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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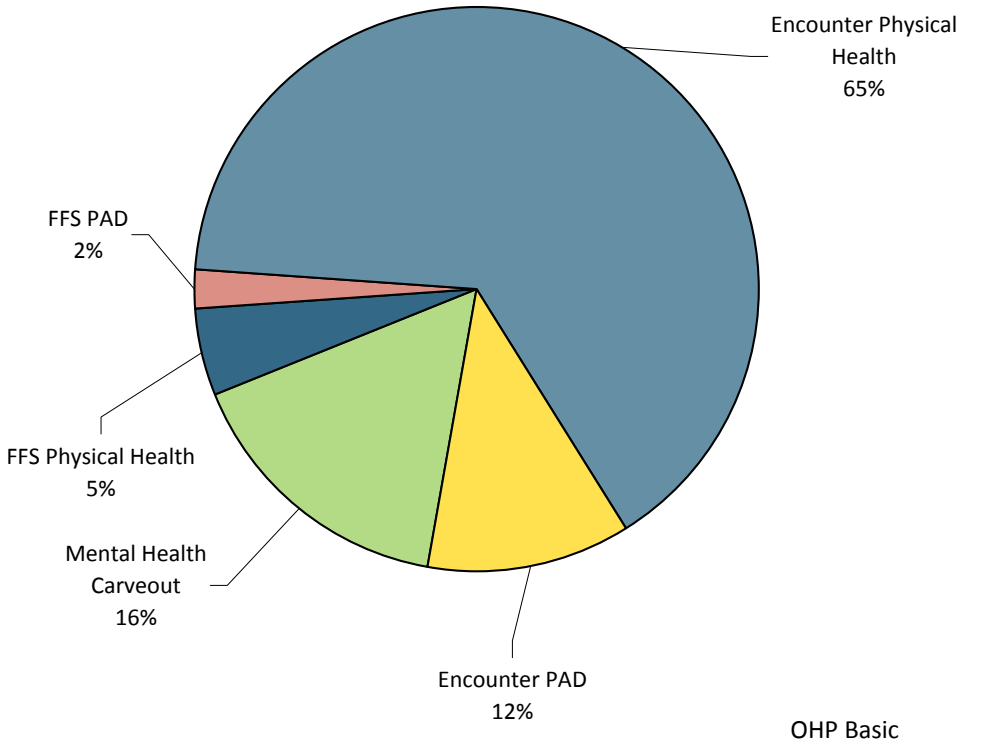
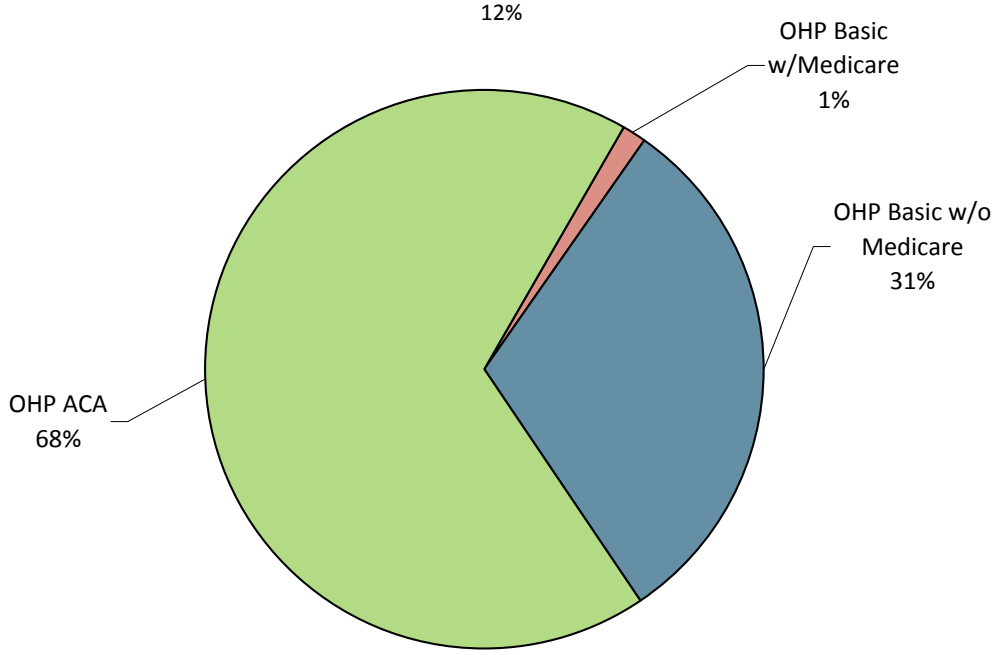
Pharmacy Utilization Summary Report: April 2015 - March 2016

