lower risk of relapse when compared to interferon beta-1a 30 mcg IM (Avonex) [RR 0.24; 95% CI 0.07 to 0.76] and interferon beta-1a 22 mcg SC (Rebif) [RR 0.27; 95% CI 0.08 to 0.89] but not interferon beta-1a 44 mcg SC (RR 0.33; 95% CI 0.10 to 1.07). Treatment with ocrelizumab 2000 mg IV is associated with lower risk of relapse compared to interferon beta-1a 30 mcg IM (RR 0.31; 95% CI 0.11 to 0.87). These conclusions are based on low strength evidence.

2. Does the relationship between neutralizing antibodies and outcomes differ by treatment?

- Neutralizing antibodies are known to develop in some patients taking beta interferons, potentially interfering with effectiveness. One systematic review focused solely on interferon therapy and analyzed 9 comparative observational studies that reported the presence of neutralizing antibodies in patients taking interferons. Interferon beta-1a IM (Avonex®) appeared to have the lowest immunogenicity, with rates of development of neutralizing antibodies of 0% to 14% reported, starting around 9 months of treatment. With interferon beta-1a SC (Rebif®), antibodies also appeared around 9 months, with rates of immunogenicity from 11% to 46%; with interferon beta-1b SC (Betaseron®), neutralizing antibodies appeared as early as 3 months into treatment in 15% to 45% of patients. No difference in relapse is seen for any of the interferons in trials with short follow-up (2 years or less) and there is inadequate evidence to conclude there is an impact on disease progression.

3. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?

- There were no head-to-head trials of included drugs in patients with clinically isolated syndrome (CIS). The DERP NMA of the comparative effectiveness of the 3 interferons and 2 doses of teriflunomide found no statistically significant differences in rates of progression to MS through indirect analysis.

4. Do disease-modifying treatments for multiple sclerosis or a clinically isolated syndrome differ in harms?

To evaluate study drug tolerance/safety, the DERP reviewers conducted an NMA with withdrawals due to adverse events/study drug discontinuations as the outcome. Thirty three trials (n=19,191) evaluated study withdrawal due to adverse events. There were few significant differences between treatments. A sensitivity analysis for study withdrawal due to adverse events was not conducted. Moderate strength evidence showed that alemtuzumab 12 mg had the highest probability of being the best treatment with lower rates of study withdrawals due to adverse events (70.5%) followed by placebo (13.1%), which is consistent with the Cochrane NMA.

Comparative harms of DMDs in multiple sclerosis

Fingolimod

- In the DERP NMA, no difference was noted between fingolimod 0.5 mg and interferon beta-1a 30 mcg IM (Avonex) in study withdrawals due to adverse events (RR 1.16; 95% CI 0.65 to 2.08).

Teriflunomide

- One head-to-head trial (n=324) provided low strength evidence of fewer study withdrawals with teriflunomide (pooled data from 7 mg and 14 mg doses) compared with interferon beta-1a 44 mcg SC (Rebif) [10% vs. 22%, RR 0.44; 95% CI 0.25 to 0.76], although there was no difference between treatments in serious adverse events (8% vs 7%, RR 1.18; 95% CI 0.51 to 2.74) or in risk of experiencing any adverse event (93% vs. 96%, RR 0.97; 95% CI 0.92 to 1.02). Gastrointestinal disorders were more common in the groups receiving oral teriflunomide compared to injectable interferon (40% vs. 27%, RR 1.51; 95% CI 1.06 to 2.17) while influenza-like illness was less likely with teriflunomide (3% vs. 53%, RR 0.06; 95% CI 0.03 to 0.13).

- Treatment with teriflunomide 7 mg and 14 mg was associated with no difference in withdrawals due to adverse events when compared with interferon beta-1a 44 mcg SC (RR 0.57; 95% CI 0.32 to 1.02, and RR 0.72; 95% CI 0.42 to 1.25, respectively) based on the DERP meta-analysis, although point estimates favored teriflunomide. The NMA conducted by Cochrane found no difference at 24 months but found interferon beta-1a all doses associated with lower risk of withdrawal compared with teriflunomide all doses (RR 0.46; 95% CI 0.28 to 0.78). However, confidence limits for all comparisons lack precision.

Glatiramer acetate

- One placebo-controlled trial provided low quality evidence that glatiramer 40 mg given three times weekly was associated with a borderline increase in withdrawals due to adverse events compared with placebo (3% vs. 1%, RR 2.36; 95% CI 0.99 to 5.65).
- A fair-quality observational study analyzed patients treated for 2 years or more with glatiramer or an interferon. Ninety percent of included patients had RRMS and 10% had CIS. Rates of any adverse event were similar across the three interferon formulations (range 53% to 56%), and lower in patients given glatiramer (38.6%), though differences across all groups did not reach statistical significance (p=0.052). Flu-like symptoms did differ across treatments, as did injection-site reactions (both p<0.001).
- The DERP meta-analysis found no differences between oral dimethyl fumarate 240 mg twice daily and either glatiramer 20 mg SC (RR 0.85; 95% CI 0.49 to 1.48) or glatiramer 40 mg SC (RR 0.69; 95% CI 0.26 to 1.85) in study withdrawal due to adverse events. No differences in early withdrawal due to adverse events were noted between glatiramer 20 mg or 40 mg and any of the interferons (beta-1a 44 mcg SC, 22 mcg SC, 30 mcg IM, and beta-1b 250 mcg), including pegylated interferon, as well.

Interferons

- One trial (n=1512) compared pegylated interferon beta-1a 125 mcg SC (Plegridy) administered every 2 weeks or every 4 weeks to placebo. The study found that interferon beta-1a 125 mcg SC every 2 weeks (the approved dose) was associated with increased withdrawals due to adverse events and severe adverse events compared with placebo (5% vs. 1%, RR 3.49; 95% CI 1.52 to 7.99, and 18% vs. 11%, RR 1.66; 95% CI 1.21 to 2.28, respectively). There was little difference between the two dosing schedules of pegylated interferon on frequency of adverse events.
- In one head-to-head trial, alanine and aspartate aminotransferase levels (ALT/AST) were increased with interferon beta-1a 44 mcg SC (Rebif) (12% vs. 2%, RR 7.88; 95% CI 1.01 to 61) compared with interferon beta-1b 250 mcg SC (Betaseron). Injection site reactions were also twice as high with interferon beta-1a (28% vs. 14%, RR 1.97; 95% CI 0.96 to 4.05) compared with interferon beta-1b, whereas fatigue (14% vs. 7%, RR 3.05; 95% CI 0.86 to 11) and depression were twice as common with interferon beta-1b (13% vs. 6%, RR 2.03; 95% CI 0.64 to 6.41), although none of these differences were statistically significant. There was no difference between treatment with interferon beta-1a and interferon beta-1b in withdrawals due to adverse events (14% vs. 11%, RR 1.27, 95% CI 0.50 to 3.19).
- In one small head-to-head trial (n=188), there was no difference in withdrawal due to adverse events between interferon beta-1b 250 mcg SC (Betaseron) and interferon beta-1a 30 mcg (Avonex) IM (5% vs. 1%, RR 4.79; 95% CI 0.57 to 40).
- The DERP NM indicated no difference between either treatment with interferon beta-1a 44 mcg SC or interferon beta-1a 22 mcg SC (Rebif) and interferon beta-1b 250 mcg SC (Betaseron) in study withdrawals due to adverse events (RR 0.96; 95% CI 0.48 to 1.92, and RR 0.72; 95% CI 0.20 to 2.57, respectively). Similar results were seen between interferon beta-1a 30 mcg IM (Avonex) and interferon beta-1a 44 mcg SC or interferon beta-1a 22 mcg (Rebif) SC in study withdrawals due to adverse events (RR 0.59; 95% CI 0.33 to 1.05, and RR 0.78; 95% CI 0.23 to 2.63, respectively). Furthermore, no difference in risk of study withdrawal due to adverse events between interferon beta-1b 250 mcg SC (Betaseron) and interferon beta-1a 30 mcg (Avonex) IM (RR 1.77; 95% CI 0.80 to 3.91) was found.

- A pooled analysis of the risk of malignancy in patients treated with interferon beta-1a SC (Rebif) included evidence from 5 placebo-controlled trials. The analysis of placebo-controlled trials showed a lower incidence of cancer in patients treated with interferon than in those receiving placebo; however, the difference was not statistically significant (incidence 2.5 neoplasms per 1000 patient-years, 95% CI 0.9 to 5.4 for interferon vs. 6.3, 95% CI 2.9 to 11.9 for placebo).

Alemtuzumab

- In a publication detailing thyroid dysfunction, 42 out of 108 patients (39%) treated with alemtuzumab 12 mg and 31 out of 108 patients (29%) treated with alemtuzumab 24 mg developed thyroid dysfunction as compared with 7 out of 107 patients treated with interferon beta-1a 44 mcg SC (7%). Types of thyroid dysfunction ranged from hyperthyroidism to hypothyroidism.
- The DERP NMA found increased study withdrawals due to adverse events with interferon beta-1a 44 mcg SC (RR 3.35; 95% CI 1.76 to 6.36), but not interferon beta-1a 22 mcg SC (RR 2.51; 95% CI 0.71 to 8.89), compared with alemtuzumab 12 mg.

Ocrelizumab

- Three fair-quality trials provided safety and tolerability evidence for ocrelizumab. One placebo-controlled trial (n=218) compared ocrelizumab treatment with interferon beta-1a 30 mcg IM and found no difference between ocrelizumab 600 mg or 2000 mg compared with interferon beta-1a 30 mcg IM in withdrawals due to adverse events (4% vs. 2%, RR 1.97; 95% CI 0.18 to 21, and 2% vs. 2%, RR 0.98; 95% CI 0.06 to 15, respectively) or in serious adverse events (2% vs. 4%, RR 0.49; 95% CI 0.05 to 5.26, and 6% vs. 4%, RR 1.47; 95% CI 0.26 to 8.47, respectively). However, one patient who was treated with ocrelizumab 2000 mg died after she developed thrombocytopenia followed by disseminated intravascular coagulopathy and multi-organ-dysfunction; she suffered brain edema and died on day 15 of hospitalization from transcranial herniation. The relation to ocrelizumab is unknown. Additionally, treatment with ocrelizumab was associated with mild to moderate infusion-related reactions, especially with the initial dose which affected 39% of subjects on the first day of treatment.
- Two unpublished randomized trials (Opera I and Opera II) treated 1651 total patients with ocrelizumab 600 mg or interferon beta-1a 44 mcg SC. Opera 1 was shared at an international conference and Opera II data was shared by Genentech, the manufacturer of ocrelizumab. Withdrawals due to adverse events were similar for both trials and were lower in the ocrelizumab arms (4% vs. 6%, RR 0.58; 95% CI 0.37 to 0.91) although the same percentage of patients experienced at least one adverse event (83%) in both treatment groups. Serious adverse events were not different between groups (7% vs. 9%, RR 0.79; 95% CI 0.57 to 1.11). There was one death due to suicide in the ocrelizumab 600 mg group and two deaths in the interferon beta-1a 44 mcg SC group due to suicide and mechanical ileus (RR 0.50; 95% CI 0.05 to 5.51). The most common adverse events were infusion-related reactions in the ocrelizumab groups resulting in 11 study withdrawals (1%) during the first ocrelizumab treatment.
- Estimates of withdrawals due to adverse events from the DERP NMA are consistent with trials outlined above which indicates no difference between ocrelizumab 600 mg and either interferon beta-1a 30 mcg IM (Betaseron) or interferon beta-1a 44 mcg SC (Rebif).
- A fair-quality placebo-controlled trial of ocrelizumab in PPMS patients (n=732) provided insufficient evidence to compare all-cause mortality between the two treatment groups (RR 2.0, 95% CI 0.30 to 13; 5 deaths occurred; 4/486 in ocrelizumab group; 1/239 in placebo group). There was low-strength evidence that rates of serious adverse events did not differ between groups (RR 0.92, 95% CI 0.69 to 1.2). Overall, withdrawals were less likely with ocrelizumab (RR 0.59, 95% CI 0.46 to 0.76), but withdrawals due to adverse events were not reported. Rates of infection did not differ between treatment arms (RR 1.0, 95% CI 0.93 to 1.1). More malignancies (2.3% vs. 0.8%) occurred in patients given ocrelizumab than in those receiving placebo, but the difference was not statistically significant (RR 2.7, 95% CI 0.68 to 11).

Daclizumab

- Treatment with daclizumab 150 mg SC every 4 weeks was compared with treatment with interferon beta-1a 30 mcg IM weekly for up to 144 weeks in a RCT of 1841 RRMS patients. While almost all patients experienced at least one adverse event (91% both groups), there was low strength evidence that patients who received daclizumab were more likely to withdraw from the study due to adverse events, excluding relapse compared with patients treated with interferon beta-1a (14% vs. 9%, RR 1.57; 95% CI 1.21 to 2.03). However, there was low strength evidence that the risk of having a serious adverse event was similar between study treatments (24% vs. 21%, RR 1.14; 95% CI 0.96 to 1.35). Both infections and serious infections were more likely with daclizumab (65% vs. 57%, RR 1.14; 95% CI 1.06 to 1.23, and 4% vs. 2%, RR 2.68; 95% CI 1.49 to 4.81). Additionally, there were 5 deaths during the study, although none were considered treatment-related by investigators blinded to treatment allocation--1 death in the daclizumab group vs. 4 in the group receiving interferon (RR 0.25; 95% CI 0.03 to 2.24).
- In a randomized trial of daclizumab 150 mg and 300 mg compared with placebo, most patients experienced at least one adverse event (daclizumab doses pooled 74% vs. 79%; RR 0.94; 95% CI 0.86 to 1.03) and there were no differences between treatment in risk of experiencing any serious adverse event, excluding relapse (8% vs. 6%; RR 1.39; 95% CI 0.73 to 2.62).
- The DERP N found no difference in withdrawals due to adverse events between daclizumab 150 mg or 300 mg and interferon beta-1a 30 mcg IM (RR 1.62; 95% CI 0.94 to 2.79, and RR 2.62; 95% CI 0.85 to 8.12, respectively) but confidence intervals are imprecise.

Comparative harms of DMDs in Clinically Isolated Syndrome

- No head to head evidence in patients with CIS evaluated harms of DMDs. The DERP reviewers completed a NMA of the comparative harms of glatiramer, the 3 interferons, and 2 doses of teriflunomide in CIS. For withdrawals due to adverse events, confidence intervals for many comparisons were wide; however, available evidence suggested that withdrawal rates were higher with teriflunomide 7 mg, glatiramer, or interferon beta-1b (Betaseron), each compared with interferon beta-1a IM (Avonex). Indirect analysis showed there was also a statistically significant difference in withdrawals due to adverse events between teriflunomide 14 mg and glatiramer 20 mg (RR 0.24, 95% CI 0.07 to 0.86).

5. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?

- There were no differences found in annualized relapse rate between fingolimod 0.5 mg and interferon beta-1a 30 mcg IM when patients were stratified based on gender, age, treatment history, and number of relapses in the past 1 to 2 years. Although the treatment effect with fingolimod on annualized relapse rates were greatest in females and those under 40 years of age, confidence intervals overlapped.
- There was no difference in effect on annualized relapse rates of daclizumab 150 mg compared with interferon beta-1a 30 mcg IM based on gender (Male: ARR 0.46, 95% CI 0.35 to 0.62; Female: ARR 0.59, 95% CI 0.49 to 0.72).
- Fingolimod exposure in utero may be associated with increased risk of poor fetal outcomes. The results of 74 pregnancies (66 pregnancies with in utero exposure to fingolimod) resulted in 35 deliveries with 1 congenital unilateral posteromedial bowing of the tibia and 1 infant with acrania (both were exposed in utero). There were 25 elective abortions with 1 Tetrology of Fallot, 1 ectopic pregnancy, 1 intrauterine death, and 1 pregnancy not developing normally.

References:

1. Selph S, Holmes R, Thakurta S, et al. Disease-Modifying Drugs for Multiple Sclerosis Drug Class Review: Final Update 3 Report, May 2016. Drug Effectiveness Review Project at the Pacific Northwest Evidence Practice Center, Portland, Oregon.

2. Health Evidence Review Commission Prioritized List Overview. https://www.oregon.gov/oha/herc/Pages/Prioritized-List-Overview.aspx. Accessed August 26, 2016.

3. Mills EJ, Thorlund K, Ioannidis JPA. Demystifying trial networks and network meta-analysis. *BMJ*. 2013;346:f2914. doi:10.1136/bmj.f2914.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-Q	SYRINGE	COPAXONE	GLATIRAMER ACETATE	Y
SUB-Q	SYRINGE	GLATOPA	GLATIRAMER ACETATE	Y
INTRAMUSC	KIT	AVONEX ADMINISTRATION PACK	INTERFERON BETA-1A/ALBUMIN	Y
SUB-Q	SYRINGE	REBIF	INTERFERON BETA-1A/ALBUMIN	Y
SUB-Q	PEN INJCTR	REBIF REBIDOSE	INTERFERON BETA-1A/ALBUMIN	Y
INTRAMUSC	PEN IJ KIT	AVONEX PEN	INTERFERON BETA-1A	Y
INTRAMUSC	SYRINGE	AVONEX	INTERFERON BETA-1A	Y
INTRAMUSC	SYRINGEKIT	AVONEX	INTERFERON BETA-1A	Y
SUB-Q	KIT	BETASERON	INTERFERON BETA-1B	Y
SUB-Q	KIT	EXTAVIA	INTERFERON BETA-1B	Y
INTRAVEN	VIAL	LEMTRADA	ALEMTUZUMAB	N
ORAL	TAB ER 12H	AMPYRA	DALFAMPRIDINE	N
ORAL	CAPSULE DR	TECFIDERA	DIMETHYL FUMARATE	N
ORAL	CAPSULE	GILENYA	FINGOLIMOD HCL	N
SUB-Q	SYRINGE	COPAXONE	GLATIRAMER ACETATE	N
INTRAMUSC	PEN INJCTR	AVONEX PEN	INTERFERON BETA-1A	N
SUB-Q	VIAL	EXTAVIA	INTERFERON BETA-1B	N
INTRAVEN	VIAL	MITOXANTRONE HCL	MITOXANTRONE HCL	N
SUB-Q	SYRINGE	PLEGRIDY	PEGINTERFERON BETA-1A	N
SUB-Q	PEN INJCTR	PLEGRIDY PEN	PEGINTERFERON BETA-1A	N
ORAL	TABLET	AUBAGIO	TERIFLUNOMIDE	N

Oral Multiple Sclerosis Drugs

Goal(s):
- Promote safe and effective use of oral disease-modifying multiple sclerosis drugs
- Promote use of preferred multiple sclerosis drugs.

Length of Authorization:
- Up to 12 months

Requires PA:
- Fingolimod
- Teriflunomide
- Dimethyl Fumarate

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the patient have a diagnosis of primary or secondary progressive multiple sclerosis?	**Yes:** Pass to RPh. Deny; not funded by the OHP. See Guideline Note 95 in the Prioritized List of Health Services.	**No:** Go to #3
3. 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 Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4

Approval Criteria		
4. Has the patient failed or cannot tolerate a trial of interferon beta 1a or interferon beta 1b, and glatiramer?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta 1B, glatiramer acetate, interferon beta 1A, natalizumab, mitoxantrone)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7
7. Is the prescription for teriflunomide?	**Yes:** Go to #8	**No:** Go to #10
8. Is the patient of childbearing potential?	**Yes:** Go to #9	**No:** Approve for up to 1 year.
9. Is the patient currently on a documented use of reliable contraception?	**Yes:** Approve for up to 1 year.	**No:** Pass to RPh. Deny; medical appropriateness.
10. Is the prescription fingolimod?	**Yes:** Go to #11	**No:** Go to #14
11. Does the patient have evidence of macular edema?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #12
12. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on anti-arrhythmic, beta-blockers, or calcium channel blockers?	**Yes:** Go to #13	**No:** Approve up to 1 year.
13. Has the patient had a cardiology consultation before initiation (see clinical notes)?	**Yes:** Approve up to 1 year.	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the prescription for dimethyl fumarate?	**Yes:** Go to # 15	**No:** Pass to RPh. Deny; medical appropriateness.
15. Does patient have a baseline CBC with lymphocyte count greater than 500/µL?	**Yes:** Approve for up to 1 year	**No:** Pass to RPh. Deny; medical appropriateness.

