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

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, July 30, 2015 1:00 - 5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING AGENDA

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

I. CALL TO ORDER
- A. Roll Call & Introductions — R. Citron (OSU)
- B. Conflict of Interest Declaration — R. Citron (OSU)
- C. Approval of Agenda and Minutes — B. Origer (Chair)
- D. Department Update — L. Saris (OHA)

II. DUR ACTIVITIES
- A. Quarterly Utilization Reports — R. Citron (OSU)
- B. ProDUR Report — R. Holsapple (HP)
- C. RetroDUR Report — T. Williams (OSU)

III. DUR OLD BUSINESS
- A. Ivacaftor Prior Authorization Criteria — M. Herink (OSU)
  1. Revised Drug Update and PA Criteria
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA
- B. Pediatric SSRI High Dose Prior Authorization Criteria — T. Williams (OSU)
  1. Revised Criteria
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA
- C. Rifaximin Prior Authorization Criteria — A. Gibler (OSU)
  1. Revised Criteria
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA
- D. Codeine Prior Authorization Criteria — A. Gibler (OSU)
  1. Codeine Criteria for Pediatric Population
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA
- E. Leuprolide Hormone Therapy Prior Authorization Criteria — A. Gibler (OSU)

1. Revised Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

IV. DUR NEW BUSINESS

A. HIV Class Review / Drug Use Evaluation — A. Gibler / K. Ketchum (OSU)
1. Class Review
2. Drug Use Evaluation
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

B. Antiplatelet Class Update / Policy Evaluation — M. Herink / K. Ketchum (OSU)
1. Class Update
2. Policy Evaluation
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

C. Tetracyclines Drug Use Evaluation — T. Williams (OSU)
1. Drug Use Evaluation
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

D. Low Dose Quetiapine Policy Evaluation — A. Meeker / M. Herink (OSU)
1. Policy Evaluation
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

E. Modafinil/Armodafinil Drug Use Evaluation — K. Ketchum (OSU)
1. Drug Use Evaluation
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

F. Clinical Review of Existing Prior Authorization Criteria — A. Gibler (OSU)
1. Tesamorelin for injection
2. Becaplermin topical gel
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

V. PREFERRED DRUG LIST NEW BUSINESS

A. Secukinumab New Drug Evaluation — S. Willard (OSU)
1. Secukinumab (Cosentyx™) New Drug Evaluation
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

B. Idiopathic Pulmonary Fibrosis New Drug Evaluations — A. Gibler (OSU)
1. Pirfenidone New Drug Evaluation
2. Nintedanib New Drug Evaluation
2. Public comment
3. Discussion of Clinical Recommendations to OHA

C. Intranasal Allergy Inhalers Class Review — A. Gibler (OSU)
1. Class Review
2. Public comment
3. Discussion of Clinical Recommendations to OHA

D. Antifungals Class Update — K. Ketchum (OSU)
1. Class Update
2. Isavuconazole (Cresemba®) New Drug Evaluation
3. Public comment
4. Discussion of Clinical Recommendations to OHA

E. Calcium Channel Blockers Class Update — K. Vu (OSU)
1. Class Update
2. Public comment
3. Discussion of Clinical Recommendations to OHA

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. ADJOURN

Drug Use Research & Management Program
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Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Medical Director	Corvallis	December 2017
Caryn Mickelson, Pharm.D.	Pharmacist	Pharmacy Director	Coos Bay	December 2017
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2017
Arturo Salazar, M.D.	Physician	Pediatric Internist	Eugene	December 2017
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2017
Dave Pass, M.D.	Physician	Medical Director	West Linn	December 2016
Stacy Ramirez, Pharm.D.	Pharmacist	Community Pharmacist	Albany	December 2016
Kathryn Lueken, M.D., M.M.M.	Physician	Medical Director	Salem	December 2016
Cathy Zehrung, R.Ph.	Pharmacist	Pharmacy Manager	Silverton	December 2015
Phil Levine, Ph.D.	Public	Retired	Lake Oswego	December 2015
Vacant	Physician			December 2015