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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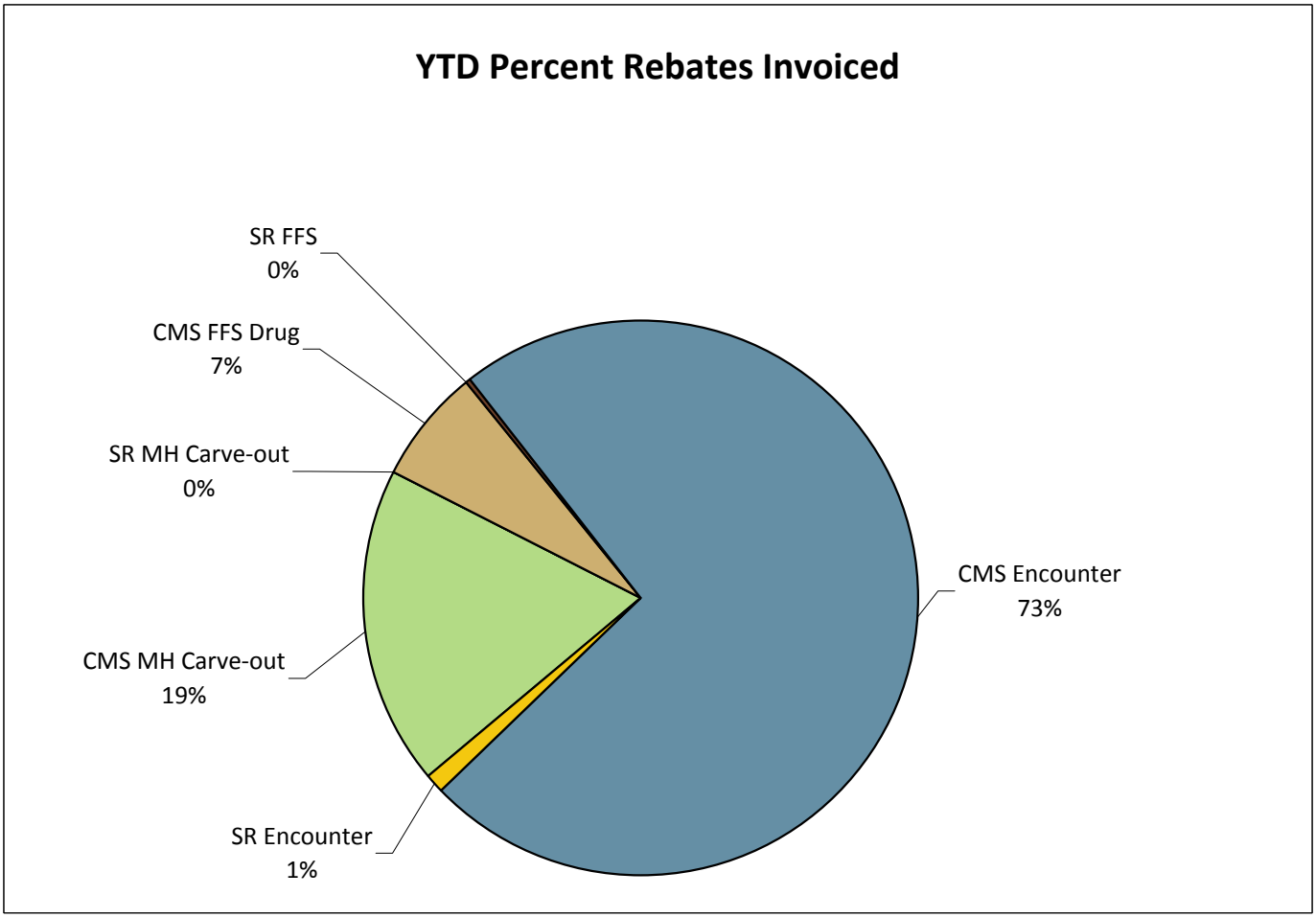
Pharmacy Utilization Summary Report: April 2015 - March 2016

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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June 2016 Volume 6, Issue 4

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.

THE OREGON STATE DRUG REVIEW©
AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter
July 2016 Volume 6, Issue 5

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]

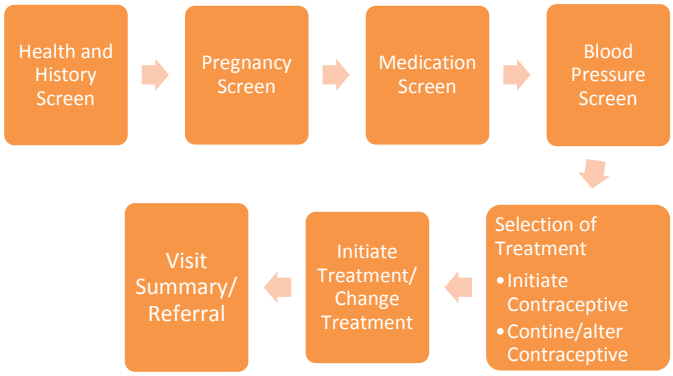
The Comprehensive Contraceptive Education and Training for Prescribing Pharmacists program is comprised of the following objectives:[6]

- 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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August 2016 Volume 6, Issue 6

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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October 2016 Volume 6, Issue 7

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**.

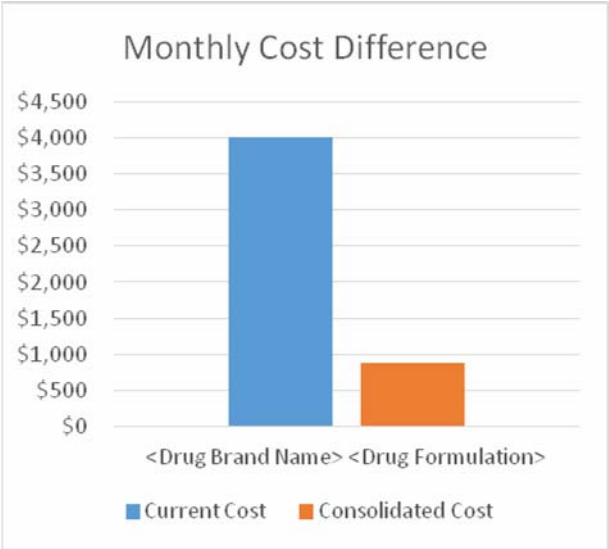
Please evaluate each patient for a **voluntary change** to a dose optimized regimen. Please take the time to review the forms and discuss them with your patient(s) as necessary.

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]