Fingolimod Clinical Notes:

- Because of bradycardia and atrioventricular conduction, patients must be observed for six hours after initial dose in a clinically appropriate area.
- Patients on antiarrhythmic, beta-blockers or calcium channel blockers or with bradycardia risk factors (h/o MI, age >70 yrs., electrolyte disorder, hypothyroidism) may be more prone to development of symptomatic bradycardia and should be initiated on fingolimod with caution and cardiology evaluation should be done before considering treatment.
- Injectable disease modifying treatments remain first line agents in MS therapy.
- An ophthalmology evaluation should be repeated 3-4 months after fingolimod initiation with subsequent evaluations based on clinical symptoms.

Teriflunomide Clinical Notes:

- Before starting Teriflunomide, screen patients for latent tuberculosis infection with a TB skin test, exclude pregnancy, confirm use of reliable contraception in women of childbearing potential, check BP, obtain a complete blood cell count within the 6 months prior to starting therapy, instruct patients receiving Teriflunomide to report symptoms of infections, and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.
- After starting Teriflunomide, monitor ALT levels at least monthly for 6 months after, consider additional ALT monitoring when Teriflunomide is given with other potentially hepatotoxic drugs, consider stopping Teriflunomide if serum transaminase levels increase (>3 times the ULN), monitor serum transaminase and bilirubin particularly in patients who develop symptoms suggestive of hepatic dysfunction, stop TER and start accelerated elimination in those with suspected TER-induced liver injury and monitor liver tests weekly until normalized, check BP periodically and manage elevated BP, check serum potassium level in TER-treated patients with hyperkalemia symptoms or acute renal failure, monitor for signs and symptoms of infection.
- Monitor for hematologic toxicity when switching from TER to another agent with a known potential for hematologic suppression, because systemic exposure to both agents will overlap.

Dimethyl Fumarate Clinical Notes:

- Dimethyl fumarate may decrease a patient's white blood cell count. In the clinical trials the mean lymphocyte counts decreased by approximately 30% during the first year of treatment with dimethyl fumarate and then remained stable. The incidence of infections (60% vs. 58%) and serious infections (2% vs. 2%) was similar in patients treated with dimethyl fumurate or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts <0.8x109/L. A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.
- Dimethyl fumarate should be held if the WBC falls below 2000/mm3 or the lymphocyte count is below 500/µL and permanently discontinued if the WBC did not increase to over 2000/mm3 or lymphocyte count increased to over 500/µL after 4 weeks of withholding therapy.
- Patients should have a CBC with differential monitored on a quarterly basis

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P&T Review: *11/16 (DM); 9/15; 9/13; 5/13; 3/12*
Implementation: *1/1/14; 6/21/2012*

Drug Class Review

Disease-modifying Drugs for Multiple Sclerosis

Final Update 3 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.

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INTRODUCTION

Multiple sclerosis is a chronic, autoimmune disease of the central nervous system affecting 2.3 million people worldwide. Prevalence estimates in the United States range from 250,000 to 400,000 people. Multiple sclerosis causes demyelination of neuronal axons that form lesions within the white matter of the central nervous system (cerebral white matter, brain stem, cerebellar tracts, optic nerves, or spinal cord) when viewed on magnetic resonance imaging (MRI). Demyelination may slow, or even block, axonal conduction, and neuronal degeneration may occur. Impaired neuronal conduction ultimately causes the neurological symptoms associated with multiple sclerosis.

The 2010 McDonald Criteria for diagnosis of multiple sclerosis combine evidence of attacks (acute demyelinating events) and central nervous system lesions on MRI. Different combinations of these criteria can support an MS diagnosis; for example, a clinical presentation of 2 or more attacks, as well as objective clinical evidence of 2 or more lesions, or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack, is adequate for diagnosis. Progression of multiple sclerosis is measured by the disability caused by the disease. Four main types of multiple sclerosis have been characterized: relapsing-remitting, secondary progressive, primary progressive, and progressive relapsing. About 85% of multiple sclerosis patients have relapsing-remitting multiple sclerosis at the onset of the disease, and about 10% have primary progressive multiple sclerosis. The treatment of multiple sclerosis involves acute relapse treatment with corticosteroids, symptom management with appropriate agents, and disease modification with disease-modifying drugs.

Scope and Key Questions

The purpose of this review is to compare the effectiveness and safety of different disease-modifying drugs for the treatment of multiple sclerosis. In consultation with the Drug Effectiveness Review Project (DERP) participating organizations, The Pacific Northwest Evidence-based Practice Center (EPC) developed the following key questions and inclusion criteria to guide this review:

1. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis?

2. Does the relationship between neutralizing antibodies and outcomes differ by treatment?

3. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?

4. Do disease-modifying treatments for multiple sclerosis or a clinically isolated syndrome differ in harms?

5. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?

METHODS

Inclusion Criteria

Populations

- Adult outpatients (age ≥18 years) with multiple sclerosis
    - Relapsing-remitting multiple sclerosis
    - Secondary progressive multiple sclerosis
    - Primary progressive multiple sclerosis
    - Progressive relapsing multiple sclerosis
- Adult outpatients with a clinically isolated syndrome (also known as "first demyelinating event," first clinical attack suggestive of multiple sclerosis, or monosymptomatic presentation).

Interventions (all formulations)

Table A. Included interventions

Agent	Dosage, route and frequency	Indication
Fingolimod Gilenya™	0.5 mg Orally once daily	Patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability
Glatiramer Acetate Copaxone®, Glatopa™[a]	20 mg in 1 mL Subcutaneously once daily, 40mg in 1 mL subcutaneously three times weekly at least 48 hours apart	Treatment of relapsing forms of multiple sclerosis
Interferon beta-1a Avonex®	30 µg Intramuscularly once weekly	Treatment of patients with relapsing forms of MS to slow accumulation of physical disability and decrease frequency of clinical exacerbations. Effective in patients who experienced first clinical episode and have MRI features consistent with MS
Interferon beta-1a Rebif®	22 or 44 µ Subcutaneously three times weekly	Treatment of relapsing forms of MS to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability
Interferon beta-1b Betaseron®, Extavia®	0.25 mg in 1 mL Subcutaneously every other day	Treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations. Effective in patients who experienced first clinical episode and have MRI features consistent with MS
Peginterferon beta-1a Plegridy™	125 µ Subcutaneously every 14 days	Treatment of relapsing forms of multiple sclerosis
Teriflunomide Aubagio®	7 mg or 14 mg Orally once daily	Treatment of relapsing forms of multiple sclerosis
Dimethyl fumarate Tecfidera®	Maintenance dose: 240 mg Orally twice daily	Treatment of relapsing forms of multiple sclerosis
Alemtuzumab Lemtrada™	Intravenous infusion for 2 treatment courses. First course: 12 mg/day for 5 days. Second course: 12 mg/day for 3 days 12 months after first treatment course	Treatment of relapsing forms of MS. Because of its safety profile, use should be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.
Daclizumab HYP Zinbryta™	NA	Submitted for approval to the FDA
Ocrelizumab[c]	NA	FDA granted Breakthrough Therapy designation for ocrelizumab in PPMS in February 2016.

Abbreviations: MRI, magnetic resonance imaging; MS, multiple sclerosis; NA, not applicable; PPMS, primary-progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.
[a]Administered 20 mg in 1 ml once daily
[b]Biologics License Application (BLA) submitted 4/29/2015
[c]Not yet submitted for FDA approval (expected first half of 2016).

Effectiveness Outcomes

Multiple sclerosis

- Disability
- Clinical exacerbation/relapse
- Quality of life
- Functional outcomes (e.g., wheel chair use, time lost from work)
- Persistence (discontinuation rates).

Clinically isolated syndrome

- Disability
- Clinical exacerbation/relapse of symptoms
- Quality of life
- Functional outcomes (e.g., wheel chair use, time lost from work)
- Persistence (discontinuation rates)
- Progression to multiple sclerosis diagnosis.

Study Designs

- For effectiveness and harms, head-to-head controlled clinical trials and good-quality comparative systematic reviews were included. Comparative observational studies with 2 concurrent arms of at least 100 patients each and duration ≥1 year are also included for evaluation of harms.
- Placebo-controlled trials (PCT) were included for network meta-analysis in the absence of head-to-head trials and the PCT is the only information for a new drug or formulation.

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 December 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 meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough to combine their results. When necessary, indirect meta-analyses were done to compare interventions for which there were no head-to-head comparisons and where there was a common comparator intervention across studies. The I^2 statistic (the proportion of variation in study estimates due to heterogeneity) was calculated to assess heterogeneity in effects between studies. When meta-analysis could not be performed, the data were summarized qualitatively.

RESULTS

Table B. Summary of the evidence

Key Question	Strength of the evidence	Type of multiple sclerosis	Conclusion
1. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis, including use of differing routes and schedules of administration?	Low	Relapsing-remitting multiple sclerosis	Ocrelizumab • There was low strength evidence that treatment with ocrelizumab 600 mg is associated with similar risk of relapse as treatment with interferon beta-1a 30 µg IM (RR 0.32, 95% CI 0.09 to 1.14) although annualized rates favored ocrelizumab • There was low strength evidence that treatment with ocrelizumab 600 mg is associated with reduced confirmed disability progression at 6 months (**HR for risk reduction 0.60, 95% CI 0.43 to 0.84**) and lower risk of relapse (**annualized relapse rate 0.16 vs. 0.29, p<0.001**) than interferon beta-1a 44 µg SC
	Low	Relapsing-remitting multiple sclerosis	Daclizumab HYP • There was low strength evidence that daclizumab HYO 150 mg is associated with less confirmed disability progression (**HR .73, 95% CI 0.55 to 0.98**) and lower risk of relapse (**HR 0.59, 95% CI 0.50 to 0.69**) compared with interferon beta-1a 30 µg IM
	Moderate	Relapsing-remitting multiple sclerosis	Alemtuzumab • There was moderate-strength evidence that treatment with alemtuzumab 12 mg resulted in improved sustained accumulation of disability at 6 months (**RR, 0.59; 95% CI, 0.40 to 0.86**) and risk of relapse (**RR, 0.61; 95% CI, 0.52 to 0.71**) compared to treatment with interferon beta-1a 44 µg SC
	Low	Relapsing-remitting multiple sclerosis	Dimethyl fumarate • Low-strength evidence indicated that dimethyl fumarate 480 mg daily and glatiramer 20 mg have similar risk of relapse (RR 0.91, 95% CI 0.73 to 1.13)
	Low	Relapsing-remitting multiple sclerosis	Teriflunomide • There was low-strength evidence that teriflunomide 7 mg, but not 14 mg, is associated with increased risk of relapse compared with interferon beta-1a 44 µg SC (**RR 2.74, 95% CI 1.66 to 4.53**; RR 1.52, 95% CI 0.87 to 2.67, respectively)
	Moderate	Relapsing-remitting multiple sclerosis	Fingolimod • Based on moderate-strength evidence, fingolimod 0.5 mg once daily resulted in lower risk of relapse than treatment with interferon beta-1a 30 µg SC (**RR 0.58, 95% CI 0.45 to 0.75**)
	Low to moderate	Relapsing-remitting multiple sclerosis	Glatiramer acetate • There was moderate strength evidence that glatiramer 40 mg thrice weekly resulted in improved annualized relapse rate over placebo (**0.33 vs. 0.51, p<0.001**) • Head-to-head trials provided low-strength evidence of no difference in relapse related outcomes with glatiramer versus beta interferons • There was moderate-strength evidence of no effect of glatiramer acetate on disease progression compared with interferon beta-1b and low strength evidence of similar disease progression between glatiramer and interferon beta-1a IM and SC

	Low-Moderate	Relapsing-remitting multiple sclerosis	Beta interferons • There was moderate strength evidence that pegylated interferon beta-1a 125 mg was associated with improved disability and disease progression outcomes compared with placebo • There was moderate strength evidence that treatment with interferon beta-1b 250 µg or interferon beta-1a 44 µg results in improved relapse outcomes compared with interferon beta-1a 30 µg IM. There was conflicting evidence on disease progression outcomes. • Current evidence is unable to identify differences between effectiveness of interferon beta-1b SC and interferon beta-1a Sc. Indirect analyses of placebo-controlled trial data agreed with these results. • The rates of disease progression in beta interferon groups in head-to-head trials at 2 years ranged from 13% to 57%. Annualized relapse rates for beta interferon groups ranged from 0.4 to 0.7 • The evidence supported a benefit of interferon beta-1b SC over interferon beta-1a IM in relapse outcomes **(% relapse-free RR, 1.51; 95% CI, 1.11 to 2.07; number needed to treat, 6**). There was conflicting evidence on disease progression outcomes with only 1 trial reporting on percent progressed and finding a significant benefit of interferon beta-1b SC over interferon beta-1a IM (**RR, 0.44; 95% CI, 0.25 to 0.79; number needed to treat, 6**), however, despite a trend toward benefit, there was no statistically significant difference in mean change in EDSS score (−0.330; 95% CI, −0.686 to +0.025). • Three head-to-head trials suggested a benefit of interferon beta-1a SC over interferon beta-1a IM in terms of relapse outcomes. No differences in disease progression outcomes were found, although the larger trial followed patients for only 16 months such that differences may not yet have been seen. Indirect analyses of placebo-controlled trial data did not result in a significant difference. • Current evidence is unable to identify differences between interferon beta-1b SC and interferon beta-1a SC in terms of effectiveness. Indirect analyses of placebo-controlled trial data agreed with these results.
	Moderate	Primary progressive multiple sclerosis	• There was moderate-strength evidence that ocrelizumab delayed disability progression compared with placebo in patients with PPMS (**HR 0.75, 95% CI 0.58 to 0.98 over 24 weeks**).
	High	Mixed populations: progressive multiple sclerosis	A good-quality systematic review concluded that interferon beta-1b had lower relapse rates over 36 months than placebo in patients with SPMS, PRMS, or PPMS.
	Very low/Low		The review found no other differences in efficacy between interferons or glatiramer and placebo.

2. Does the relationship between neutralizing antibodies and outcomes differ by treatment?	Moderate		• Evidence for interferon β-1b SC (Betaseron®) and interferon β-1a SC (Rebif®) indicates that high titers of neutralizing antibodies increase relapse rates by about 60 to 90% during longer periods of follow-up. • No difference in relapse is seen for any of the products in shorter follow-up (2 years or less), and there is inadequate evidence to conclude that there is an impact on disease progression. • Interferon β-1a IM (Avonex®) appears to have the lowest immunogenicity, with rates of development of neutralizing antibodies of 0-14% starting around 9 months of treatment. • Interferon beta-1a SC antibodies also appear around 9 months, with rates of immunogenicity from 11 to 46%. • Interferon beta-1b SC neutralizing antibodies appear as early as 3 months into treatment in 15 to 45% of patients. • Importantly, 40-50% of antibody positive patients will become antibody negative over time, while small number of patients will become antibody positive into the second year of treatment.
3. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?	Low	Clinically isolated syndrome	• No direct evidence comparing 1 DMD to another in patients with a clinically isolated syndrome was available. • Indirect analysis showed no statistically significant differences among the three interferons and two doses of teriflunomide in progression to multiple sclerosis in patients with CIS.
4. Do disease-modifying treatments for multiple sclerosis or clinically isolated syndrome differ in harms?	Low		Ocrelizumab • There was low strength evidence that treatment with ocrelizumab 600 mg is associated with fewer study withdrawals due to adverse events (**RR 0.58, 95% CI 0.37 to 0.91**) and similar risk of serious adverse events (RR 0.79, 95% CI 0.57 to 1.11) as treatment with interferon beta-1a 44 µg SC
	Low		Daclizumab • There was low strength evidence that treatment with daclizumab HYP 150 mg increased study withdrawals due to adverse events (**RR 1.57, 95% CI 1.21 to 2.03**), compared with interferon beta-1a 30 µg IM, although there was similar risk of experiencing any or any serious adverse event.
	Moderate		Alemtuzumab • There was moderate-strength evidence that treatment with alemtuzumab 12 mg is associated with lower probability of withdrawing from the study due to an adverse event (**RR 0.31, 95% CI 0.17 to 0.55**) compared with interferon beta-1a 44 µg SC. However, treatment with alemtuzumab was associated with increased risk of thyroid dysfunction and immune thrombocytopenic purpura.

	Low	Dimethyl fumarate • Low-strength evidence indicated that treatment with dimethyl fumarate 480 mg daily increased the risk of experiencing any adverse event compared with glatiramer 20 mg (**RR, 1.09; 95% CI, 1.04 to 1.14**) but there was no difference in withdrawal due to adverse events or in risk of experiencing a serious adverse event
	Low	Teriflunomide • One randomized trial provided low strength evidence of fewer study withdrawals due to adverse events with teriflunomide compared with interferon beta-1a 44 µg (**RR 0.44, 95% CI 0.25 to 0.76**), although there were no differences in risks of experiencing any adverse event or serious adverse event
	Low	Fingolimod • Differences in adverse events between fingolimod 0.5 mg once daily and interferon beta-1a were found for some specific adverse events: • Higher rates of pyrexia (**RR, 4.26; 95% CI, 2.62 to 6.97**), influenza-like illness (**RR, 10.55; 95% CI, 6.39 to 17.57**), and myalgia (**RR, 3.13; 95% CI, 1.76 to 5.59**) were found with interferon beta-1a • A higher rate of increased alanine aminotransferase (**RR, 3.52; 95% CI, 1.66 to 7.50**) was found with fingolimod • Fingolimod 1.25 mg was associated with higher risk of herpes virus infections than fingolimod 0.5 mg (**RR, 2.61; 95% CI, 1.75 to 5.49**) or interferon beta-1a (**RR, 1.97; 95% CI, 1.01 to 3.86**). • After the first dose of fingolimod, dose-dependent bradycardia and atrioventricular block occurred in the first 6 to 8 hours; none persisted or occurred later in treatment
	Low	Glatiramer acetate • There was low strength of evidence of no differences between glatiramer and the beta interferons in study withdrawals due to adverse events • Patients treated with glatiramer acetate were more likely to have higher rates of injection site reactions and lipoatrophy while patients treated with the interferons experienced higher rates of flu-like syndrome and elevated liver enzymes • There was low strength evidence that treatment with glatiramer 40 mg three times weekly was associated with increased withdrawals due to adverse events than placebo (RR 2.36, 95% CI 0.99 to 5.65)

	Moderate	Beta interferons • Comparative adverse event reporting was limited with multiple studies using different doses of the same product, most frequently with interferon beta-1a SC (Rebif®). We have used data pertaining to interferon beta-1a SC (Rebif®) 44µg SC 3 times weekly dosing when pooling all trial data. • Although generally well tolerated, adverse events were reported frequently with all 3 beta interferon products and although the ranges were wide, some differences between the products were apparent • There was moderate strength evidence that compared with other interferons: treatment with interferon beta-1a 30 µg IM results in lower risk of flu-like syndrome. Also compared with other interferons treatment with interferon beta-1b 250 µg is associated with higher risk of fever and greatest likelihood of withdrawal from the study due to adverse events • Treatment with pegylated interferon beta-1a 125 µg resulted in increased withdrawals due to adverse events (**RR 3.49, 95% CI 1.52 to 7.99**) and increased severe adverse events (**RR 1.66, 95% CI 1.21 TO 2.28**) than placebo
		Ocrelizumab
	Insufficient	• A trial comparing ocrelizumab to placebo in patients with PPMS provided insufficient evidence to compare mortality across treatment arms (5 patients died).
	Low	• The trial showed no difference in serious adverse events between ocrelizumab and placebo (RR 0.92, 95% CI 0.69 to 1.2)
	Low	Clinically isolated syndrome • Indirect analysis suggested that: o Withdrawals due to adverse events were more likely in patients with CIS treated with teriflunomide 7 mg, glatiramer, or interferon beta-1b (Betaseron®), each compared with interferon beta-1a IM (Avonex®). o Withdrawals due to adverse events were less likely with teriflunomide 14 mg than with glatiramer (**RR 0.24, 95% CI 0.07 to 0.86**).

5. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?	Low-Moderate	• Alemtuzumab outperformed interferon beta-1a in sustained accumulation of disability, relapse rate, clinical disease activity, and sustained reduction in disability for all subgroups analyzed (e.g., gender, age, disease duration); Europeans had significantly reduced clinical disease activity than US patients • There was no difference between fingolimod 0.5 mg and interferon beta-1a 30 µg IM based on subgroups from the TRANSFORMS study. Although treatment effects with fingolimod were greater in females and those less than 40 years of age, confidence intervals overlapped. • Based the findings of 1, good-quality systematic review, there was moderate-strength evidence that maternal exposure to beta interferons was associated with lower birth weight babies with shorter mean birth length and preterm birth, but not spontaneous abortion, cesarean delivery, or low birth weight • In utero exposure to fingolimod may result in increased risk for poor fetal outcomes • A post hoc subgroup analysis of a head-to-head trial of interferon beta-1a products (Avonex® and Rebif®) found that African-American patients experienced more exacerbations and were less likely to be exacerbation-free compared with white patients over the course of the study • There was some evidence that response to beta interferons and glatiramer differs in men and women, but there was no evidence that this difference favors 1 product over another

Abbreviations: ALT, alanine aminotransferase; EDSS, Expanded Disability Status Scale; IM, intramuscular; DMD; disease-modifying drug; MS, multiple sclerosis; NAb, neutralizing antibody; PRMS, progressive relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; SC, subcutaneous.

Limitations of this Report

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English. The main limitations of the included studies were:

- There were many comparisons without any direct head-to-head evidence.
- Few studies evaluated newly approved or unapproved drugs.
- Populations other than relapsing-remitting multiple sclerosis were not well represented in the included studies.

CONCLUSIONS

In drugs approved for multiple sclerosis, there is moderate evidence in patients with relapsing-remitting multiple sclerosis that alemtuzumab is associated with reduced relapse rates compared with interferon beta-1a 44µgSC, while fingolimod is associated with lower risk of relapse compared with interferon beta-1a 30µgIM, but both agents may also be associated with increased adverse events. There was low strength evidence that dimethyl fumarate is associated with increased adverse events compared with glatiramer but similar serious adverse events and

adverse event withdrawals. Relapse rates were increased with teriflunomide 7 mg, but not 14 mg, versus interferon beta-1a 44µgSC but treatment with teriflunomide resulted in fewer study withdrawals due to adverse events. Our network meta-analysis and currently available trial results suggest that the two included, but unapproved, drugs (ocrelizumab and daclizumab HYP) may be promising additions to current treatments for multiple sclerosis in the future. However additional comparative research is needed for these two drugs, as well as for alemtuzumab, fingolimod, dimethyl fumarate, and teriflunomide in order to draw definitive conclusions regarding benefits and harms. Limited evidence was available for populations other than relapsing-remitting MS.

Drug Use Research & Management Program
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New Drug Evaluation: ixekizumab injection, subcutaneous

Date of Review: November 2016
Generic Name: ixekizumab
PDL Class: Biologics for Autoimmune Diseases

End Date of Literature Search: June 2016
Brand Name (Manufacturer): Taltz™ (Eli Lilly)
AMCP Dossier Received: yes

Research Questions:

- How does the efficacy of ixekizumab compare with other systemic or biologic therapies for the treatment of moderate to severe plaque psoriasis?
- How does the safety of ixekizumab compare with other systemic or biologic therapies for the treatment of moderate to severe plaque psoriasis?
- Are there any specific subgroups based on demographics in which ixekizumab is more efficacious or less harmful than other systemic or biologic therapies for the treatment of moderate to severe plaque psoriasis?

Conclusions:

- Three phase 3 randomized, controlled clinical trials provide moderate-quality evidence ixekizumab (IXE) 80 mg every 2 weeks for 12 weeks is superior to placebo for two co-primary efficacy endpoints assessing treatment of moderate-to-severe plaque psoriasis: the percentage of subjects who achieve a 75% reduction in Psoriasis Areas and Severity Index (PASI-75) (number needed-to-treat [NNT] of 2 vs. placebo) and the percentage of subjects achieving a 0 or 1 on the static Physician's Global Assessment (sPGA) (NNT 2 vs. placebo) at week 12. Subgroup analyses provide supportive low-quality evidence that IXE may be superior to etanercept for PASI-75 and sPGA 0 or 1 at 12 weeks (NNT 2-3 vs. etanercept for both endpoints).
- Two 60-week trials provide low-quality evidence that IXE 80 mg every 4 weeks is superior to placebo in maintaining response (sPGA 0 or 1 at Week 60) in patients who previously responded to IXE in the initial 12-week studies (NNT 2).
- Potential risks associated with immunomodulating monoclonal antibodies include infection, neutropenia, cardiovascular and cerebrovascular events, malignancies, autoimmune disorders, and administration and immune reactions. During the entire 60-week treatment period, subjects treated with IXE had greater rates of infection (38% vs. 23%), serious infections (0.7% vs. 0.4%), neutropenia (11% vs. 3%), adverse events (AEs) (67% vs. 48%), and serious AEs (3% vs. 2%) than subjects treated with placebo. During the induction period, neutropenia Grade 3 or higher occurred at similar rates (0.2% IXE vs. 0.1% placebo).
- About 22% of IXE subjects developed antibodies for which about 10% of these cases were neutralizing antibodies that are associated with loss of efficacy long-term. Due to assay limitations, the incidence of neutralizing antibodies could be underestimated and the long-term efficacy of IXE is unclear.
- Patients are advised to monitor for infection and inflammatory bowel disease (IBD), be evaluated for tuberculosis and immunization needs, and avoid live vaccines. Because the clinical trials are of short duration compared with the chronic nature of psoriasis, the full extent of adverse effects remains undetermined. In addition, subjects with neurologic or psychological disorders (e.g., depression) were excluded from these trials. Non-white subjects were also significantly underrepresented in these trials. Therefore, limited data concerning the effectiveness of IXE in these subpopulations are available.

Recommendations:

- Incorporate ixekizumab into current prior authorization criteria (see **Appendix 2**). No other changes to criteria recommended.
- Evaluate comparative drug costs in the executive session to determine PDL status for ixekizumab.

Background:

IXE is the second interleukin-17A (IL-17A) inhibitor that has been approved for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy; the other IL-17A agent is secukinumab. Other approved biologic treatments include the tumor necrosis factor (TNF) blockers adalimumab, etanercept, infliximab and the IL-12 and IL-23 inhibitor ustekinumab. Approved conventional systemic agents include acitretin, methotrexate, cyclosporine, and apremilast. Non-systemic therapies include topical treatments and phototherapy (PUVA or UVB).[1,2]

In the U.S., about 80% of the estimated 7.5 million people with psoriasis have plaque psoriasis. Plaque psoriasis is characterized by disfiguring, scaling, erythematous plaques that are often pruritic and painful.[3] About 20% of patients with plaque psoriasis have moderate to severe disease involving more than 5% of the body surface area (BSA) or affecting vulnerable areas such as the hands, feet, face, scalp, intertriginous areas, or genitals.[3] Psoriasis may also result in functional, psychological, and social morbidity that significantly impacts quality of life (QOL) to an extent comparable to patients with type 2 diabetes, myocardial infarction, and cancer.[3, 4 ,5] Increased risks for cardiovascular disease, metabolic syndrome, and other autoimmune disorders also are associated with psoriasis.[3,6]

Treatment for moderate-to-severe psoriasis may include a combination of topical and phototherapy or a combination of topical and conventional or biologic systemic therapy.[6] United States, Canadian, and German guidelines have not been updated since the introduction of IL-17A inhibitors; however, the UK has published Technology Appraisal Guidance for secukinumab, and the US, Canadian, and German guidelines address the use of biologic agents as a class.[4,6,7,8] Treatment decisions should be based on the efficacy and safety profile of the therapy, previous therapies used by the patient, the patient's preference, the duration and severity of the disease, comorbidities and medical risk factors, and QOL. [8,9,10]

The Oregon Health Plan (OHP) Prioritization List of Health Services covers biologics for severe plaque psoriasis after documented failure of first-line agents (i.e., topical agents, phototherapy, and methotrexate) and a second-line agent (other non-biologic systemic agents and oral retinoids).[11] German guidelines, which were updated in 2015 and are evidence- and consensus-based, recommend a biologic (i.e., adalimumab, etanercept, infliximab, and ustekinumab) for long-term treatment if phototherapy and conventional systemic agents have failed.[4] The NICE recommend phototherapy (second-line) combined with conventional systemic therapy (third-line therapy) in moderate or severe psoriasis when topical therapy is insufficient; for example, when there is greater than 10% BSA involvement, the psoriasis is at least "moderate" on the PGA, and when topical therapy has shown to be ineffective.[12,13]

In practice, severity of psoriatic disease is broadly defined and rather subjective. Clinicians may use the following to assess severity: (1) PGA, for which both the physician and patient both provide his or her perspective on the severity using the descriptors such as clear, nearly clear, mild, moderate, and severe; (2) BSA affected, with moderate disease for 5 to 10% involvement and severe disease with more than 10% involvement; (3) plaque thickness; (4) disease location, including the presence of psoriasis in high impact or vulnerable areas; (5) the presence of systemic upset (e.g., fever, malaise); (6) the impact on functional, social, and psychological well-being.[3,12,14] The OHP defines severe inflammatory skin disease as functional impairment (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) AND either ≥10% BSA involvement; hand, foot or mucous membrane involvement; or both.[11]

In clinical trials, moderate or severe psoriasis is commonly distinguished from mild disease based on scores from one or more clinical metrics, such as the PASI, the PGA, percentage BSA affected, and the DLQI.[6] PASI, which is considered the gold standard for assessing severity of disease, measures overall severity and coverage by assessing BSA, erythema, induration, and scaling. Researchers primarily use a 75% reduction in PASI to document effectiveness of experimental therapies in patients with extensive disease. Some consider PASI a more sensitive instrument in patients with a BSA involvement of at least 10%.[3,15]

The PGA is the second most commonly used tool; however, a variety of PGA instruments exist, with no consensus on the number of points on the scale, scale descriptors, and definitions.[3] The analysis of IXE used the sPGA, which investigators used to evaluate overall lesions for induration, erythema, and scaling on a five-point system, where 0, 1, 2, 3, 4, and 5 indicate clear, mild, minimal, moderate, severe, and very severe, respectively.[16] A static scale evaluates the subject's disease state at the time of the assessment, without comparison to baseline or any other previous disease states.[3]

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

Clinical Efficacy:
The FDA approved IXE based on three phase 3, multicenter, double-blind, randomized-controlled trials: UNCOVER-1 (RHAZ), UNCOVER-2 (RHBA), and UNCOVER-3 (RHBC). All three studies assessed the superiority of IXE over PLA over a 12-week period. UNCOVER-2 and UNCOVER-3 also assessed the superiority of IXE over etanercept, and UNCOVER-1 and UNCOVER-2 included a maintenance-of-response period of up to 60 weeks. The studies enrolled 3866 adult subjects with plaque psoriasis with at least 10% BSA involvement, a score of ≥3 on sPGA, and a score of ≥12 on PASI. All three trials randomized subjects to receive placebo or to receive either IXE 80 mg every 2 weeks or 80 mg every 4 weeks for Weeks 2 through 10 after an initial dose of 160 mg at Week 0. The UNCOVER-2 and UNCOVER-3 trials also included an active control arm that received etanercept 50 mg twice weekly Weeks 0 through 11.[2,16] Subjects were well-balanced for baseline characteristics within studies and, for the most part, between studies. Baseline characteristics for the three studies pooled were as follows: mean age (45.5 years), North American (51.3%), ethnicity (92.6% white), duration of psoriasis symptoms (18.8 years), mean PASI score (20.2), sex (67.8% male), sPGA >3 (49.7%), mean DLQI score (12.5).[2,16]

The co-primary efficacy endpoints for all 3 trials were the proportion of subjects who achieved a sPGA score of 0 (clear) or 1 (minimal) with a ≥2-point improvement at Week 12 and a PASI-75 at week 12. Key secondary endpoints included the proportion of subjects achieving (1) a sPGA score of 0 at Week 12; (2) a PASI-100 at week 12; and (3) a DLQI of 0 or 1 at Week 12. A statistically significant greater proportion of subjects who received IXE achieved co-primary endpoints versus placebo (see Comparative Evidence Table for details).[2,16,17]

To assess maintenance of response in the UNCOVER-1 and UNCOVER-2 trials, subjects who had originally received IXE and were responders (achieved an sPGA score of 0 or 1 at Week 12) were re-randomized to placebo or to either IXE 80 mg every 4 weeks (approved dosage regimen) or 80 mg every 12 weeks for Weeks 16 through 60, following a 160 mg dose at Week 12. For the approved IXE dosage compared with placebo, a statistically significant greater proportion of subjects randomized to IXE maintained a sPGA 0 or 1 for 60 weeks versus subjects randomized to placebo (See Comparative Evidence Table for details).

The clinical trials for IXE had the following limitations: There was a minor difference between the approved dosage regimen and the tested regimen, since the approve regimen dose does not include a 160 mg dosage in the transition from the every 2 weeks to the every 4 week regimen at Week 12. Although two clinical

trials included a maintenance phase, 60 weeks is still a relatively short period of time for a chronic illness and response to IXE could decline with longer-term use. Patients with a history of suicide attempt, uncontrolled neuropsychiatric disease, or frequent active suicidal ideation were excluded from the trials; therefore, the effectiveness of IXE in this subpopulation is unknown. Also, most of the subjects included in the studies were white; therefore, the effectiveness in non-white subjects is unclear.

Clinical Safety: [1]

Adverse reactions in general

During the 12-week induction period, adverse events (AEs) occurred in 58% of the IXE group and 47% of the placebo group. Both the IXE group and the placebo group had serious adverse event (SAE) rates of 2%. However, in the two clinical trials that included etanercept, the etanercept group had a lower SAE rate (0.7%). Adverse reactions that occurred in the IXE group at rates 1% or higher compared to placebo included: injection site reactions (17% vs. 3%), which were predominantly mild to moderate; upper respiratory tract infections (14% vs. 13%), nausea (2% vs. 1%), and tinea infections (2% vs. <1%). During the 48-week maintenance period of two clinical trials, AEs occurred in 80% of IXE-treated subjects and 58% of placebo-treated subjects. SAEs occurred in 4% of IXE-treated subjects and no placebo-treated subjects. During the entire 60-week treatment period, 67% of IXE-treated subjects and 48% of placebo-treated subjects experienced AEs; 3% of IXE-treated subjects and 2% of subjects on placebo had SAEs.

Infection

During the 12-week induction period (n=1167 IXE and n=791 placebo), the IXE group had a higher infection rate than the placebo group (27% vs. 23%), primarily including upper respiratory tract infections (14% vs. 13%). The IXE group also had a higher rate of infections than the group that received etanercept (18%) in the 2 trials that included an etanercept arm. During the 48-week maintenance period of 2 clinical trials, infections occurred in 57% of IXE-treated subjects and 32% of placebo subjects. Serious infections occurred in 0.9% of IXE-treated subjects but none occurred in placebo-treated subjects. During the entire 60-week treatment period, infections were reported in 38% of IXE-treated subjects and 23% of placebo-treated subjects. Serious infections occurred in 0.7% of IXE-treated subjects and in 0.4% placebo-treated subjects. Consequently, patients should be advised to monitor for signs and symptoms of infection, be evaluated for tuberculosis and immunization needs, and avoid live vaccines.

Neutropenia and thrombocytopenia

During the 12-week induction period, neutropenia (≥Grade 3) occurred in 0.2% of the IXE group and 0.1% of the placebo group. Most cases of neutropenia were Grade 2 or 1 (9% IXE vs. 3.3% for placebo). Neutropenia was not associated with a greater rate of infection in the 12-week induction period. During the entire 60-week treatment period, neutropenia occurred in 11% of subjects treated with IXE and 3% of placebo-treated subjects.

Autoimmune disorders

During the induction period, the IXE group had a greater incidence of Crohn's disease (0.1%) and ulcerative colitis (0.2%), including exacerbations, than placebo subjects (0%). Therefore, patients should be monitored for inflammatory bowel disease (IBD) and exacerbations.

Immune reactions

During all clinical trials, the IXE group experienced serious hypersensitivity reactions, including angioedema and urticaria (each ≤0.1%), so the drug should be permanently discontinued if serious hypersensitivity occurs. By week 12, about 9% IXE-treated subjects developed antibodies to IXE. During the entire 60-week treatment period, about 22% of subjects treated with IXE developed antibodies. About 10% of these subjects had neutralizing antibodies, which are associated with loss of efficacy. Due to assay limitations, the incidence of neutralizing antibodies could be underestimated.

Pharmacology and Pharmacokinetic Properties:

Parameter	
Mechanism of Action	Ixekizumab, a human IgG4 monoclonal antibody, inhibits the release of pro-inflammatory cytokines and chemokines by selectively binding to IL-17A, thereby inhibiting IL-17A's interaction with the IL-17 receptor. Psoriatic plaques contain elevated levels of IL-17A, which is a naturally occurring cytokine involved in normal inflammatory and immune responses.
Absorption	Bioavailability ranges from 60% to 81% following subcutaneous injection
Distribution and Protein Binding	Volume of distribution at steady-state was 7.11 L
Metabolism	Not characterized
Half-Life	13 days
Elimination	Not characterized

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Symptom control (Percent who achieve PASI 75 or sPGA ≤1)
2) Quality of life (Percent who achieve DLQI ≤1)
3) Serious adverse events
4) Discontinuation due to adverse event(s)

Co-primary Study Endpoints:

1) Percent who achieve PASI-75 at Week 12
2) Percent who achieve sPGA 0 or 1 at Week 12, with at least a 2-point improvement from baseline

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. UNCOVER-1 (RHAZ) FDA Med Review[2] Clinicaltrials.gov[18] Gordon 2016[17] Dec 2011 to June 2014 105 sites Phase 3, DB, PC, RT	Induction period 1. IXE Q4 2. IXE Q2 3. PLA Duration: 12 wks Maintenance period 1. IXE Q2→Q4 2. IXE Q2→PLA Duration: 48 wks	Demographics: IXEQ4, IXEQ2, PLA • Age (yr): 46, 45, 46 • Male (%): 67, 67, 70 • White (%): 92, 93, 93 • Psoriasis duration (yr): not available • PASI: 20, 20, 20 • BSA involved (%): 27, 28, 27 • sPGA ≥4 (%): 54, 47, 53 • DLQI: 13, 13, 13 • Previous biologic (%): 39, 40, 42 Key Inclusion Criteria: • Aged ≥18 years • Chronic psoriasis vulgaris for ≥6 months • Candidates for phototherapy and/or systemic therapy • ≥10% BSA involvement • sPGA score ≥3 • PASI score ≥12 Key Exclusion Criteria: • Other forms of psoriasis • Active vasculitis or uveitis • Current/history of lymphoproliferative disease • Mental disability or significant mental illness • Serious disorder or illness other than plaque psoriasis	Induction (12 wks) ITT: 1. 432 2. 433 3. 431 Attrition: 1. 24 2. 18 3. 24 Maintnce (48 wks) 1. 119 2. 117	Primary Endpoint: %PASI 75 at wk 12: 1. IXE Q4: 82.6% p<0.001 vs PLA 2. IXE Q2: 89.1% p<0.001 vs PLA 3. PLA: 3.9% %sPGA 0 or 1 at wk 12: 1. IXE Q4: 76.4% p<0.001 vs PLA 2. IXE Q2: 81.8% p<0.001 vs PLA 3. PLA: 3.2% Secondary Endpoint: % responders maintaining an sPGA 0 or 1 at wk 60: (data are for the FDA-approved dose) 1. IXE Q2→Q4: 75% 2. IXEQ2→PLA: 8%	79/2 85/2 73/2 79/2 67/2	*Induction period pooled safety analysis of UNCOVER-1, -2, -3 (n=1296, 1221, 1341, respectively))* TEAE, all: 1. IXE Q4: 58.8% 2. IXE Q2: 58.4% 3. PLA: 46.8% TEAE, severe: 1. IXE Q4: 3.5% 2. IXE Q2: 3.1% 3. PLA: 3.5% TEAE, moderate: 1. IXE Q4: 23.1% 2. IXE Q2: 21.9% 3. PLA: 18% TEAE, related to Drug: 1. IXE Q4: 24.5% 2. IXE Q2: 29.7% 3. PLA: 13% SAE: 1. IX EQ4: 2.2% 2. IXE Q2: 1.7% 3. PLA: 1.5% D/C due to AE: 1. IXE Q4: 2.1% 2. IXE Q2: 2.1% 3. PLA: 1.1% Neutropenia: 1. IXE Q4: 4.5% 2. IXE Q2: 4.9% 3. PLA: 1.4% Allergic reactions/ hypersensitivity:	NA NA NA NA NA NA NA NA NA NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Although similar across baseline characteristics and allocation was performed by computer-generated random sequence interactive voice response system, the method of allocation concealment lacked sufficient detail. Performance Bias: Low. Injections for both investigational drug and placebo using same regimen. Induction and maintenance period double blind. Detection Bias: Low Attrition Bias: Low. Attrition was low. ITT analysis used. Missing values imputed as non-responses. Reporting Bias: Unclear. Study protocol available. Sponsored by Eli Lilly and designed by the scientific steering committee and Eli Lilly personnel. Site investigators collected data, Eli Lilly personnel performed data analyses. All coauthors participated in manuscript development with a medical writer paid by Eli Lilly. **Applicability**: Patient: 51.9% of subjects North American. However, broad exclusion criteria of those with comorbidities used. Subjects mostly white, so performance in non-white population unclear. Excluded subjects with mental disability or significant mental illness. However, patients who have psoriasis are known to suffer disproportionately from depression and suicidality. Also, there is concern of increased risk of mental illness for patients taking IL-17A inhibitors. Intervention: Limited to 12 weeks only. Comparator: No active comparators Outcomes: Assessed outcomes appropriate for psoriasis studies. Setting: Most appropriate for care to come from dermatologist experienced in psoriasis treatment with biologics.