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, May 28, 2015 1:00-5:00 PM
Wilsonville Training Center
29353 SW Town Center
Wilsonville, OR 97070

MEETING MINUTES

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

Members Present: Cathy Zehrung, RPh; Phillip Levine, PhD; Tracy Klein, PhD., FNP;

Members Present by Phone: Kathryn Lueken, MD; James Slater, PharmD; Caryn Mickelson, PharmD; Dave Pass, MD; James Slater, PharmD; Stacy Ramirez, PharmD;

Staff Present: Kathy Ketchum, RPh, MPA:HA; Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD; Shannon Jasper; Amanda Meeker, PharmD; Andrew Gibler, PharmD; Dee Weston; Jamal Furqan; Linnea Saris;

Staff Present by Phone:

Audience: Barry Benson (Merck), Connie Brooks (Vertex); Gregg Rasmussen (Vertex); Shane Hall (Purdue); Paul Bonham (Novo); Diana Dills (Pfizer)*; Bob Gustafson (Lundbeck); Lee Stout (Chiesi); Steve hall (Boehringer Ingelheim)*; Jim Graves (BMS); Saumya 'Mia' Varghese , student; Theresa Gatti, student; Patrick Moty (Supernus); Samantha Min (Otsuka); Jamie Tobitt (Vertex)*; Don Stecher (Novartis); Mike Willitt (Pfizer); Mary Kernhus (Novartis); Tracey Meeks (Vertex); Jeana Colabianchi (Sunovion); William Davis (Astellas); Venus Holder (Lilly); Stephanie Kendall (J&J); Dr. Michael Powers (OHSU)*;

(*) Provided verbal testimony

I. CALL TO ORDER

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

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

c. Approval of agenda and minutes presented by Dr. Klein after correction of name. (pages 1 - 7)

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

d. Department updates for OHA.

II. DUR ACTIVITIES

a. Quarterly Utilization Reports (pages 8 - 12)
   Mr. Citron presented the quarterly utilization report.
b. ProDUR Report (pages 13 – 15)
   Mr. Holsapple presented the quarterly ProDUR reports.

c. RetroDUR Report (pages 16 – 19)
   Dr. Williams presented the quarterly RetroDUR reports.

d. Oregon State Drug Reviews (pages 20 – 23)
   Dr. Sentena presented the following reviews:
   1. Evaluation of High Dose SSRI Initiation in Pediatrics
   2. The Opioid Epidemic: Are Abuse-deterrent Formulations the Answer?

III. DUR OLD BUSINESS

a. PDL Status of Simeprevir (pages 24 - 29)
   Dr. Herink clarified the following status:

   1. Make Olysio non-preferred on PMPDP.

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

b. Pediatric SSRI High Dose DUE Clarification (pages 30 - 41)
   Dr. Williams presented the following clarification:

   1. Maximum initial dose for children <5 years old.
   2. Will bring back to the July meeting, add criteria for consultation for prescribers that are not psychiatric specialists.

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

c. Tapering Clarification for PPI PA Criteria (pages 42 - 45)
   Dr. Gibler presented the following clarification and PA criteria update:

   1. Approve updated PA criteria.
   2. Retrospective DUR education, contact prescribers thru licensing boards, end grandfather for existing chronic users after one year.

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

IV. DUR NEW BUSINESS

a. Ivacaftor Drug / Policy Update (pages 46 – 55)
   Dr. Herink presented the following updates:

1. Await published data supporting statistically significant improvements in FEV1, or other clinically relevant outcomes, in patients with the R117H mutation in the CFTR gene and in pediatric patients aged 2 to 5 years before approving use in these populations.
2. Expand Cystic Fibrosis Class to include non-inhaled products.

Public Comment:
Jamie Tobitt from Vertex.
Dr. Michael Powers from OHSU.