2. UNCOVER-2 (RHBA) Griffiths 2015[16] FDA Med Review[2] May 2012 to Dec 2013 121 sites Phase 3 DB, PC, AC, RT	Induction period 1. IXE Q4 2. IXE Q2 3. PLA 4. ETN *US Subgroup:* 1. IXE Q4 2. IXE Q2 3. PLA 4. USE Duration: 12 wks Maintenance period 1. IXE Q2→Q4 2. IXE Q2→PLA Duration: 48 wks	Demographics: IXE Q4, IXE Q2, PLA, ETN, respectively • Age (yr): 45, 45, 45, 45 • Male (%): 70, 63, 71, 66 • White (%): 92, 94, 94, 89 • Psoriasis duration (yr): 19, 18, 19, 19 • PASI: 20, 19, 19, 21 • BSA involved (%): 27, 25, 27, 25 • sPGA ≥4 (%): 52, 49, 49, 48 • DLQI: 12, 12, 13, 13 • Previous biologic (%): 25, 24, 26, 21 Key Inclusion Criteria: Same as UNCOVER-1 Key Exclusion Criteria: Same as UNCOVER-1 plus the following: • Prior use of etanercept • Women of childbearing potential or not on contraceptive • Presence of significant uncontrolled cerebro- or cardiovascular, respiratory, hepatic, renal, GI, endocrine, hematologic, neurologic or neuropsychiatric disorders; infection; or abnormal lab values at screening that, in investigator's opinion,	Induction (12 wks) ITT 1. 347 2. 351 3. 168 4. 358 *US Subgroup*: 1. 105 2. 104 3. 49 4. 111 ITT Attrition: 1. 19 2. 9 3. 10 4. 25 Maintnce (48 wks) 1. 62 2. 86	Co-primary endpoints:* %PASI 75 at wk 12: 1. IXE Q4: 77.5% Difference vs. PLA: 75% (97.5% CI, 69.5 to 80.8%; p<0.0001) 2. IXE Q2: 89.7% Difference vs PLA: 87.4% (97.5% CI, 82.9 to 91.8%; p<0.0001) 3. PLA: 2.4% *US subgroup %PASI-75 at wk 12 vs USE:* 1. IXE Q4: 67.6% p<0.001 vs PLA 2. IXE Q2: 85.6% P<0.001 vs PLA 3. USE: 32.4% % sPGA 0 or 1 at wk 12: 1. IXE Q4: 72.9% Difference vs. PLA: 70.5% (97.5% CI, 64.6 to 76.5%; p<0.0001) 2. IXE Q2: 83.2% Difference from PLA: 80.8% (97.5% CI, 75.6 to 86%; P<0.001) 3. PLA: 2.4% *US subgroup % sPGA 0 or 1 at wk 12 vs USE*: 1. IXE Q4: 61% p<0.001 vs PLA 2. IXE Q2: 70.2% p<0.001 vs PLA	75/2 87/1 68/2 86/1 71/2 81/1 39/3 49/2	1. IXE Q4: 4% 2. IXE Q2: 3.5% 3. PLA: 2.1% MACE: 1. IXE Q4: 0.8% 2. IXE Q2: 0% 3. PLA: 0.6%	NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Similar across baseline characteristics. Allocation was performed using computer-generated random sequence interactive voice response system. Patients, investigators, and study personnel masked to treatment allocation. Double-dummy design used in which PLA's appearance was same as IXE and EUE+USE Performance Bias: Low. Injections for both investigational drug and placebo using same regimen. Induction and maintenance period double blind. Detection Bias: Low Attrition Bias: Low. Attrition was low. ITT analysis used. Missing values imputed as non-responses. Reporting Bias: Unclear. Study protocol available. Designed jointly by consultants and representatives of Eli Lilly. Data collected by investigators, gathered by Parexel International, and analyzed by Eli Lilly. All coauthors participated in manuscript development with a medical writer paid by Eli Lilly **Applicability**: Patient: Patient population likely to reflect those in OHP. Severity of disease consistent with moderate-to-severe psoriasis population. 41/121 sites in the US. However, broad exclusion criteria of those with comorbidities used. Subjects predominantly white, so performance in non-white population unclear. Excluded subjects with mental disability or significant mental illness. However, patients who have psoriasis are known to suffer disproportionately from depression and suicidality. Also, there is concern of increased risk of mental illness for patients taking IL-17A inhibitors. Intervention: Topical steroids allowed. Comparator: Comparators were placebo and etanercept. US subjects received US-sourced etanercept, while other subjects received European-sourced etanercept, which is a

		pose an unacceptable risk to the patient if or of interfering with data interpretation.		3. USE: 21.6% <u>Key secondary endpoints:</u> <u>% PASI-100 at wk 12</u>: 1. IXE Q4: 30.8% Difference vs. PLA: 30.2% (97.5% CI, 24.5 to 36%; p<0.001) 2. IXE Q2: 40.5 Difference vs PLA: 39.9% (97.5% CI, 33.8 to 45.9%; P<0.0001) 3. PLA: 0.6% <u>% DLQI 0 or 1 at wk 12:</u> 1. IXE Q4: 59.9% Difference vs PLA: 54% (97.5% CI, 46.8 to 61.2%; P<0.0001) 2. IXE Q2: 64.1% Difference vs PLA: 58.2% (97.5% CI, 51.1 to 65.2%; P<0.0001) 3. PLA: 6% <u>% responders at wk 12 maintaining an sPGA 0 or 1 at wk 60:</u> (data are for the FDA-approved dose) 1. IXEQ2→Q4: 76% 2. IXEQ2→PLA: 7%	30/4 40/3 54/2 58/2 69/2			different formulation. <u>Outcomes</u>: Assessed outcomes appropriate for psoriasis studies <u>Setting</u>: Most appropriate for care to come from dermatologist experienced in psoriasis treatment with biologics

3. UNCOVER-3 (RHBC) Griffiths 2015[16] FDA Med Review[2] Aug 2012 to Feb 2014 119 sites Phase 3 DB, PC, AC, RT	1. IXE Q4 2. IXE Q2 3. PLA 4. ETN *US Subgroup*: 1. IXE Q4 2. IXE Q2 3. PLA 4. USE	Demographics: IXE Q4, IXE Q2, PLA, ETN, respectively • Age (yr): 46, 46, 46, 46 • Male (%): 67, 66, 71, 70 • White (%): 93, 94, 91, 92 • Psoriasis duration (yr): 18, 18, 18, 18 • PASI: 21, 21, 21, 21 • BSA involved (%): 28, 28, 29, 28 • sPGA ≥4 (%): 46, 46, 52, 50 • DLQI: 12, 12, 13, 12 • Previous biologic (%): 15, 15, 17, 16 Key Inclusion Criteria: Same as UNCOVER-2 Key Exclusion Criteria: Same as UNCOVER-2	ITT 1. 386 2. 385 3. 193 4. 382 *US Subgroup:* 1. 147 2. 141 3. 69 4. 146 ITT Attrition 1. 26 2. 22 3. 10 4. 13	Co-primary endpoints:* %PASI 75 at wk 12: 1. IXE Q4: 84.2% Difference vs PLA: 76.9% (97.5% CI, 71 to 82.8%; P<0.0001) 2. IXE Q2: 87.3% Difference vs PLA: 80% (97.5% CI, 74.4 to 85.7%; P<0.0001) 3. PLA: 7.3% *US subgroup %PASI 75 at wk 12 vs USE:* 1. IXE Q4: 80.3% p<0.001 vs PLA 2. IXE Q2: 87.9% p<0.001 vs PLA 3. USE: 46.6% % sPGA 0 or 1 at wk 12 vs PLA: 1. IXE Q4: 75.4% Difference vs PLA: 68.7% (97.5% CI, 62.3 to 75%; P<0.0001) 2. IXE Q2: 80.5% Difference vs PLA: 73.8% (97.5% CI, 67.7 to 79.9%; P<0.0001) 3. PLA: 6.7% *US subgroup % sPGA 0 or 1 at wk 12 vs USE:* 1. IXE Q4: 65.3% p<0.001 vs PLA 2. IXE Q2: 74.5%	77/2 80/2 34/3 41/3 69/2 74/2 34/3 43/3			**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Same as UNCOVER-2 Performance Bias: Low. Same as UNCOVER-2 Detection Bias: Low. Same as UNCOVER-2 Attrition Bias: Low. Same as UNCOVER-2 Reporting Bias: Unclear. Same as UNCOVER-2 **Applicability**: Patient: Same as UNCOVER-2, except 45/119 sites in the US Intervention: Same as UNCOVER-2 Comparator: Same as UNCOVER-2 Outcomes: Same as UNCOVER-2 Setting: Same as UNCOVER-2

				p<0.001 vs PLA 3. USE: 31.5% <u>Key secondary endpoints:</u> <u>% PASI-100 at wk 12</u>: 1. IXE Q4: 35% Difference vs PLA: 35% (97.5% CI, 29.5 to 40.4%; p<0.0001) 2. IXE Q2: 37.7% Difference vs PLA: 37.7% (97.5% CI, 32.1 to 43.2%; p<0.0001) 3. PLA: 0% <u>% DLQI 0 or 1 at wk 12:</u> 1. IXE Q4: 63.7% Difference vs PLA: 56% (97.5% CI, 49 to 62.9%; P<0.0001) 2. IXE Q2: 64.7% Difference vs PLA: 56.9% (97.5% CI, 49.9 to 63.9%; P<0.0001) 3. PLA: 7.8%	35/3 38/3 56/2 57/2			

<u>Abbreviations</u>: AC = active comparator; AE = Adverse event; ARR = absolute risk reduction; BSA = body surface area; CI = confidence interval; DLQI = dermatology life quality index; ETN = European Union-sourced etanercept and US-approved etanercept; GI = gastrointestinal; IBD = inflammatory bowel disease; ITT = intention to treat; IXE = ixekizumab; IXE Q2 = ixekizumab subcutaneous 160 mg starting dose followed by 80 mg dose every 2 weeks; IXE Q4 = ixekizumab subcutaneous 160 mg starting dose followed by 80 mg dose every 4 weeks; MACE = major adverse cardiovascular events; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PASI = psoriasis area and severity index on a scale of 0 to 72 with higher scores indicating more severe disease; PASI 75 = a reduction of ≥75% in baseline PASI score; PC = placebo-controlled; PLA = placebo; PP = per protocol; SAE = serious adverse events; sPGA = static physician global assessment 0=clear, 1=mild, 2=minimal, 3=moderate, 4=severe, 5=very severe disease; TEAE = treatment emergent adverse events; US =United States; USE = US-approved etanercept; wk = week
*Active comparator data reported here only for US-approved etanercept when available

References:

1. Taltz prescribing information. Eli Lilly and Company: Indianapolis, IN. March 2016
2. Food and Drug Administration Center for Drug Evaluation and Research. Application Number: 125521Orig1s000 Medical Review. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed May 8, 2016.
3. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J. Am. Acad. Dermatol.* 2008;58(5):826-850. doi:10.1016/j.jaad.2008.02.039.
4. Nast A, Jacobs A, Rosumeck S, Werner RN. Methods Report: European S3-Guidelines on the systemic treatment of psoriasis vulgaris--update 2015--EDF in cooperation with EADV and IPC. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2015;29(12):e1-22. doi:10.1111/jdv.13353.
5. Rapp SR, Feldman SR, Exum M, Fleischer AB, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *Journal of the American Academy of Dermatology*. 1999;41(3):401-407. doi:10.1016/S0190-9622(99)70112-X.
6. Hsu S, Papp KA, Lebwohl MG, et al. Consensus guidelines for the management of plaque psoriasis. *Archives of dermatology*. 2012;148(1):95-102. doi:10.1001/archdermatol.2011.1410.
7. National Institute for Health and Care Excellence. Secukinumab for treating moderate to severe plaque psoriasis: Technology appraisal guidance. nice.org.uk/guidance/ta350. Accessed July 10, 2016.
8. American Academy of Dermatology and AAD Association. Position Statement on Treatment of Psoriatic Patients. https://www.aad.org/education/clinical-guidelines. Accessed April 22, 2015.
9. Barker J, Hoffmann M, Wozel G, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). *Br. J. Dermatol.* 2011;165(5):1109-1117. doi:10.1111/j.1365-2133.2011.10615.x.
10. Saurat J, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *The British journal of dermatology*. 2008;158(3):558-566. doi:10.1111/j.1365-2133.2007.08315.x.
11. Oregon Health Authority Health Evidence Review Commission. 7-1-2016 prioritization list of health services. http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx. Accessed June 4, 2014.
12. Samarasekera E, Sawyer L, Parnham J, Smith CH. Assessment and management of psoriasis: summary of NICE guidance. *BMJ (Clinical research ed.)*. 2012;345:e6712.
13. Samarasekera EJ, Smith CH. Psoriasis: guidance on assessment and referral. *Clinical medicine (London, England)*. 2014;14(2):178-182. doi:10.7861/clinmedicine.14-2-178.
14. Kupetsky EA, Keller M. Psoriasis vulgaris: an evidence-based guide for primary care. *J Am Board Fam Med*. 2013;26(6):787-801. doi:10.3122/jabfm.2013.06.130055.
15. Langley RGB, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. *J Dermatolog Treat*. 2015;26(1):23-31. doi:10.3109/09546634.2013.865009.
16. Griffiths CEM, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): Results from two phase 3 randomised trials. *The Lancet*. 2015;386(9993):541-551. doi:10.1016/S0140-6736(15)60125-8.
17. Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis. *The New England journal of medicine*. 2016;375(4):345-356. doi:10.1056/NEJMoa1512711.
18. Clinicaltrials.gov: a service of the U.S. National Institutes of Health. A Phase 3 Study in Participants With Moderate to Severe Psoriasis (UNCOVER-1): ClinicalTrials.gov Identifier: NCT01474512. https://clinicaltrials.gov/ct2/show/NCT01474512?term=RHAZ&rank=1. Accessed May 8, 2016.

Appendix 1: Highlights of Prescribing Information

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

TALTZ (ixekizumab) injection, for subcutaneous use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------
TALTZ™ is a humanized interleukin-17A antagonist indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. (1)

----------DOSAGE AND ADMINISTRATION----------
- Administer by subcutaneous injection. (2.1)
- Recommended dose is 160 mg (two 80 mg injections) at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Autoinjector
- Injection: 80 mg/mL solution in a single-dose prefilled autoinjector. (3)

Prefilled Syringe
- Injection: 80 mg/mL solution in a single-dose prefilled syringe. (3)

----------CONTRAINDICATIONS----------
Serious hypersensitivity reaction to ixekizumab or to any of the excipients. (4)

----------WARNINGS AND PRECAUTIONS----------
- Infections: Serious infections have occurred. Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a serious infection develops, discontinue TALTZ until the infection resolves. (5.1)
- Tuberculosis (TB): Evaluate for TB prior to initiating treatment. (5.2)
- Hypersensitivity: If a serious allergic reaction occurs, discontinue TALTZ immediately and initiate appropriate therapy. (5.3)
- Inflammatory Bowel Disease: Crohn's disease and ulcerative colitis, including exacerbations, occurred during clinical trials. Patients who are treated with TALTZ and have inflammatory bowel disease should be monitored closely. (5.4)

----------ADVERSE REACTIONS----------
Most common (≥1%) adverse reactions associated with TALTZ treatment are injection site reactions, upper respiratory tract infections, nausea, and tinea infections. (6.1)

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

---------- DRUG INTERACTIONS ----------
Live Vaccines: Live vaccines should not be given with TALTZ. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 03/2016

Biologics for Autoimmune Diseases

Goal(s):

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

Length of Authorization:

Up to 12 months

Requires PA:

- All biologics except for biologics approved by the FDA for the following indications:
  - Non-Hodgkin Lymphoma (ICD-10 C85.8x, C85.9x)
  - Chronic Lymphocytic Leukemia (ICD-10 C91.10, C91.11, C91.12)
  - Juvenile Idiopathic Arthritis (ICD-10 M08)
  - Multiple Sclerosis (ICD-10 G35)
  - Non-infectious posterior uveitis (ICD-10 H44.13)

Covered Alternatives:

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

Table 1. Approved Indications for Biologic Immunosuppressants.

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Hidradenitis Suppurativa	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Uveitis (non-infectious)	Other
Abatacept **(ORENCIA)**				≥6 yo			≥18 yo			
Adalimumab **(HUMIRA)**	≥18 yo	≥6 yo	≥18 yo	≥2 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	
Alefacept **(AMEVIVE)**					≥18 yo					
Anakinra **(KINERET)**							≥18 yo			NOMID
Apremilast **(OTEZLA)**					≥18 yo	≥18 yo				
Canakinumab **(ILARIS)**				≥2 yo						FCAS ≥4 yo MWS ≥4 yo
Certolizumab **(CIMZIA)**	≥18 yo	≥18 yo				≥18 yo	≥18 yo			
Etanercept **(ENBREL)**	≥18 yo			≥2 yo	≥18 yo	≥18 yo	≥18 yo			
Golimumab **(SIMPONI)**	≥18 yo					≥18 yo	≥18 yo	≥18 yo		
Infliximab **(REMICADE)**	≥18 yo	≥6 yo			≥18 yo	≥18 yo	≥18 yo	≥6 yo		
Ixekizumab **(TALTZ)**					≥18 yo					
Natalizumab **(TYSABRI)**		≥18 yo								MS ≥18 yo
Rituximab **(RITUXAN)**							≥18 yo			CLL ≥18 yo NHL ≥18 yo GPA ≥18 yo
Secukinumab **(COSENTYX)**	≥18 yo				≥18 yo	≥18 yo				
Tocilizumab **(ACTEMRA)**				≥2 yo			≥18 yo			
Tofacitinib **(XELJANZ)**							≥18 yo			
Ustekinumab **(STELARA)**					≥18 yo	≥18 yo				
Vedolizumab **(ENTYVIO)**		≥18 yo						≥18 yo		

Abbreviations: CLL = chronic lymphocytic leukemia; FCAS = familial cold autoinflammatory syndrome; GPA = granulomatosis with polyangiitis (Wegener's granulomatosis); MS = multiple sclerosis; MWS = Muckle-Wells syndrome; NHL = non-Hodgkin's lymphoma; NOMID = neonatal onset multi-systemic inflammatory disease; yo = years old.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP? Note: Medical treatment for Hidradenitis Suppurativa (ICD-10 L73.2) is not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Will the prescriber change to a preferred product? <u>Message</u>: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Go to #4
4. Is the prescription for rituximab for non-Hodgkin Lymphoma (ICD-10 C85.8x; C85.9x) or Chronic Lymphocytic Leukemia (ICD-10 C91.10; C91.11; C91.12)?	**Yes:** Approve for length of treatment.	**No:** Go to #5
5. Is the prescription for natalizumab, prescribed for the management of relapsing multiple sclerosis?	**Yes:** Approve for length of treatment.	**No:** Go to #6
6. Is the diagnosis juvenile idiopathic arthritis (ICD-10 M08), non-infectious posterior uveitis, or ankylosing spondylitis (ICD-10 M45) and the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for length of treatment.	**No:** Go to #7
7. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for *severe* plaque psoriasis is funded by the OHP.	**Yes:** Go to #8	**No**: Go to #10

Approval Criteria		
8. Is the plaque psoriasis severe in nature, which has resulted in functional impairment (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or more of the following: • At least 10% body surface area involvement; or • Hand, foot or mucous membrane involvement?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; not funded by the OHP.
9. Has the patient failed to respond to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); and • At least one other topical agent: calcipotriene, tazarotene, anthralin; and • Phototherapy; and • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate?	**Yes**: Document each therapy with dates: _____ Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
10. Is the diagnosis rheumatoid arthritis or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #11	**No:** Go to #14
11. Has the patient failed to respond to at least one of the following disease-modifying antirheumatic drugs (DMARD) for ≥6 months: • Methotrexate, leflunomide, or sulfasalazine or hydroxychloroquine; or • Have a documented intolerance or contraindication to DMARDs?	**Yes:** Document each therapy with dates: _____ If applicable, document intolerance or contraindication(s): _____ Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
12. Is the request for tofacitinib?	**Yes:** Go to #13	**No:** Approve for up to 12 months
13. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine or cyclosporine? Note: Tofacitinib may be used concurrently with methotrexate or other oral DMARD drugs.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for up to 12 months
14. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #15	**No:** Go to #16
15. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy?	**Yes:** Document each therapy with dates: _____ If applicable, document intolerance or contraindication(s): _____ Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
16. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *induction* of remission?	**Yes:** Approve for length of treatment	**No:** Go to #19
17. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *maintenance* of remission?	**Yes:** Go to #18	**No:** Go to #19

Approval Criteria		
18. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for maintenance of remission, in conjunction with a low-dose corticosteroid, for ≥6 months: • Azathioprine, leflunomide, or methotrexate • Have a documented intolerance or contraindication to DMARDs?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
19. Is the diagnosis a variant cryopyrin-associated periodic syndrome (Familial Cold Auto-inflammatory Syndrome, Muckle-Wells Syndrome, or chronic infantile neurologic cutaneous articular syndrome [also known as neonatal onset multi-systemic inflammatory disease]) and the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

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

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A Class Update: Non-statins for Hyperlipidemia

Date of Review: November 2016

Date of Last Review: September 2014
PSCK9 inhibitors in November 2015
Mipomersen and lomitapide in May 2016

Current Status of PDL Class: Non-statins
See **Appendix 1**.

Research Questions:

1. Is there any new comparative evidence for non-statin lipid-lowering agents in reducing cardiovascular (CV) outcomes or mortality in adult patients being treated for the primary or secondary prevention of CV disease?
2. Is there any new comparative evidence for harms of non-statin lipid-lowering agents in patients being treated for the primary or secondary prevention of CV disease?
3. Are there subpopulations of patients based on demographics (e.g., age, sex, race, and diagnoses) for which one non-statin agent is more effective or associated with more harm than other non-statin agents?

Conclusions:

- Four systematic reviews evaluated comparative evidence for ezetimibe, niacin, fibrates, or omega 3 fatty acids on all-cause mortality, cardiovascular mortality, stroke, and myocardial infarction (MI) with or without concurrent statin therapy. [1–4]
    - There is moderate quality evidence that ezetimibe combined with a statin results in a modest improvement in cardiovascular outcomes. In the IMPROVE-IT trial, the primary endpoint was a composite of death from cardiovascular disease, a major coronary event (non-fatal MI, unstable angina requiring hospitalization, coronary revascularization), or non-fatal stroke in patients that had been recently hospitalized for acute coronary syndrome.[5] At 7 years, the Kaplan-Meier event rate for the composite endpoint was 32.7% in the ezetimibe/statin group compared to 34.7% in the statin monotherapy group (absolute risk difference, 2.0 %, hazard ratio (HR), 0.936, 95% confidence interval (CI), 0.89 to 0.99, p = 0.016). [5] There were no differences noted in all- cause mortality (HR, 0.95, 95% CI, 0.91 to 1.07, p = 0.78) or cardiovascular death (HR, 1.00, 95% CI, 0.89-1.13, p=1.00) between the two groups.[5]
    - Moderate quality evidence from systematic reviews compared statin monotherapy to a statin in combination with ezetimibe, niacin, fibrates or omega 3 fatty acids and revealed inconsistent effects on CV outcomes and no significant differences in reducing all- cause mortality, death from CHD (coronary heart disease) or stroke.[1–4]
- There is insufficient data to support any role for omega 3 fatty acids to reduce all-cause mortality and CV outcomes.[4]

- Moderate quality evidence shows proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are efficacious at reducing low-density lipoprotein cholesterol (LDL-C) levels by over 50% from baseline. However, evidence is insufficient at this time to support the use of PCSK9 inhibitors to reduce adverse CV outcomes including all-cause mortality.[6–8]
- There is moderate quality evidence from short term trials that the incidence of adverse events is similar between ezetimibe combined with a statin and statin monotherapy.[9]
- Moderate quality evidence from short term trials suggests PCSK9 inhibitors are associated with increased neurocognitive adverse events compared to placebo.[8] The FDA has directed developers of PCSK9 inhibitors to monitor for neurocognitive adverse effects in ongoing clinical trials. A higher frequency of neurocognitive adverse events was observed with both evolocumab (0.9% versus 0.3% for placebo) and alirocumab (1.2% versus 0.5% for placebo).[10]
- Current guidance do not recommend combining statin therapy with fibrates, niacin, bile acid sequestrants, or omega 3 fatty acids for primary or secondary prevention of adverse CV events due to insufficient evidence that demonstrates CV risk reduction. [11–14] Ezetimibe may be used as an alternative for patients intolerant to statins or high risk patients unable to attain effective LDL-C lowering with statin monotherapy. The PCSK9 inhibitors are currently recommended for patients at high risk for cardiovascular disease (CVD) and persistently elevated LDL levels despite use of other lipid-lowering agents, including high intensity statin therapy. These recommendations are based on short term, multicenter, manufacturer-sponsored Phase 3 RCTs. [15–17] The PCSK9 inhibitors can be used as an adjunct to maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) who require additional lowering of LDL-C.

Recommendations:

- Revise prior authorization criteria for omega-3 fatty acids (see **Appendix 5**) to remove requirement of failure or contraindication to niacin therapy as condition for approval. No changes recommended to clinical prior authorization criteria for PCSK9 Inhibitors, mipomersen or lomitapide at this time.
- No changes to the PDL recommended based on updated evidence. Review comparative drug costs in the executive session.

Previous Conclusions:

- There remains insufficient evidence for improved CV outcomes for non-statin lipid lowering agents.
- For high risk patients, it may be reasonable to add a non-statin lipid-lowering agent in high-risk patients who have a less than anticipated response to statins, who are unable to tolerate a less than recommended intensity of a statin or who are completely statin intolerant.
- There is moderate quality evidence that gemfibrozil as monotherapy may reduce the risk for stroke and CV mortality.
- There is no clinical evidence of superiority of one fenofibrate agent over another.
- There is insufficient evidence comparing iscopaent ethyl (ICP) to any of the current therapies. When compared to the efficacy of current treatments such as fibrates or niacin, ICP has similar TG lowering ability but there is insufficient data to compare CV risk lowering or pancreatitis risk lowering in any of these therapies. ICP is at least as safe as fibrates or niacin and has significantly fewer treatment-associated adverse effects.
- In patients with familial hypercholesterolemia, there is insufficient evidence that directly compares efficacy and harms between PCSK9 inhibitors.
    - In patients with heterozygous familial hypercholesterolemia already on a statin and ezetimibe, there is low quality evidence from short-term data that alirocumab can improve LDL-C by a difference of -57% compared to placebo; however, there is high quality evidence from short-term data that evolocumab can improve LDL-C by a difference of -61% compared to placebo.
    - In patients with homozygous familial hypercholesterolemia already on a statin and ezetimibe, there is insufficient evidence to use alirocumab; however, there is low quality evidence from short-term data that evolocumab can improve LDL-C by a difference of -32% compared to placebo.

- In patients with non-familial hypercholesterolemia intolerant to statins, there is insufficient evidence that directly compares efficacy and harms between PCSK9 inhibitors.
    - In addition, there is insufficient evidence for use of alirocumab in this population; however, there is low quality evidence from short-term data that evolocumab can improve LDL-C by a difference of -47% compared to ezetimibe alone.
- In patients with non-familial hypercholesterolemia who cannot achieve adequate LDL-C reduction with their current lipid-lowering regimen, there is insufficient evidence that directly compares efficacy and harms between PCSK9 inhibitors.
    - However, there is high quality evidence from short-term data that use of alirocumab can result in a significantly higher proportion of patients at high risk for (CV) events to achieve an LDL-C of less than 70 mg/dL versus placebo, with as much as a -62% greater reduction in LDL-C.
    - However, there is low quality evidence of no difference in CV events between alirocumab and placebo at 52- and 78-week follow-up when alirocumab and placebo were continued long-term with concomitant statin therapy. In addition, there is moderate quality evidence of no difference in CV events between alirocumab and ezetimibe at 52-week follow-up when both treatments were continued long-term with concomitant statin therapy.
    - There is high quality evidence from short-term data that use of evolocumab can result in a significantly higher proportion of patients at high risk for CV events to achieve an LDL-C of less than 70 mg/dL versus placebo. When compared to the addition of ezetimibe, there is low quality evidence that the addition of evolocumab can also result in higher achievement rates of target LDL-C of less than 70 mg/dL.
- In a mix of all populations studied above, there is insufficient evidence to draw conclusions on the effect of evolocumab on CV outcomes.
- There is insufficient evidence to differentiate between differences in harms between PCSK9 inhibitors. It is unknown if significantly lowering LDL-C will adversely affect gastrointestinal, metabolic and neurocognitive functions.

Previous Recommendations

- Designate alirocumab and evolocumab as non-preferred. Preferred status cannot be made at this time due to limited evidence of long-term CV benefit and harms.
- Restrict use of PCSK9 Inhibitors to populations with clinical atherosclerotic disease and 1) non-familial hypercholesterolemia unable to achieve at least 50% LCL-C reduction despite high-intensity statin therapy and ezetimibe; 2) familial hypercholesterolemia; or 3) history of rhabdomyolysis or creatinine kinase levels greater than 10-times the upper limit of normal with muscle symptoms.
- Make iscopaent ethyl a non-preferred lipotropic agent and use the non-PDL prior authorization criteria due to its use as an alternative to a fibric acid derivative and niacin for hypertriglyceridemia.
- Make ezetimibe a non-preferred agent due to insufficient outcome data, and implement the non-PDL prior authorization criteria for use.
- Niacin drug products are not preferred due to questionable evidence for reduction in CV outcomes.

Background:

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines advocate for a substantial shift in strategies to assess and manage elevated cholesterol to reduce CV disease (CVD).[11] Recommendations were derived from randomized trials, meta-analyses, and observational studies that were considered high quality using National Heart, Lung and Blood Institute (NHLBI) criteria.[11] The previous Adult Treatment Panel (ATP) III guidelines focused on reducing LDL-C and non-high density lipoprotein cholesterol (non-HDL-C) to specific target levels. The updated ACC/AHA guidelines recommend adjusting the intensity of statin therapy to reduce CVD risk in patients most likely to benefit from therapy using a risk estimator.[11] According to the ACC/AHA, non-statin therapies do not provide acceptable CVD risk reduction benefits.[11] For high risk patients including those with

atherosclerotic CVD, LDL ≥ 190 mg/dl and diabetics who are statin intolerant or unable to achieve sufficient response to statins, non-statin options such as niacin, fibric acid derivatives, ezetimibe, or omega-3 fatty acids can be considered to further lower LDL-C.[11] However, the benefit of CVD risk reduction with non-statin therapy should be evaluated against the risks of adverse effects and drug-drug interactions.[11] The PCSK9 inhibitors were not part of the ACC/AHA practice guidelines since they were not yet approved in 2013.

This class update will focus on recent evidence regarding the safety and efficacy of non-statin therapy including niacin, fibric acid derivatives, bile acid sequestrants, ezetimibe, omega 3 fatty acids and PCSK9 inhibitors in management of hyperlipidemia to reduce adverse CV outcomes and mortality. **Table 1** in **Appendix 4** outlines the effects of each of these agents on specific lipoproteins and their Food and Drug Administration (FDA)-approved indications. Mipomersen and lomitapide, two agents approved for management of homozygous familial hypercholesterolemia (HoFH), were reviewed by this committee at the May 2016 meeting so they are not included in this review.

The effectiveness of niacin extended release (ER) when added to statin therapy is questionable after 2 recent RCTs did not demonstrate significant reductions in CV events in patients with established coronary artery disease and low HDL-C.[2, 3] The AIM-HIGH trial was stopped after a mean follow-up of 3 years due to lack of efficacy in reducing CV events and an increased rate of ischemic stroke in the niacin group.[20] The HPS2-THRIVE trial was designed to assess the effect of adding niacin ER in combination with laropiprant to simvastatin 40 mg with or without ezetimibe in patients with CV disease.[19] Laropiprant is a prostaglandin antagonist was used to reduce the adverse effect of flushing commonly associated with niacin therapy. After a mean 3.9 years of follow-up, niacin–laropiprant was not associated with a statistically significant reduction in the incidence of major CV events but was associated with more fatal and nonfatal serious adverse events, including worsening glucose control in patients with diabetes, gastrointestinal adverse effects, excessive rates of infection and bleeding.[19] Prescribing information for niacin was updated in April 2015 to state that the addition of niacin ER does not reduce CV morbidity or mortality in patients treated already on statin therapy.[21] In April 2016, the FDA withdrew approval for Advicor®(niacin ER and lovastatin) and Simcor® (niacin ER and simvastatin) as results from these trials showed that the risks of combination therapy outweighs the benefits.[22]

Fibric acid derivatives include gemfibrozil, fenofibric acid, and fenofibrate. In the ACCORD trial, fenofibrate was studied in combination with simvastatin in patients with diabetes mellitus to assess the impact on CV disease. After a mean follow-up of 4.7 years, no significant benefit in fatal or non-fatal CV events was noted with fenofibrate and simvastatin versus simvastatin alone.[23] According to the ACC/AHA guidelines, fenofibrate may only be considered to be used concomitantly with a low- or moderate-intensity statin if the benefits from CVD risk reduction or triglyceride-lowering (when triglycerides are >500 mg/dL) are judged to outweigh the potential risk for adverse effects.[11] The prescribing information for fenofibrate was revised to remove the indication about co-administration with a statin due to the fact that the risks outweigh the benefits of combination therapy.[24] Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis.[11]

The efficacy of ezetimibe as monotherapy has not been evaluated in comparison with statin therapy and there are no published trials that have evaluated ezetimibe in primary prevention of CVD. Although ezetimibe effectively lowers LDL-C, the long-term effects on CV morbidity and mortality are unclear. Two RCTs (ENHANCE and SEAS) failed to show a statistically significant reduction in the progression of atherosclerosis among patients with heterozygous familial hypercholesterolemia who were treated with ezetimibe/simvastatin versus simvastatin alone.[6, 7] The SEAS trial investigators reported cancer in 105/1873 (11.1%) patients in the ezetimibe/simvastatin cohort compared to 70/1873 (7.5%) of the patients in the placebo group.[27] The FDA subsequently reviewed cancer prevalence data from the SEAS, SHARP and IMPROVE-IT trials. Based on an assessment of cancer risk in a larger number of patients (n=20,167) the FDA did not find a significant correlation between cancer and ezetimibe therapy.[28] The IMPROVE-IT trial provides modest evidence for use of ezetimibe in combination with a statin for secondary prevention of CVD. In this trial, simvastatin was compared to the combination of simvastatin/ezetimibe in patients who had been

hospitalized for an acute coronary syndrome within the preceding 10 days. The primary endpoint was a composite of multiple different endpoints: CV death, nonfatal myocardial infarction, unstable angina requiring re-hospitalization, coronary revascularization, or nonfatal stroke.[5] Ezetimibe produced an incremental reduction in the primary composite endpoint, and specifically reduced nonfatal ischemic stroke, but did not reduce all-cause mortality or CV mortality.[5] The manufacturer of ezetimibe applied for an additional indication for the expanded use of ezetimibe in combination with statin therapy for reduction of CV events in patients with coronary heart disease but an FDA advisory committee voted against the expanded indication as they felt the ezetimibe/simvastatin combination provides a weak and not particularly robust effect on CV outcomes.[29]

Bile-acid sequestrants (BAS) include cholestyramine, colestipol, and colesevelam. No RCTs have evaluated combination therapy of BAS with statins and their impact on CV outcomes. When used as monotherapy, there is evidence BAS can lower LDL-C levels. The ACC/AHA guidelines recommend against the use of BAS in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia due to elevated risk for severe hypertriglyceridemia.[11] It is reasonable to use BAS with caution if baseline triglyceride levels are 250 to 299 mg/dL; however, BAS therapy should be discontinued if triglycerides exceed 400 mg/dL.[11]

Omega-3 fatty acids (i.e., Lovaza®) and icosapent are two FDA-approved legend drugs for the treatment of severe hypertriglyceridemia.[30,31] However, the effect of omega-3 fatty acids on reducing CV risk in patients with hypertriglyceridemia has not been proven.[22, 23] The ongoing REDUCE-IT trial plans to evaluate the effect of icosapent ethyl in reducing long-term CV events in hypertriglyceridemic patients maintained on statin therapy.[32]

The first PCSK9 two inhibitors evolocumab and alirocumab were approved in 2015. Bococizumab is a third agent in this class currently being studied in Phase 3 trials but has not yet been approved by the FDA.[33] The PCSK9 inhibitors can lower LDL-C by more than 50% but their capacity to reduce adverse CV events is not clear and these agents are currently being evaluated in long-term clinical trials.[34]

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 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:

Ezetimibe, Niacin, Fibrates, or Omega 3 Fatty Acids on Mortality and Cardiovascular Outcomes with or without Statin Therapy:

A systematic review published in 2015 assessed the safety and efficacy of ezetimibe.[1] A total of 9 RCTs (n=2,212) published through December 2013 were evaluated. Two trials compared ezetimibe in combination with simvastatin to placebo. Seven trials compared ezetimibe and another lipid-lowering drug to the respective lipid-lowering drug alone at the same dosage: 5 compared ezetimibe to simvastatin 20 to 80 mg daily, 2 compared ezetimibe to atorvastatin 10 mg daily, and one trial compared ezetimibe to fenofibrate 160 mg daily. All trials followed participants for at least 24 weeks. The following outcomes were evaluated: all-cause mortality, CV mortality, stroke, MI, cancer, and serious adverse events (SAEs). The trials were of low to medium quality with uncertain risk of bias due to poor reporting of study parameters or selective reporting of outcomes. When results were pooled for meta-analysis, ezetimibe/simvastatin did not demonstrate significant differences in outcomes compared to placebo: MI (Relative Risk (RR) 0.81; 95% CI 0.66-to 1.00); all-cause mortality (RR 1.02; 95% CI 0.95 to 1.09); CV death (RR 0.91; 95% CI 0.80 to 1.04); non-CV mortality (RR 1.08; 95% CI 0.99 to 1.1); stroke (RR 0.86; 95% CI 0.72 to1.04;); cancer (RR 1.18; 95% CI 0.8 to 1.74; and SAEs (RR 1.01; 95% CI 0.96 to 1.06).[1] When the fixed-dose combination ezetimibe/simvastatin was compared to simvastatin alone, there were non-significant effects for all-cause mortality (RR 2.52; 95% CI 0.65 to 9.74), CV mortality (RR 3.04; 95% CI 0.48 to 19.21), non-CV mortality (RR 3.03; 95% CI 0.12 to 73.50), MI (RR 1.91; 95% CI 0.42 to 8.70), stroke (RR 2.38; 95% CI 0.46 to 12.35), cancer (RR 11.11; 95% CI 0.62 to 198.29), and SAEs (RR 1.45; 95% CI 0.95 to 2.23).[1] The increased risk of cancer with ezetimibe may be due to the inclusion of one trial that found an increased risk of cancer with ezetimibe by post-hoc analysis.[26] The primary limitation of this meta-analysis was that the data did not yield precise results due to the small number of reported events.[17] The authors concluded ezetimibe in combination with simvastatin compared to a statin alone or placebo had inconsistent effects on CV outcomes and no firm conclusions could be drawn in regards to the efficacy of combination ezetimibe/statin therapy at reducing the risk of adverse CV outcomes.[1]