***ACTION:** After executive session. All in Favor. Approved
3. *Defer action, request clinical criteria improvement for specific to age group 2-5.
4. *Bring back to the July meeting for follow up.

b. Oral Anticoagulants Class Update / Policy Evaluation (pages 56 – 88)
Dr. Sentena and Ms. Ketchum presented the following class update and policy evaluation:

1. Discontinue the clinical PA requirement for all DOACs.
2. Develop a Retrospective DUR program to monitor appropriate dosing and use in the presence of contraindications.
3. Review utilization in one year.

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

4. *Make all DOACs preferred.

Public Comment:
Dr. Diana Dills from Pfizer.
Steve Hall from Boehringer Ingelheim.

c. Leuprolide Drug / Policy Update (pages 89 – 93)
Dr. Meeker presented the following drug update and policy:

1. Modify PA criteria allow approval of leuprolide in adolescents with documented gender dysphoria at the beginning of puberty confirmed by pubertal levels of hormone but no earlier than Tanner stages 2-3.
2. Add must be “Prescribed by Pediatric Endocrinologist” to criteria.

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

V. PREFERRED DRUG LIST NEW BUSINESS

a. Otic Antibiotics Class Update (pages 94 – 101)
Dr. Gibler presented the following class update:

1. Keep either ofloxacin or ciprofloxacin / dexamethasone as a preferred product for treatment of acute otitis media in patients with tympanostomy tubes.
2. Keep at least one ototopical aminoglycoside antibiotic as an option for otitis externa.
3. Maintain finafloxacin as non-preferred due to its limited indication for otitis externa only and lack of comparative evidence, unless it is cost-effective.
4. Evaluate comparative costs in executive session.

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

5. Make finafloxacin non-preferred when added to the drug file.

b. Oxazolidinone Antibiotic Class Review (pages 102 – 111)
Ms. Ketchum presented the following class review:

1. Create a new Preferred Drug List Oxazolidinone Antibiotics Class including linezolid and tedizolid.
2. Prefer linezolid because of proven benefit.
3. Implement proposed PA criteria.

ACTION: Motion, 2nd, all in favor. Approved.

4. *Make tedizolid non-preferred.

c. Rifaximin New Drug Evaluation (pages 112 – 123)
Dr. Gibler presented the following drug evaluation:

1. Implement proposed criteria after removing criteria #3 of PA criteria.

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

d. Drug Class Literature Scans

1. Antibiotics for *Clostridium difficile* infection (pages 124 – 132)
Dr. Gibler presented the following class scan:

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

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

c. *No PMPDP changes recommended.

2. Fluoroquinolones (pages 133 – 142)
Dr. Gibler presented the following class scan:

a. Continue to maintain at least one FQ with broad coverage of gram-negative bacteria (ciprofloxacin, levofloxacin) and at least one “respiratory” third generation FQ (gemifloxacin, levofloxacin, moxifloxacin).
b. No further review or research needed at this time.
c. Evaluate comparative costs in executive session.

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

d. *No PMPDP changes recommended.

3. Ophthalmic Anti-inflammatory Drugs (pages 143 – 160)
Dr. Gibler presented the following class scan:

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

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

c. *No PMPDP changes recommended.

4. Inhaled Cystic Fibrosis Drugs (pages 161 – 165)
   Dr. Herink presented the following class scan:

   a. Maintain at least one formulation of either inhaled tobramycin or aztreonam as preferred on the PDL for the treatment of chronic infection with *P. aeruginosa*.
   b. Evaluate comparative cost in executive session.

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

   c. *Make Tobi Podhaler and KITABIS PAK preferred and accept SR and make Kalydeco non-preferred.

5. Gout Agents (pages 166 – 170)
   Dr. Herink presented the following class scan:

   a. Continue to include one xanthine oxidase inhibitor as preferred on the PMPDP for the treatment of chronic gout and hyperuricemia.
   b. No further review or research needed.
   c. Evaluate comparative costs in executive session.

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

   d. *No PMPDP changes recommended.

6. Short-acting Opioids (pages 171 – 182)
   Dr. Meeker presented the following class scan:

   a. Update current PA criteria for excessive dose limits on opioid / non-narcotic combination products and remove deleted products.
   b. No further review or research needed at this time.
   c. Evaluate comparative costs in executive session.

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

   d. *Make all rectal subclass products, all ACETAMINOPHEN WITH CODEINE products and all ibuprofen containing products preferred on the PMPDP and make all butalbital products non-preferred.
   e. *Maintain liquid hydrocodone / APAP 500 mg formulation in table.
   f. *Age restrictions on all codeine products from 0 – 6 years of age. PA required.
   g. *Add hydrocodone / APAP solution as a preferred agent.

7. Tetracyclines (pages 183 – 189)
   Dr. Williams presented the following class scan:

   a. Recommend inclusion of one or more agents from this class including doxycycline.
   b. No further review or research needed at this time.
   c. Evaluate comparative costs in executive session.

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

   d. *No PMPDP changes recommended.

8. DERP Scan Summaries
    a. Second-generation Antihistamines (pages 190 – 208)
    Dr. Gibler presented the following class scan:

        1. Update PA criteria with minor administrative edits.
        2. No further review or research needed at this time.
        3. Evaluate comparative costs in executive session.

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

        4. *No PMPDP changes recommended.

    b. Beta-blockers (pages 209 – 224)
    Dr. Gibler presented the following class scan:

        1. Based on previous recommendations, prefer either carvedilol or metoprolol succinate; as well as either acebutolol, carvedilol, metoprolol tartrate, propranolol or timolol; and either atenolol, nadolol, propranolol or propranolol extended-release.
        2. No further review or research needed.
        3. Evaluate comparative costs in executive session.

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

        4. *Add metoprolol succinate to the PMPDP as preferred.

    c. Overactive Bladder Drugs (pages 225 – 238)
    Dr. Gibler presented the following class scan:

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

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

        3. *No PMPDP changes recommended.

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

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Pharmacy Utilization Summary Report: January 2014 - December 2014

Eligibility	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Avg Monthly
Total Members (FFS & Encounter)	819,426	852,414	899,321	933,189	961,855	969,341	981,835	997,487	1,008,231	1,021,045	977,740	998,873	951,730
FFS Members	140,103	133,822	155,785	137,326	138,745	136,943	132,379	140,158	134,462	132,913	140,236	139,950	138,569
OHP Basic with Medicare	27,575	27,629	27,787	27,903	28,145	28,393	28,468	28,659	28,804	29,015	29,111	29,136	28,385
OHP Basic without Medicare	26,374	24,867	24,408	24,179	24,696	24,989	24,836	24,911	24,494	23,833	21,350	18,720	23,971
ACA	83,884	79,176	99,440	82,228	82,479	80,139	79,075	86,588	81,164	80,065	89,775	92,094	84,676
Encounter Members	679,323	718,592	743,536	795,863	823,110	832,398	849,456	857,329	873,769	888,132	837,504	858,923	813,161
OHP Basic with Medicare	37,758	37,903	38,017	38,134	38,244	38,302	38,419	38,620	38,770	38,810	38,812	38,946	38,395
OHP Basic without Medicare	227,448	228,120	227,677	226,830	224,805	222,503	220,955	219,511	215,256	205,287	164,063	131,637	209,508
ACA	413,355	450,189	474,533	524,688	552,052	562,718	590,082	599,198	619,743	644,035	634,629	688,340	562,797