A 2015 systematic review evaluated the impact on adverse CV outcomes and mortality when a lipid-lowering drug was added to statin therapy.[2] Major adverse CV events (MACE), defined as a composite of death from coronary heart disease (CHD), non-fatal MI or stroke, were evaluated.[2] No trials with bile acid sequestrants or PCSK9 inhibitors met the inclusion criteria. Eight RCTs (n=77,118) randomized patients to either: statin/niacin or statin (n=29,254); statin/omega 3 fatty acid or statin (n=23,482); statin/fenofibrate or statin (n=5,518 patients); or statin/ezetimibe or statin (n=18,864 patients). One RCT that evaluated omega 3 fatty acids was open-label but the other 7 trials were double-blinded. The follow-up period ranged from 1.5 to 6 years. The authors rated the evidence as high quality with low risk of bias. The IMPROVE-IT, HPS2-THRIVE, ACCORD and AIM-HIGH trials were all included in the meta-analysis. In the overall analysis, the incidence of MACE with statin combination therapies was 0.22% lower than statin monotherapy (9.70% vs. 9.92%, respectively; RR 0.99; 95% CI 0.93 to 1.05, p=0.76).[2] In subgroup analyses, no significant findings were noted for statins combined with niacin (RR 1.03; 95% CI 0.85 to 1.25, p=0.79), omega 3 fatty acids (RR 0.98; 95% CI 0.88 to 1.09, p=0.70), or fenofibrate (RR 0.93; 95% CI 0.80 to 1.09, p=0.38) compared to a statin alone.[2] However, results with ezetimibe combined with a statin found a small statistically significant reduction in MACE (RR 0.92; 95% CI 0.87 to 0.97, p=0.004) compared to a statin alone.[2] The overall meta-analysis of individual CV events did not find statistically significant differences between statin combinations and statin monotherapy for death from CHD or stroke (RR 0.97; 95% CI 0.90 to 1.05, p=0.47 and RR 1.04; 95% CI 0.89 to 1.22, p=0.63, respectively).[2] Subgroup analyses for each statin combination also did not show a statistically significant reduction in death from CHD or stroke. The overall meta-analysis of risk for non-fatal MI was also not statistically significant (RR 0.96; 95% CI 0.89 to 1.04, p=0.28) between statin combinations and statins alone; however, subgroup analysis showed a statistically significant reduction in non-fatal MI (RR 0.89; 95% CI 0.82 to 0.95, p=0.001) for ezetimibe combined with a statin versus a statin alone.[2] Adding lipid-lowering therapy to statins increased the risk of liver injury (675/34,943 versus 435/34,959; p=0.031).[2] No statistically significant increase in creatine kinase levels between the 2 comparisons were

found (194/22,015 versus 189/22,106, p=0.778).[2] The authors concluded that the addition of niacin, omega 3 fatty acids or fibrates to statin therapy do not result in improved long-term CV outcomes but the addition of ezetimibe to statin therapy may provide a very modest clinical benefit for patients at high risk of CVD.[2]

A 2014 meta-analysis completed in 2014 investigated the effects of non-statin therapies that increase HDL levels on CV outcomes.[3] The benefit of niacin (n=11 studies) and fibrates (n=20 studies) on all-cause mortality, CHD mortality, non-fatal MI and stroke was evaluated in 81,410 patients randomized to 31 trials conducted from 1966 through 2013.[3] The authors noted that maintenance of blinding in the niacin studies would have been difficult due to the high risk of flushing associated with niacin therapy. Otherwise, the authors assessed the niacin trials as having low risk of bias. The methodology of older fibrate trials had limited trial quality but later trials provided adequate study design. No statistically significant effects were seen for niacin or fibrates on all-cause mortality (odds ratio (OR) 1.03, 95% CI 0.92 to 1.15, p=0.59 for niacin and OR 0.98, 95% CI 0.89 to 1.08, p=0.66 for fibrates), on CHD mortality (OR 0.93, 95% CI 0.76 to 1.12, p=0.44 for niacin and OR 0.92, 95% CI 0.81 to 1.04, p=0.19 for fibrates); [3] Niacin monotherapy was associated with a statistically significant reduction in non-fatal MI (OR 0.69, 95% CI 0.56 to 0.85, p=0.0004) but addition of niacin to a statin did not reduce non-fatal MI (OR 0.96, 95% CI 0.85 to 1.09, p=0.52).[3] A similar trend was found with fibrates: fibrate monotherapy reduced non-fatal MI (OR 0.78, 95% CI 0.71 to 0.86, p<0.001) but no difference was found with addition of fibrate therapy in patients on a statin (OR 0.83, 95% CI 0.69 to 1.01, p=0.07).[3] The authors concluded neither niacin nor fibrate in combination with a statin reduce all-cause mortality, coronary CHD mortality, MI, or stroke.[3]

In 2016, the Agency for Healthcare Research and Quality (AHRQ) published an updated systematic review that evaluated the evidence from 2002 through June 2015 for omega 3 fatty acids and their impact on CV outcomes and risk factors for CV outcomes.[4] Outcomes evaluated in the search included all-cause death, CV events, cerebrovascular events, and peripheral vascular events, major CVD risk factors (blood pressure and key plasma lipids), and adverse events. One hundred forty-seven articles met the inclusion criteria; 61 RCTs (in 82 articles) and 37 longitudinal observational studies (in 65 articles). The studies were evaluated as having a low risk of bias. The most common risks of bias were lack of intention-to-treat, unclear blinding, and attrition bias.[4] The observational studies were primarily conducted in generally healthy populations while the RCTs were conducted in populations at increased risk for CVD, largely related to dyslipidemia. Overall, there was insufficient evidence regarding the effect of omega 3 fatty acids on clinical CV outcomes or CVD risk factors. No significant association was noted between omega 3 fatty acid intake and all-cause death (RR 0.97; 95% CI 0.92 to 1.03) or MACE (RR 0.96; 95% CI 0.91 to 1.02).[4] In addition, there was insufficient evidence for preventing cardiac death, heart failure death, ischemic stroke death, hemorrhagic stroke death, revascularization, acute coronary syndrome, angina pectoris, ventricular arrhythmia, and hypertension with the use of omega 3 fatty acids.[4] There was high quality evidence for the effect of omega 3 fatty acids on lowering triglycerides (TG) [net change in TG = -24 mg/dL; 95% CI -31 to -18 mg/dL].[4] The authors concluded that evidence regarding the impact of omega 3 fatty acids on reducing CV outcomes is insufficient.[4]

The focus of a 2015 systematic review was to evaluate the safety of co-administration of ezetimibe with statins.[9] A total of 20 RCTs published between 2002 through 2014 met inclusion criteria (n=14,856). The included trials lasted from 6 to 12 weeks. The authors noted a low risk of bias in most of the studies.[9] However, some studies had a high risk of bias due to incomplete outcome data or selective reporting. Total adverse events were reported in 16 studies, with 1165 events occurring in 3856 patients (30%) treated with ezetimibe and statins, compared with 1198 events in 4171 patients (29%) treated with statins alone.[9] There was no significant difference in total adverse events between the 2 groups (95% CI 0.85 to 1.06; p=0.34).[9] Co-administration of ezetimibe and statins did not result in significant increases in serious adverse events (2% vs. 1.6% with statin alone; 95% CI 0.75 to 1.45 , p=0.81) or allergic reactions (0.9% vs. 1.3% with statin alone; 95% CI 0.41 to 1.35, p=0.33).[9] This analysis provides moderate evidence that the incidence of adverse events is similar between ezetimibe and statin combination therapy and statin monotherapy.

Safety and Efficacy of PCSK9 Inhibitors

A 2015 systematic review evaluated the safety and efficacy of PCSK9 inhibitors in 25 RCTs (n=12,200).[6] The trials were published or unpublished and presented at major conferences between 2012 and 2014. Most trials had low to unclear risk of bias due to inadequate descriptions of study parameters, unclear role of sponsorship, or inadequate description of data management.[6] Primary efficacy endpoints were reductions in LDL-C. Safety outcomes were evaluated by assessment of rates of adverse events. Twelve trials compared evolocumab to placebo or ezetimibe and 13 trials compared alirocumab to placebo or ezetimibe. The rates of common adverse events were not statistically significantly different between PCSK9 inhibitors and placebo (or ezetimibe), except that alirocumab was associated with an increased rate of injection-site reactions (RR 1.48; 95% CI 1.05 to 2.09, p=0.02).[6] By week 12, monthly evolocumab treatment significantly reduced LDL-C compared to placebo (mean reduction: -54.6 %; 95% CI -58.7 to -50.5%) and when compared to ezetimibe (mean reduction: -36.3%; 95% CI -38.8 to -33.9%). All evolocumab doses except for the monthly 280 mg dose increased HDL when compared to placebo by 7.6 % (95% CI 5.7 to 9.5%) and by 6.9% versus ezetimibe (95% CI 5.4 to 8.4%).[6] Biweekly alirocumab therapy lowered LDL by a mean reduction of -52.6% (95% CI -58.2 to -47.0%) versus placebo, by a mean reduction of -29.9% (95% CI -32.9 to -26.9%) versus ezetimibe, and increased HDL by 8.0% (95% CI 4.2-11.7%) versus placebo.[6] In the short term evolocumab and alirocumab appear to be safe and effective, however long term safety data and clinically relevant outcomes are still being evaluated.

Another 2015 systematic review assessed the efficacy and safety of PCSK9 inhibitors in adults with hypercholesterolemia.[7] Phase 2 and 3 RCTs that compared PCSK9 inhibitors to placebo or ezetimibe were included. The authors rated the quality of evidence as moderate to high with minimal bias. Most of the patients in the trials were also maintained on statin therapy. Trials lasted from 8 to 48 weeks. Twenty-four trials (n=10,159 patients) met inclusion criteria for the analysis. Primary clinical endpoints were all-cause mortality and CV mortality. Secondary clinical endpoints included MI, unstable angina, and SAEs. Primary efficacy endpoints were percent change from baseline in LDL-C and HDL-C levels. Overall, the meta-analysis revealed a statistically significant 0.22% reduction in all-cause mortality with use of PCSK9 inhibitors compared to placebo or ezetimibe (0.31% vs. 0.53%, respectively; OR 0.45; 95% CI 0.23 to 0.86, p=0.015).[7] Reduction in CV mortality with use of PCSK9 inhibitors was not statistically significantly different from placebo or ezetimibe (0.19% vs. 0.33%, respectively; OR 0.50, 95% CI 0.23 to 1.10, p=0.084).[7] Compared with placebo or ezetimibe, treatment with PCSK9 inhibitors markedly reduced LCL-C (mean difference (MD) -47.49%; 95% CI -69.64% to -25.35%, p<0.001).[7] Serious adverse events did not significantly increase with administration of PCSK9 inhibitors. There was no significant difference in the overall incidence of adverse effects among patients treated with PCSK9 inhibitors (9.26%) and patients who received placebo or ezetimibe (7.73%) [OR 1.01; 95% CI 0.87 to 1.18, p=0.879].[7] This meta-analysis provides moderate evidence that PCSK9 inhibitors are safe and effective in lowering LDL. The effect on cardiovascular events and mortality are currently being investigated in long term trials.

A 2015 systematic review of RCTs in patients with primary hypercholesterolemia compared the impact of PCSK9 inhibitors with placebo and ezetimibe on lipoproteins, all-cause mortality, and CV events.[8] Seventeen trials randomized 13,083 patients to PCKS9 inhibitors (n=8250), placebo (n=3957), ezetimibe (n=846) or a combination of ezetimibe with PCSK9 inhibitors (n=30). In almost all of the studies the patients were on statins as baseline therapy. The duration for most of the trials was 12 weeks, although 4 trials lasted 24 weeks and one trial was conducted over 52 weeks. [8] The 17 trials were assessed as having low risk of bias using the Cochrane Collaboration tool and were deemed high quality using the GRADE system.[8] The PCSK9 inhibitors reduced LDL by a mean difference of -59.56 (95% CI -60.54 to -58.58).[8] Odd ratios were generated with random-effects models to compare outcomes.[8] In comparison to placebo, PCSK9 inhibitors reduced the incidence of all-cause mortality (OR 0.43, 95% CI 0.22 to 0.82, p=0.01).[8] However, the impact of PCSK9 inhibitors on CV mortality and major cardiac events was not different from placebo (OR 0.50 95% CI 0.22 to 1.13, p=0.10 and OR 0.67, 95% CI 0.43 to 1.04, p = 0.07 respectively).[8] The authors did not specify which major cardiac events were included in the meta-analysis. When PCSK9 inhibitors were compared to ezetimibe, there were no significant differences in all-cause mortality or CV events. An increased incidence of neurocognitive adverse events with PCSK9 inhibitors was found compared with placebo (OR 2.34, 95% CI 1.11

to 4.93, p=0.02).[8] This meta-analysis reveals there is a risk of adverse neurocognitive effects in conjunction with PCSK9 therapy. In addition, more RCTs adequately powered to assess long term clinical outcomes are needed to determine the role of PCSK9 inhibitors in managing hyperlipidemia.

New Guidelines:

National Lipid Association (NLA)

In 2014, the NLA published recommendations in an attempt to synthesize evidence from both the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III and the 2013 ACC/AHA guidelines.[13,35] The committee adapted a hybrid of NHLBI evidence rating which was used in the AHA/ACC 2013 guidelines in addition to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system of evidence rating in guideline development.[36] Due to the volume of information the panel had compiled for dissemination, the report was published in two parts. The expert panel was guided by the primary principle that reducing elevated levels of non-HDL cholesterol reduces the risk for CVD.[13] The NLA authors agreed with the ACC/AHA approach of statin based-intensity therapy, but noted it was imperative to target specific numeric lipoprotein goals to assess risk reduction. The NLA recommendations advocate for an LDL-C goal less than 100 mg/dL for everyone except the highest risk patients.[13] In patients with CVD or diabetes mellitus (DM), the goal LDL-C is less than 70 mg/dL.[13] In contrast to the 2013 ACC/AHA guidelines, the NLA supports additional or alternative lipid-lowering therapies for at-risk patients not at non-HDL-C or LDL-C goals or who cannot tolerate statins.[35]

The NLA recommends that the following statin combination therapies be considered in the indicated order:

1. Ezetimibe 10 mg daily is recommended as a first-line statin combination therapy since it has been shown to reduce CVD events when added to a statin in a controlled clinical trial.[35]
2. Colesevelam 625 mg 3 tablets twice a day (or 3.75 g powder form every day or in divided doses) is recommended as a second-line statin combination therapy because the drug class has been shown to reduce CVD events when used alone and it is better tolerated than the other resins.[35]
3. Extended release niacin titrated to a maximum of 2000 mg daily is recommended as a third-line statin combination therapy because it has demonstrated lower CVD events when used alone, and may have benefit when given with a statin to patients with LDL-C or non-HDL-C levels not at goal. However, it provides only modest LDL-C lowering efficacy, and use of niacin in combination with a statin is not recommended for patients whose LDL-C is less than 70 mg/dL based on evidence for no benefit and possible harm in this group.[35]
4. Patients with dyslipidemia (elevated TG and VLDL-C plus low HDL-C) may need targeted therapy with fibrates and/or omega-3 fatty acids to achieve lipid goals.[35]

The NLA acknowledged that PCSK9 inhibitors have a role in managing patients with CVD risk despite statin and lifestyle therapy. Until CV outcomes trials are completed the PCSK9 inhibitors should be considered for the following situations:

1. Patients with CVD who have LDL-C ≥100 mg/dL (non-HDL-C ≥130 mg/dL) while on maximally-tolerated statin (±ezetimibe) therapy[35]
2. HeFH patients without CVD who have LDL-C ≥130 mg/dL (non-HDL-C ≥160 mg/dL) while on maximally-tolerated statin (±ezetimibe) therapy[35]

There is low quality evidence to employ PCSK9 inhibitors for secondary prevention in patients that have not met treatment goals (i.e. LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL) or in selected high-risk patients who meet the definition of statin intolerance and require substantial cholesterol reduction. Such uses should be based on clinical judgment after the potential but unknown benefits are weighed against the risks and extreme high cost of therapy.[35]

National Institute for Health and Care Excellence (NICE)

The United Kingdom's NICE guidance for utilizing lipid-lowering therapy for CVD risk reduction was updated as of July 2016.[14] Similar to ACC/AHA, the statins are considered first-line drug therapy to prevent CVD in addition to lifestyle modification. Fibrates, niacin, BAS and omega 3 fatty acids are not recommended in combination with statins for primary or secondary prevention of CV disease including patients with CKD or diabetes.[14] The NICE committee evaluated the relevance of the IMPROVE-IT trial (ezetimibe/simvastatin vs. simvastatin) and concluded that the population studied in IMPROVE-IT was not representative of the population receiving ezetimibe in the current British National Health Service.[37] In IMPROVE‑IT, patients had acute coronary syndrome and were being treated for secondary prevention and not primary prevention of CV disease.[38]

The specific NICE guidance for ezetimibe therapy is as follows:

1. Ezetimibe monotherapy is recommended as an option for treating primary hypercholesterolemia in adults in whom initial statin therapy is contraindicated or in patients who cannot tolerate statin therapy.[38]
2. Addition of ezetimibe to current statin therapy is recommended as an option for treating primary hypercholesterolemia in adults who have:
    a. total cholesterol or LDL-C is not controlled after appropriate dose titration of initial statin or because dose titration is limited by intolerance to the initial statin therapy; and
    b. a change from initial statin therapy to an alternative statin is being considered.[38]

NICE guidance regarding PCSK9 inhibitors was published in June 2016. Alirocumab and evolocumab are recommended as options for treatment of primary hypercholesterolemia or mixed dyslipidemia only if LDL-C concentrations are persistently above the thresholds specified for high or very high risk of CVD despite maximal tolerated lipid-lowering therapy.[15] In other words, either the maximum statin dose has been reached or further titration is limited by intolerance. NICE created a separate guidance document for each PCSK9 medication. The recommendations for evolocumab have specific dosing parameters in addition to guidance for which patients warrant therapy. Without evidence for the monthly dosage, the committee was unable to recommend evolocumab 420 mg monthly for primary hypercholesterolemia (heterozygous-familial and non-familial) or mixed dyslipidemia.[37] Evolocumab and alirocumab are recommended as options in combination with a statin or as monotherapy for treatment of primary hypercholesterolemia or mixed dyslipidemia as outlined Table 1.

Table 1: Low density lipoprotein cholesterol concentrations above which alirocumab and evolocumab are recommended per NICE guidance[15,37]

Diagnosis	**Without CVD**	**With CVD**	
		High Risk of CVD*	**Very High Risk of CVD****
Primary non-familial hypercholesterolemia or mixed dyslipidemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C‑C concentration is persistently above 155 mg/dL	Recommended only if LDL-C‑C concentration is persistently above 135 mg/dL
Primary heterozygous- familial hypercholesterolemia	Recommended only if LDL-C concentration is persistently above 190 mg/dL	Recommended only if LDL-C‑C concentration is persistently above 135 mg/dL	
*High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalization), coronary or other arterial revascularization procedures, chronic heart disease, ischemic stroke, or peripheral arterial disease. **Very high risk of CVD is defined as recurrent CV events or CV events in more than 1 vascular bed.			

International Atherosclerosis Society (IAS)

IAS updated their recommendations for the management of dyslipidemia in 2014. The international panel reached consensus after reviewing epidemiologic studies, genetic studies and clinical trials. The recommendations were further determined by a review of pathologic studies, pharmacology, metabolic studies, clinical trials, meta-analyses of clinical trials, and animal studies.[12] The committee identified non HDL-C as the major atherogenic lipoprotein and defined atherogenic cholesterol as either LDL-C or non-HDL-C cholesterol and recommended optimal target levels for each lipoprotein level.[12] For primary prevention in high risk adults, an optimal LDL-C is less than 100 mg/dL and the optimal non-HDL-C level is less than 130 mg/dL.[12] Consistent with other guidelines, statins are recommended as first-line drug therapy for primary and secondary prevention after lifestyle interventions have been implemented. For high risk patients intolerant to statins, alternative agents such as ezetimibe, BAS and niacin are recommended for lowering LDL-C in primary prevention. For secondary prevention, IAS recommends adding ezetimibe or BAS to statin therapy. For patients with high triglycerides, niacin or fibric acid derivatives are reasonable alternatives.[12]

Canadian Agency for Drugs and Technologies in Health (CADTH)

CADTH recommends alirocumab or evolocumab be used as an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) who require additional lowering of LDL-C if the following clinical criteria and conditions are met:[16,17]

1. Patient has a confirmed diagnosis of HeFH; and
2. Patient is unable to reach the target LDL-C level specified in current guidelines (i.e. LDL-C <135 mg/dL); and
3. Patient is currently receiving maximally tolerated statin therapy with or without ezetimibe

Alirocumab is also recommended as an adjunct to diet and maximally tolerated statin therapy in adult patients at high risk for CV events who require additional lowering of LDL-C if the following clinical criteria and conditions are met:[16]

1. Patient is at high risk for CV events
2. Patient is unable to reach the target LDL-C level (< 155 mg/dl); and
3. Patient is currently receiving maximally tolerated statin therapy with or without ezetimibe

CADTH guidance does not recommend evolocumab as adjunctive therapy for clinical atherosclerotic CV disease due to insufficient evidence to evaluate the risks of therapy compared to benefits for this indication.[17]

Safety Updates:

Gemfibrozil (March 2016): The combination therapy of gemfibrozil with dasabuvir is contraindicated.[39] Gemfibrozil is a CYP2C8 inhibitor, which may increase exposure of CYP2C8 substrates when administered concomitantly. Co-administration of gemfibrozil with dasabuvir increased dasabuvir AUC and maximum drug concentrations (ratios: 11.3 and 2.01, respectively) due to CYP2C8 inhibition. Increased dasabuvir exposure may increase the risk of QT prolongation.[40]

New Formulations or Indications:

The FDA approved a device that can deliver a single monthly injection of evolocumab, the PCSK9 inhibitor manufactured by Amgen in July 2016.[41] Evolocumab is currently administered by subcutaneous injection in a 140-mg dose every 2 weeks or as a 420 mg monthly dose. The monthly dose had been given as 3 separate 140 mg/mL injections administered consecutively within 30 minutes. The Pushtronex™ system is an on-body infusor with a prefilled cartridge of evolocumab that delivers 420 mg in 3.5 mL over 9 minutes subcutaneously. The device adheres to the body and is hands-free. While receiving the injection, patients are able to perform moderate physical activities such as walking, bending or reaching.[42]

Randomized Controlled Trials:

A total of 158 citations were manually reviewed from the literature search. After manual review, 154 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. Full abstracts are included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Cannon, et al.[5] DB, RCT, MC N=18,144 39 countries Median follow-up: 6 years	Simvastatin 40 mg + Ezetimibe 10 mg vs Simvastatin 40 mg + Placebo	Adults age ≥50 years hospitalized for ACS with LDL-C 50-125 mg/dL if not on lipid-lowering therapy or LDL-C 50-100 mg/dL if already on lipid-lowering therapy Exclusion: CABG, CrCl <30 mL/min, active liver disease, >40 mg simvastatin dose or equivalent	Composite endpoint: CV death, non- fatal MI, unstable angina requiring re-hospitalization, coronary revascularization (≥ 30 days after randomization), or nonfatal stroke	Simvastatin + ezetimibe: 32.7% Simvastatin + placebo: 34.7% ARR 2.0% (HR 0.936; 95% CI 0.89-0.99; p=0.016) Secondary Endpoint: Median time weighted average LDL-C: Simvastatin + ezetimibe: 53.7 mg/dL Simvastatin + placebo: 69.5 mg/dL p<0.001
Maki, et al.[43] DB, PG, RCT, PC, MC n=647 96 sites in US Duration: 6 weeks (after 6 week run-in)	Statin + OM3-FFA 2 gm vs Statin + OM3-FFA 4 gm vs Statin + OO (placebo)	Adults age ≥18 years at high risk for CV disease with fasting TG 200-500 mg/dL treated with maximally tolerated statin or statin with ezetimibe Exclusion: non-HDL-C < 90 mg/dL, h/o pancreatitis, T1DM, HbA1C >10%, BP ≥160/100 mmHg, hypothyroidism, elevated LFTs	Primary endpoint: Percent change from baseline in non-HDL-C	**Percent change in non-HDL-C from baseline*** Statin + OM3-FFA 2 gm: -3.9% (p<0.05 vs. OO) Statin + OM3-FFA 3 gm: -6.9% (p<0.001 vs. OO) Statin + OO: -0.9% Secondary Endpoints: Percent change in TG from baseline* Statin + OM3-FFA 2 gm: -14.6% (p<0.001 vs. OO) Statin + OM3-FFA 3 gm: -20.6% (p<0.001 vs. OO) Statin + OO: -5.9% Percent change in HDL-C from baseline* Statin + OM3-FFA 2 gm: +2.6% (p=? vs. OO) Statin + OM3-FFA 3 gm: +3.3% (p=? vs. OO) Statin + Olive Oil: +2.2% *95% CIs not reported

Kastelein, et al.[44] DB, RCT, MC, PG n=399 74 sites in US, Europe, and India Duration: 12 weeks (after 6 week run-in)	OM3-FFA 2 gm vs OM3-FFA 3 gm vs OM3-FFA 4 gm vs OO 4 gm	Adults age ≥18 years with TG 500-2000 mg/dL treated on stable dose of statin and/or CAI or untreated Exclusion: pancreatitis, HbA1C ≥9%, recent CV event, hypothyroidism, BP ≥ 160/100 mmHg, elevated LFTs, CrCl <30 mL/min, platelets <60 x$10^{9/}$L or Hgb <10 g/dL	Primary endpoint: Percent change in TG from baseline	**Percent change in TG from baseline:** OM3-FFA 2 gm: -25.9% (95% CI -32.8 to -18.3%; p <0.01 vs. OO) OM3-FFA 3 gm: -25.5% (95% CI -32.4 to -17.8%; p <0.01 vs. OO) OM3-FFA 4 gm: -30.9% (95% CI -37.3 to -23.7%; p<0.001 vs. OO) OO: -4.3% (95% CI -13.1-5.4%) Secondary Endpoints: Percent change in non-HDL-C from baseline: OM3-FFA 2 gm: -7.6% (95% CI -12.0 to -3.0%; p<0.05 vs. OO) OM3-FFA 3 gm: -6.9% (95% CI -11.4 to -2.2%; p<0.05 vs. OO) OM3-FFA 4 gm: -9.6% (95% CI -14.o to -5.1%; p<0.01 vs. OO) OO: 2.5% (95% CI -2.3 to 7.6%) Percent change in HDL-C from baseline: OM3-FFA 2 gm: 7.4% (95% CI 3.2 to 11.7%; p=? vs. OO) OM3-FFA 3 gm: 3.8% (95% CI -0.3 to 8.0%; p=? vs. OO) OM3-FFA 4 gm: 5.8% (95% CI 1.7 to 10.1%; p=? vs. OO) OO: 1.9% (95% CI -2.0 to 6.0%)
Nissen, et al.[45] DB, PC, CO, RCT n=511s 48 weeks (initial 4 week washout, 24 weeks of therapy then 2 week washout before second 24	Phase A: atorvastatin 20 mg vs. placebo Phase B: randomized 2:1 to evolocumab 420 mg SC once a month vs. ezetimibe 10 mg PO daily	Adults age 18-80 years with uncontrolled LDL-C* and h/o intolerance to ≥2 statins *Defined as: pts with CHD and LDL ≥100 mg/dL; pts w/o CHD and LDL ≥ 130 mg/dL plus ≥2 risk factors; LDL-C >160 mg/dL with 1 risk factor; or LDL >190 mg/dL with no risk factors	Co-Primary Endpoints 1. Mean % change in LDL-C from baseline to the mean at weeks 22 and 24 2. Mean % change in LDL-C from baseline to week 24	**Mean % change in LDL-C from baseline to the mean for week 22 and 24** Ezetimibe: -16.7%; 95% CI -20.5 to -12.9%, p<0.001 (week 22) vs. -16.7 (95% CI -20.8 to -12.5 p < 0.001 (week 24) Evolocumab: -54.5% ;95% CI -57.2 to -51.8%, p<0.001 (week 22) vs -52.8 ;95% CI -55.8 to -49.8 p < 0.001 (week24) **Mean % change in LDL-C from baseline LDL-C to week 24** Ezetimibe: -16.7% (95% CI -20.8 to -12.5%, p<0.001) Evolocumab: -54.5% (95% CI -55.8 to -49.8%, p<0.001)

week phase)		Exclusion: h/o MI, unstable angina, coronary revascularization, or stroke 3 months before study enrollment		

Abbreviations: ACS = acute coronary syndrome; ARR = absolute risk reduction; BP = blood pressure; CABG = coronary artery bypass graft; CHD = coronary heart disease; CrCl = creatinine clearance; DB = double blind; CAI =cholesterol absorption inhibitor; CI = confidence interval; CO = crossover; CV = cardiovascular; dL = deciliter; HbA1c = glycosylated hemoglobin; HDL-C = high density lipoprotein cholesterol; h/o = history of; HR = hazard ratio; LDL-C = low density lipoprotein cholesterol; LFT = liver function tests; MC = multi-centered; mg = milligram; MI = myocardial infarction; OM3-FFA = omega-3 fatty acid; PC = placebo controlled; PG = parallel group; RCT = randomized controlled trial; T1DM = type 1 diabetes mellitus; TLC = therapeutic lifestyle changes; TG = triglycerides; OO = olive oil; PO = oral; SC = subcutaneous

References:

1. Battaggia A, Donzelli A, Font M, Molteni D, Galvano A. Clinical efficacy and safety of Ezetimibe on major cardiovascular endpoints: systematic review and meta-analysis of randomized controlled trials. [Review]. *PLoS ONE [Electronic Resource]*. 2015;10(4). doi:10.1371/journal.pone.0124587.

2. Ip C, Jin D, Gao J, et al. Effects of add-on lipid-modifying therapy on top of background statin treatment on major cardiovascular events: A meta-analysis of randomized controlled trials. *Int J Cardiol*. 2015;191:138-148. doi:10.1016/j.ijcard.2015.04.228.

3. Keene D, Price C, Shun-Shin MJ, Francis DP. Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117,411 patients. *BMJ*. 2014;349:g4379.

4. Omega-3 Fatty Acids and Cardiovascular Disease: An Updated Systematic Review. Agency for Healthcare Research and Quality. 8/2016. https://www.effectivehealthcare.ahrq.gov/ehc/products/609/2262/fatty-acids-cardiovascular-disease-report-160812.pdf. Accessed September 8, 2016.

5. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *New England Journal of Medicine*. 2015;372(25):2387-2397. doi:10.1056/NEJMoa1410489.

6. Zhang X-L, Zhu Q-Q, Zhu L, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. *BMC Medicine*. 2015. doi:10.1186/s12916-015-0358-8.

7. Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis. *Ann Intern Med*. 2015;163(1):40-51. doi:10.7326/M14-2957.

8. Lipinski MJ, Benedetto U, Escarcega RO, et al. The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolaemia: a network meta-analysis. *Eur Heart J*. 2016;37(6):536-545. doi:10.1093/eurheartj/ehv563.

9. Luo L, Yuan X, Huang W, et al. Safety of coadministration of ezetimibe and statins in patients with hypercholesterolaemia: a meta-analysis. *Internal Medicine Journal*. 2015;45(5):546-557. doi:10.1111/imj.12706.

10. PCSK9 Inhibitor Monoclonal Antibodies for the Treatment of Hypercholesterolemia | CADTH.ca. https://www.cadth.ca/dv/pcsk9-inhibitor-monoclonal-antibodies-treatment-hypercholesterolemia. Accessed July 18, 2016.

11. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *Circulation*. January 2013:01.cir.0000437738.63853.7a. doi:10.1161/01.cir.0000437738.63853.7a.

12. Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel members. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia--full report. *J Clin Lipidol*. 2014;8(1):29-60. doi:10.1016/j.jacl.2013.12.005.

13. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1--full report. *J Clin Lipidol*. 2015;9(2):129-169. doi:10.1016/j.jacl.2015.02.003.

14. Cardiovascular disease: risk assessment and reduction, including lipid modification. Guidance and guidelines .National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg181. Accessed August 2, 2016.

15. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Guidance and guidelines . National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ta393. Accessed July 18, 2016.

16. Canadian Agency for Drugs and Technologies Final Recommendation for Praluent - SR0469_complete_Praluent_Jul-20-16.pdf. https://www.cadth.ca/sites/default/files/cdr/complete/SR0469_complete_Praluent_Jul-20-16.pdf. Accessed August 4, 2016.

17. Canadian Agency for Drugs and Technologies in Health. Common Drug Review: Evolocumab (Repatha). https://www.cadth.ca/sites/default/files/cdr/complete/SR0441_complete_Rapatha-Feb-23_16_e.pdf. Accessed August 4, 2016.

18. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *Journal of the American College of Cardiology*. 2016;68(1):92-125. doi:10.1016/j.jacc.2016.03.519.

19. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J*. 2013;34(17):1279-1291. doi:10.1093/eurheartj/eht055.

20. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *New England Journal of Medicine*. 2011;365(24):2255-2267. doi:10.1056/NEJMoa1107579.

21. Niacin extended release (Niaspan) Prescribing Information. North Chicago, IL: Abbvie, Inc.; April 2015.

22. AbbVie, FDA Withdraw Two Cholesterol Drugs from US Market as Benefits No Longer Outweigh Risks | RAPS. http://www.raps.org/Regulatory-Focus/News/2016/04/15/24777/AbbVieFDA-Withdraw-Two-Cholesterol-Drugs-from-US-Market-as-Benefits-No-Longer-Outweigh-Risks/.aspx. Accessed August 23, 2016.

23. ACCORD Study Group, Ginsberg HN, Elam MB, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1563-1574. doi:10.1056/NEJMoa1001282.

24. Fenofibrate (Fenoglide) Prescribing Information. San Diego, CA: Santarus, Inc.: October 2012.

25. Kastelein JJP, Akdim F, Stroes ESG, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med*. 2008;358(14):1431-1443. doi:10.1056/NEJMoa0800742.

26. Farmer JA. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis (the SEAS trial). *Curr Atheroscler Rep*. 2009;11(2):82-83.

27. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359(13):1343-1356. doi:10.1056/NEJMoa0804602.

28. Research C for DE and. Drug Safety Information for Heathcare Professionals - Follow-Up to the August 2008 Early Communication About an Ongoing Safety Review of Ezetimibe/Simvastatin (marketed as Vytorin), Simvastatin (marketed as Zocor) and Ezetimibe (marketed as Zetia) - FDA Investigates a Report from the SEAS Trial. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm194964.htm. Accessed August 19, 2016.

29. FDA Briefing Document: Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) - UCM476505.pdf. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM476505.pdf. Accessed July 27, 2016.

30. Icosapent ethyl (Vascepa) Prescribing Information. Dublin, Ireland: Amarin, Pharma, Inc. June 2016.

31. Omega-3-acid ethyl esters (Lovaza) Prescribing Information. Research Triangle Park, NC: GlaxoSmithKline. September 2015.

32. A Study of AMR101 to Evaluate Its Ability to Reduce Cardiovascular Events in High Risk Patients With Hypertriglyceridemia and on Statin. The Primary Objective is to Evaluate the Effect of 4 g/Day AMR101 for Preventing the Occurrence of a First Major Cardiovascular Event. - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01492361?term=icosapent&rank=15. Accessed July 26, 2016.

33. Rosei EA, Salvetti M. Management of Hypercholesterolemia, Appropriateness of Therapeutic Approaches and New Drugs in Patients with High Cardiovascular Risk. *High Blood Press Cardiovasc Prev*. 2016;23(3):217-230. doi:10.1007/s40292-016-0155-2.

34. Hassan M. OSLER and ODYSSEY LONG TERM: PCSK9 inhibitors on the right track of reducing cardiovascular events. *Glob Cardiol Sci Pract*. 2015;2015(2):20. doi:10.5339/gcsp.2015.20.

35. Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2. *J Clin Lipidol*. 2015;9(6 Suppl):S1-122.e1. doi:10.1016/j.jacl.2015.09.002.

36. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD.

37. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Guidance and guidelines. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ta394. Accessed July 18, 2016.

38. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia .Guidance and guidelines . National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ta385?unlid=979832004201631511465 1,97563078920166304611. Accessed July 18, 2016.

39. U.S. Food and Drug Administration. Safety Information - Lopid (gemfibrozil) tablets. http://www.fda.gov/safety/medwatch/safetyinformation/ucm175927.htm. Accessed September 8, 2016.

40. Lopid (gemfibrozil) Prescribing Information. New York, NY, Pfizer, Inc., March 2016.

41. CardioBrief: PCSK9 Drug Approved for Single Monthly Injection. http://www.medpagetoday.com/Cardiology/CardioBrief/59008. Published July 11, 2016. Accessed July 13, 2016.

42. Repatha (evolocumab) Prescribing Information. Thousand Oaks, CA; Amgen, Inc. , July 2016.

43. Maki KC, Orloff DG, Nicholls SJ, et al. A highly bioavailable omega-3 free fatty acid formulation improves the cardiovascular risk profile in high-risk, statin-treated patients with residual hypertriglyceridemia (the ESPRIT trial). *Clin Ther*. 2013;35(9):1400-1411-3. doi:10.1016/j.clinthera.2013.07.420.

44. Kastelein JJP, Maki KC, Susekov A, et al. Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial. *J Clin Lipidol*. 2014;8(1):94-106. doi:10.1016/j.jacl.2013.10.003.

45. Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial. *JAMA*. 2016;315(15):1580-1590. doi:10.1001/jama.2016.3608.

46. Micromedex Solutions (Internet Database). Truven Health Analytics. 2016.

47. Lexicomp Online. (Internet Database). Hudson, OH: Wolters Kluwer, Inc. Updated June 2016.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	POWD PACK	CHOLESTYRAMINE	CHOLESTYRAMINE (WITH SUGAR)	Y
ORAL	POWD PACK	CHOLESTYRAMINE LIGHT	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	POWD PACK	PREVALITE	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	POWD PACK	QUESTRAN	CHOLESTYRAMINE (WITH SUGAR)	Y
ORAL	POWDER	CHOLESTYRAMINE	CHOLESTYRAMINE (WITH SUGAR)	Y
ORAL	POWDER	CHOLESTYRAMINE LIGHT	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	POWDER	PREVALITE	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	POWDER	QUESTRAN	CHOLESTYRAMINE (WITH SUGAR)	Y
ORAL	POWDER	QUESTRAN LIGHT	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	TABLET	FENOFIBRATE	FENOFIBRATE	Y
ORAL	TABLET	GEMFIBROZIL	GEMFIBROZIL	Y
ORAL	TABLET	LOFIBRA	FENOFIBRATE	Y
ORAL	TABLET	LOPID	GEMFIBROZIL	Y
ORAL	CAPSULE	JUXTAPID	LOMITAPIDE MESYLATE	N
ORAL	GRANULES	COLESTID	COLESTIPOL HCL	N
ORAL	GRANULES	COLESTIPOL HCL	COLESTIPOL HCL	N
ORAL	PACKET	COLESTID	COLESTIPOL HCL	N
ORAL	PACKET	COLESTIPOL HCL	COLESTIPOL HCL	N
ORAL	POWD PACK	WELCHOL	COLESEVELAM HCL	N
ORAL	TABLET	COLESTID	COLESTIPOL HCL	N
ORAL	TABLET	COLESTIPOL HCL	COLESTIPOL HCL	N
ORAL	TABLET	WELCHOL	COLESEVELAM HCL	N
SUB-Q	PEN INJCTR	PRALUENT PEN	ALIROCUMAB	N
SUB-Q	PEN INJCTR	REPATHA SURECLICK	EVOLOCUMAB	N
SUB-Q	SYRINGE	KYNAMRO	MIPOMERSEN SODIUM	N
SUB-Q	SYRINGE	PRALUENT SYRINGE	ALIROCUMAB	N
SUB-Q	SYRINGE	REPATHA SYRINGE	EVOLOCUMAB	N
ORAL	CAPSULE	ANTARA	FENOFIBRATE,MICRONIZED	N
ORAL	CAPSULE	FENOFIBRATE	FENOFIBRATE	N
ORAL	CAPSULE	FENOFIBRATE	FENOFIBRATE,MICRONIZED	N
ORAL	CAPSULE	LIPOFEN	FENOFIBRATE	N
ORAL	CAPSULE	LOFIBRA	FENOFIBRATE,MICRONIZED	N
ORAL	CAPSULE	OMEGA-3 ACID ETHYL ESTERS	OMEGA-3 ACID ETHYL ESTERS	N
ORAL	CAPSULE	VASCEPA	ICOSAPENT ETHYL	N

ORAL	CAPSULE DR	FENOFIBRIC ACID	FENOFIBRIC ACID (CHOLINE)	N
ORAL	CAPSULE ER	NIACIN	NIACIN	N
ORAL	TAB ER 24H	NIACIN ER	NIACIN	N
ORAL	TAB ER 24H	NIASPAN	NIACIN	N
ORAL	TABLET	FENOFIBRATE	FENOFIBRATE	N
ORAL	TABLET	FENOFIBRATE	FENOFIBRATE NANOCRYSTALLIZED	N
ORAL	TABLET	FENOFIBRIC ACID	FENOFIBRIC ACID	N
ORAL	TABLET	FENOGLIDE	FENOFIBRATE	N
ORAL	TABLET	FIBRICOR	FENOFIBRIC ACID	N
ORAL	TABLET	NIACOR	NIACIN	N
ORAL	TABLET	ZETIA	EZETIMIBE	N
ORAL	CAPSULE DR	TRILIPIX	FENOFIBRIC ACID (CHOLINE)	
ORAL	TABLET	TRICOR	FENOFIBRATE NANOCRYSTALLIZED	
ORAL	TABLET	TRIGLIDE	FENOFIBRATE NANOCRYSTALLIZED	

Appendix 2: Abstracts of Clinical Trials

Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. New England Journal of Medicine. 2015; 372(25):2387-2397. Doi :10.1056/NEJMoa1410489.

BACKGROUND: Statin therapy reduces low-density lipoprotein (LDL-C) cholesterol levels and the risk of CV events, but whether the addition of ezetimibe, a non-statin drug that reduces intestinal cholesterol absorption, can reduce the rate of CV events further is not known.

METHODS: We conducted a double-blind, randomized trial involving 18,144 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and had LDL-C cholesterol levels of 50 to 100 mg per deciliter (1.3 to 2.6 mmol per liter) if they were receiving lipid-lowering therapy or 50 to 125 mg per deciliter (1.3 to 3.2 mmol per liter) if they were not receiving lipid-lowering therapy. The combination of simvastatin (40 mg) and ezetimibe (10 mg) (simvastatin-ezetimibe) was compared with simvastatin (40 mg) and placebo (simvastatin monotherapy). The primary end point was a composite of CV death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke. The median follow-up was 6 years.

RESULTS: The median time-weighted average LDL-C cholesterol level during the study was 53.7 mg per deciliter (1.4 mmol per liter) in the simvastatin-ezetimibe group, as compared with 69.5 mg per deciliter (1.8 mmol per liter) in the simvastatin-monotherapy group (P<0.001). The Kaplan-Meier event rate for the primary end point at 7 years was 32.7% in the simvastatin-ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (absolute risk difference, 2.0 percentage points; hazard ratio, 0.936; 95% confidence interval, 0.89 to 0.99; P=0.016). Rates of prespecified muscle, gallbladder, and hepatic adverse effects and cancer were similar in the two groups.

CONCLUSIONS: When added to statin therapy, ezetimibe resulted in incremental lowering of LDL-C cholesterol levels and improved CV outcomes. Moreover, lowering LDL-C cholesterol to levels below previous targets provided additional benefit. (Funded by Merck; IMPROVE-IT ClinicalTrials.gov number, NCT00202878.)

Maki KC, Orloff DG, Nicholls SJ, et al. A highly bioavailable omega-3 free fatty acid formulation improves the CV risk profile in high-risk, statin-treated patients with residual hypertriglyceridemia (the ESPRIT trial). Clin Ther. 2013;35(9):1400-1411-3. doi:10.1016/j.clinthera.2013.07.420.

BACKGROUND: A novel omega-3 formulation in free fatty acid form (OM3-FFA) has as much as 4-fold greater bioavailability than ethyl ester forms and reduces triglyceride (TG) levels in patients with severe hypertriglyceridemia.

OBJECTIVE: This study was designed to evaluate the efficacy of adding OM3-FFA (2 or 4 g/d) to statin therapy for lowering non-HDL-C and TG levels in subjects with persistent hypertriglyceridemia and at high risk for CV disease.

METHODS: In this double-blind, parallel-group study, 647 diet-stable patients with fasting TG levels ≥ 200 mg/dL and <500 mg/dL (treated with a maximally tolerated dose of statin or statin with ezetimibe) and at high risk for CV disease were randomized to 6 weeks of treatment with capsules of control (olive oil [OO]) 4 g/d, OM3-FFA 2 g/d (plus 2 g/d OO), or OM3-FFA 4 g/d. Assessments included fasting serum levels of lipids and apolipoproteins (apo); plasma concentrations of eicosapentaenoic acid, docosahexaenoic acid, docosapentaenoic acid, and arachidonic acid; and laboratory safety values and adverse events.

RESULTS: In the 627 subjects in the intention to treat sample, non-HDL-C levels were reduced with OM3-FFA 2 g/d and OM3-FFA 4 g/d (-3.9% and -6.9%, respectively) compared with OO (-0.9%) (both, P < 0.05), as were TG levels (-14.6% and -20.6%, respectively, vs -5.9%; both, P < 0.001). LDL-C levels increased with OM3-FFA 2 g/d (4.6%) compared with OO (1.1%) (P = 0.025) but not with OM3-FFA 4 g/d (1.3%). Total cholesterol and VLDL-C concentrations were reduced compared with OO with both OM3-FFA dosages, and the total cholesterol/HDL-C ratio and apo AI and apo B levels were significantly lowered with OM3-FFA 4 g/d only (all at least P < 0.05). Percent changes from baseline in HDL-C did not differ between OO and either OM3-FFA group. Plasma concentrations of docosahexaenoic acid, eicosapentaenoic acid, and docosapentaenoic acid were significantly increased and arachidonic acid was significantly reduced in both OM3-FFA treatment groups compared with the OO responses (all, P < 0.001). Withdrawals related to treatment-emergent adverse events ranged from 0.9% with OO to 3.2% with OM3-FFA 4 g/d.

CONCLUSIONS: OM3-FFA was well tolerated and lowered non-HDL-C and TG levels at both 2- and 4-g/d dosages in patients with persistent hypertriglyceridemia taking a statin, with the 4-g/d dosage providing incremental improvements compared with 2 g/d.

Kastelein JJP, Maki KC, Susekov A, et al. Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial. J Clin Lipidol. 2014;8(1):94-106. doi:10.1016/j.jacl.2013.10.003.

BACKGROUND: Omega-3 fatty acids in free fatty acid form have enhanced bioavailability, and plasma levels are less influenced by food than for ethyl ester forms.

OBJECTIVE: The aim was to evaluate the safety and lipid-altering efficacy in subjects with severe hypertriglyceridemia of an investigational pharmaceutical omega-3 free fatty acid (OM3-FFA) containing eicosapentaenoic acid and docosahexaenoic acid.
METHODS: This was a multinational, double-blind, randomized, out-patient study. Men and women with triglycerides (TGs) ≥ 500 mg/dL, but <2000 mg/dL, took control (olive oil [OO] 4 g/d; n = 99), OM3-FFA 2 g/d (plus OO 2 g/d; n = 100), OM3-FFA 3 g/d (plus OO 1 g/d; n = 101), or OM3-FFA 4 g/d (n = 99) capsules for 12 weeks in combination with the National Cholesterol Education Program Therapeutic Lifestyle Changes diet.

RESULTS: Fasting serum TGs changed from baseline by -25.9% (P < .01 vs OO), -25.5% (P < .01 vs OO), and -30.9% (P < .001 vs OO) with 2, 3, and 4 g/d OM3-FFA, respectively, compared with -4.3% with OO. Non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol-to-HDL-C ratio, very low-density lipoprotein cholesterol, remnant-like particle cholesterol, apolipoprotein CIII, lipoprotein-associated phospholipase A2, and arachidonic acid were significantly lowered (P < .05 at each OM3-FFA dosage vs OO); and plasma eicosapentaenoic acid and docosahexaenoic acid were significantly elevated (P < .001 at each OM3-FFA dosage vs OO). With OM3-FFA 2 and 4 g/d (but not 3 g/d), low-density lipoprotein cholesterol was significantly increased compared with OO (P < .05 vs OO). High-sensitivity C-reactive protein responses with OM3-FFA did not differ significantly from the OO response at any dosage. Fewer subjects reported any adverse event with OO vs OM3-FFA, but frequencies across dosage groups were similar. Discontinuation due to adverse event, primarily gastrointestinal, ranged from 5% to 7% across OM3-FFA dosage groups vs 0% for OO.

CONCLUSIONS: OM3-FFA achieved the primary end point for TG lowering and secondary end point of non-HDL-C lowering at 2, 3, and 4 g/d in persons with severe hypertriglyceridemia.

Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial. JAMA. 2016;315(15):1580-1590. doi:10.1001/jama.2016.3608.

OBJECTIVE: To identify patients with muscle symptoms confirmed by statin rechallenge and compare lipid-lowering efficacy for 2 non-statin therapies, ezetimibe and evolocumab.

Design, Setting, and Participants Two-stage randomized clinical trial including 511 adult patients with uncontrolled low-density lipoprotein cholesterol (LDL-C) levels and history of intolerance to 2 or more statins enrolled in 2013 and 2014 globally. Phase A used a 24-week crossover procedure with atorvastatin or placebo to identify patients having symptoms only with atorvastatin but not placebo. In phase B, after a 2-week washout, patients were randomized to ezetimibe or evolocumab for 24 weeks.

INTERVENTIONS: Phase A: atorvastatin (20 mg) vs placebo. Phase B: randomization 2:1 to subcutaneous evolocumab (420 mg monthly) or oral ezetimibe (10 mg daily).

MAIN OUTCOME AND MEASURES: Co-primary end points were the mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels and from baseline to week 24 levels.

RESULTS: Of the 491 patients who entered phase A (mean age, 60.7 [SD, 10.2] years; 246 women [50.1%]; 170 with coronary heart disease [34.6%]; entry mean LDL-C level, 212.3 [SD, 67.9] mg/dL), muscle symptoms occurred in 209 of 491 (42.6%) while taking atorvastatin but not while taking placebo. Of these, 199 entered phase B, along with 19 who proceeded directly to phase B for elevated creatine kinase (N = 218, with 73 randomized to ezetimibe and 145 to evolocumab; entry mean LDL-C level, 219.9 [SD, 72] mg/dL). For the mean of weeks 22 and 24, LDL-C level with ezetimibe was 183.0 mg/dL; mean percent LDL-C change, −16.7% (95% CI, −20.5% to −12.9%), absolute change, −31.0 mg/dL and with evolocumab was 103.6 mg/dL; mean percent change, −54.5% (95% CI, −57.2% to −51.8%); absolute change, −106.8 mg/dL (P < .001). LDL-C level at week 24 with ezetimibe was 181.5 mg/dL; mean percent change, −16.7% (95% CI, −20.8% to −12.5%); absolute change, −31.2 mg/dL and with evolocumab was 104.1 mg/dL; mean percent change, −52.8% (95% CI, −55.8% to −49.8%); absolute change, −102.9 mg/dL (P < .001). For the mean of weeks 22 and 24, between-group difference in LDL-C was −37.8%; absolute difference, −75.8 mg/dL. For week 24, between-group difference in LDL-C was −36.1%; absolute difference, –71.7 mg/dL. Muscle symptoms were reported in 28.8% of ezetimibe-treated patients and 20.7% of evolocumab-treated patients (log-rank P = .17). Active study drug was stopped for muscle symptoms in 5 of 73 ezetimibe-treated patients (6.8%) and 1 of 145 evolocumab-treated patients (0.7%).

CONCLUSIONS: Among patients with statin intolerance related to muscle-related adverse effects, the use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C levels after 24 weeks. Further studies are needed to assess long-term efficacy and safety.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to June 5 Week 1 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 7, 2016

1 HYPERLIPIDEMIA.mp. or exp Hyperlipidemias/ 40720
2 exp Cholestyramine Resin/ 501
3 exp Fenofibrate/ 1927
4 exp Gemfibrozil/ 838
5 LOMITAPIDE.mp. 77
6 exp Colestipol/ 64
7 ALIROCUMAB.mp. 88
8 EVOLOCUMAB.mp. 55
9 FENOFIBRATE MICRONIZED.mp. 3
10 Hypertriglyceridemia/ or Fatty Acids, Omega-3/ or Docosahexaenoic Acids/ or OMEGA-3 ACID ETHYL ESTERS.mp. or Eicosapentaenoic Acid/ 18738
11 Eicosapentaenoic Acid/ 3658
12 exp Niacin/ 2411
13 Ezetimibe, Simvastatin Drug Combination/ or Ezetimibe/ 1567
14 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 25451
15 limit 14 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 practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) and last 3 years) 1286
16 limit 15 to last 2 years 835
17 16 and 1 158

Appendix 4: Effect on Lipoproteins for non-Statin Medications

Table 1: Effect on Lipoproteins for non-Statin Medications.[43, 44]

Drug	LDL-C	HDL-C	TG	Approved Indications
Bile Acid Sequestrants				
Cholestyramine	↓15-30%	Minimal Effects	May ↑	Adjunct in the treatment of hypercholesterolemia
Colesevelam	↓ 15-20%	Minimal Effects	May ↑	-Management of elevated LDL-C in adults with primary HL -Type 2 Diabetes -Management of HeFH
Colestipol	↓ 15-30%	Minimal Effects	May ↑	Adjunct in the treatment of hypercholesterolemia
Fibric Acid Derivatives				
Fenofibrate	↓ 20-30%	↑ 10-15%	↓ 30-50%	- Adjunct to diet in the treatment of hypercholesterolemia -Adjunct to diet for treatment of hypertriglyceridemia
Gemfibrozil	↓ 5-10%	↑ 10-20%	↓ 40-60%	-Adjunct to diet in the treatment of hypercholesterolemia -Adjunct to diet for treatment of hypertriglyceridemia
Omega 3 Fatty Acids				
Lovaza	↑ up to 49%	↑ 10%	↓ 25-45%	Reduce TG in patients with TG > 500 mg/dl
Icosapent (Vascepa)	No effect	↑ 10%	↓ 25-45%	Reduce TG in patients with TG > 500 mg/dl
PCSK9 Inhibitors				
Alirocumab	↓ 43-58%	↑ 8%	Unknown	Adjunct to diet and maximally tolerated statin therapy in the treatment of hypercholesterolemia
Evolocumab	↓ 55-75%	↑ 4-9%	↓ 2-23%	-Adjunct to diet and maximally tolerated statin therapy in the treatment of hypercholesterolemia -Adjunct to diet and other LDL-C lowering therapies for treatment of HoFH
Other Agents				
Ezetimibe	↓ 15-20%	Minimal Effects	Minimal Effects	-Combination therapy with statins or fenofibrate to treat primary HL -As adjunct therapy to diet to treat primary HL -Combination therapy with statins to treat HoFH
Niacin	↓ 10-25%	↑ 15-35%	↓ 20-50%	-Treatment of dyslipidemia as mono or adjunctive therapy -Reduce the risk of MI in patients with a history of MI and HL -Adjunctive therapy for the treatment of TG

Abbreviations: LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; HeFH = Heterozygous Familial Hypercholesterolemia; HL = hyperlipidemia, HoFH = Homozygous Familial Hypercholesterolemia

Omega-3 Fatty Acids

Goal(s):

- Promote safe and effective therapies for lipid lowering agent.

Length of Authorization:

Up to 12 months

Requires PA:

- Omega-3-Acid Ethyl Esters (Lovaza®)
- Icosapent Ethyl (Vascepa®)

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 an OHP funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products have received evidence-based reviews for comparative effectiveness and safety by the Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4
4. Does the patient have clinically diagnosed hypertriglyceridemia with triglyceride levels ≥ 500 mg/dL?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
5. Has the patient failed or have a contraindication to an adequate trial (at least 8 weeks) of a fibric acid derivative (fenofibrate or gemfibrozil) at a maximum tolerable dose (as seen in dosing table below)**.** ~~**AND**~~ ~~**niacin 1-2 mg/day**~~ **OR** Is patient taking a statin and is unable to take a fibric acid derivative due to an increased risk of myopathy?	**Yes:** Approve up to 1 year.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of other agent(s).

Table 1: Dosing of fenofibrate and derivatives for hypertriglyceridemia

Drug	Recommended dose	Maximum dose
Antara (micronized)	43-130 mg once daily	130 mg once daily
Fenoglide	40-120 once daily	120 mg once daily
Fibricor	25-105 mg once daily	105 mg once daily
Lipofen	50-150 mg once daily	150 mg once daily
Lofibra (micronized)	67-200 mg once daily	200 mg once daily
Lofibra (tablets_	54-160 mg once daily	160 mg once daily
TriCor	48-145 mg once daily	145 mg once daily
Triglide	50-160 mg once daily	160 mg once daily
Trilipix	45-135 mg once daily	135 mg once daily
Gemfibrozil	600 mg twice daily	600 mg twice daily

P&T/DUR Review: *11/16 (DM); 3/14*
Implementation: *5/1/14*

PCSK9 Inhibitors

Goal:

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

Length of Authorization:

- Up to 12 months

Requires PA:

- All PCSK9 inhibitors

Covered Alternatives:

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

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	**Yes:** Go to Renewal Criteria	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Does the patient have clinical atherosclerotic CV disease, defined as documented history of ≥1 of the following: • Myocardial infarction • Unstable angina • Coronary revascularization procedure (PCI or CABG) • Diagnosis of clinically significant coronary heart disease by coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging	**Yes:** Go to #4	**No:** Go to #6

Approval Criteria		
4. Has the patient taken a daily high-intensity statin (see table below) and ezetimibe 10 mg daily for at least 12 months with <50% LDL-C reduction? Prescriber to submit chart documentation of: 1) Doses and dates initiated of statin and ezetimibe; 2) Baseline LDL-C (untreated); 3) Recent LDL-C (within last 12 weeks).	**Yes:** Confirm documentation; go to #5 1. Statin: Dose: Date Initiated: 2. Ezetimibe 10 mg daily Date Initiated: Baseline LDL-C _____ mg/dL Date:_____ Recent LDL-C _____ mg/dL Date:_____	**No:** Go to #6
5. Is the patient adherent with a high-intensity statin and ezetimibe?	**Yes:** Approve for up to 12 months Note: pharmacy profile may be reviewed to verify >80% adherence (both lipid-lowering prescriptions refilled 5 months' supply in last 6 months)	**No:** Pass to RPh. Deny; medical appropriateness
6. Does the patient have a history of rhabdomyolysis caused by a statin; or alternatively, a history of creatinine kinase (CK) levels >10-times upper limit of normal with muscle symptoms determined to be caused by a statin? Note: Prescriber must provide chart documentation of diagnosis or CK levels. A recent LDL-C level (within last 12 weeks) must also be submitted.	**Yes:** Confirm chart documentation of diagnosis or labs and approve for up to 12 months Recent LDL-C _____ mg/dL Date:_____	**No:** Go to #7

Approval Criteria		
7. Does the patient have a diagnosis of homozygous or heterozygous familial hypercholesterolemia and already takes a maximally tolerated statin and/or ezetimibe? Note: Prescriber must provide chart documentation of diagnosis and recent LDL-C (within last 12 weeks).	**Yes:** Document diagnosis and approve for up to 12 months Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh. Deny; medical appropriateness.

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

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

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

References:
1. NICE Clinical Guideline 181. Lipid modification: CV risk assessment and the modification of blood lipids for the primary and secondary prevention of CV disease. Available at: guidance.nice.org.uk/cg181. Accessed 18 September 2015.

2. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic CV Risk in Adults. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;129(25 Suppl 2):S1-45. doi: 10.1161/01.cir.0000437738.63853.7a.

P&T Review: *11/16 (DM); 11/15*
Implementation: *1/1/16*

Mipomersen and Lomitapide

Goal(s):

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

Length of Authorization:

Up to 6 months

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the drug prescribed by or in consultation with a specialist in lipid disorders?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis homozygous familial hypercholesterolemia?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient tried and failed or does the patient have a medical contraindication to maximum lipid lowering therapy with a combination of traditional drugs (high-intensity statin with ezetimibe; see Table 1)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5.Has the patient failed or are they not appropriate for LDL-C apheresis **OR** Is LDL-C apheresis not available to them?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Table 1. High-intensity Statins.

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

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

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