Gross Cost Figures for Drugs	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	YTD Sum
Total Amount Paid (FFS & Encounter)	$40,938,327	$40,941,196	$45,238,634	$43,117,443	$47,202,933	$49,946,699	$53,132,675	$50,738,874	$54,183,983	$56,958,136	$49,846,206	$58,946,093	$591,191,199
Mental Health Carve-Out Drugs	$8,909,476	$8,432,230	$9,404,959	$9,878,456	$10,180,980	$10,281,236	$10,921,674	$10,588,025	$11,072,974	$11,558,114	$10,236,122	$11,028,779	$122,493,026
OHP Basic with Medicare	$9,185	$12,723	$13,217	$10,812	$13,664	$9,967	$4,573	$5,442	$2,452	$5,630	$6,949	$10,422	$105,036
OHP Basic without Medicare	$6,295,791	$5,682,206	$6,124,180	$6,222,199	$6,157,090	$6,158,408	$6,348,075	$6,058,902	$6,191,009	$6,281,657	$5,362,128	$5,468,698	$72,350,342
ACA	$2,580,219	$2,715,366	$3,246,275	$3,623,617	$3,945,852	$4,026,349	$4,470,302	$4,438,711	$4,785,138	$5,188,930	$4,801,929	$5,505,669	$49,328,356
FFS Physical Health Drugs	$3,592,519	$3,478,073	$3,436,172	$3,327,528	$3,275,037	$3,348,501	$3,394,260	$3,222,584	$3,477,819	$3,449,164	$3,306,505	$3,792,580	$41,100,744
OHP Basic with Medicare	$274,554	$247,884	$268,493	$265,906	$278,862	$269,577	$270,866	$240,008	$244,614	$246,416	$228,081	$251,397	$3,086,657
OHP Basic without Medicare	$1,692,212	$1,616,927	$1,525,120	$1,450,688	$1,430,593	$1,419,716	$1,360,975	$1,254,951	$1,444,294	$1,375,246	$1,212,628	$1,292,974	$17,076,324
ACA	$1,559,845	$1,536,132	$1,563,485	$1,525,057	$1,478,133	$1,571,387	$1,665,913	$1,640,058	$1,706,537	$1,744,438	$1,792,657	$2,168,255	$19,951,897
FFS Physician Administered Drugs	$1,646,151	$1,233,892	$1,405,829	$1,498,879	$1,442,472	$1,580,677	$1,379,064	$1,525,864	$1,848,586	$1,669,336	$1,356,975	$1,384,121	$17,971,846
OHP Basic with Medicare	$151,443	$113,323	$167,654	$185,345	$132,200	$220,708	$182,939	$154,986	$155,504	$177,379	$134,520	$178,784	$1,954,785
OHP Basic without Medicare	$565,764	$465,818	$411,295	$646,491	$442,913	$562,692	$425,879	$443,656	$531,028	$423,735	$500,987	$282,212	$5,702,469
ACA	$569,447	$382,452	$613,897	$448,192	$647,791	$600,722	$561,857	$676,180	$940,237	$869,638	$556,360	$752,134	$7,618,908
Encounter Physical Health Drugs	$21,225,746	$22,560,175	$25,909,357	$22,806,704	$26,308,077	$28,738,858	$30,274,471	$29,412,182	$31,254,252	$32,951,469	$28,975,978	$35,588,090	$336,005,359
OHP Basic with Medicare	$258,176	$226,586	$188,096	$156,053	$177,887	$196,505	$193,686	$195,549	$201,593	$199,118	$196,335	$196,602	$2,386,186
OHP Basic without Medicare	$12,273,560	$12,275,984	$13,326,665	$11,269,475	$12,485,630	$13,205,678	$13,846,045	$12,792,727	$13,269,767	$13,430,639	$10,864,216	$12,333,488	$151,373,873
ACA	$8,569,106	$9,965,122	$12,284,919	$11,202,852	$13,319,740	$14,986,265	$15,901,806	$16,121,818	$17,480,482	$19,038,154	$17,643,983	$22,871,059	$179,385,305
Encounter Physician Administered Drugs	$5,564,435	$5,236,826	$5,082,318	$5,605,876	$5,996,367	$5,997,427	$7,163,205	$5,990,217	$6,530,351	$7,330,054	$5,970,626	$7,152,523	$73,620,225
OHP Basic with Medicare	$227,381	$200,491	$167,211	$174,757	$188,679	$184,374	$202,856	$175,051	$154,676	$191,303	$146,010	$143,961	$2,156,750
OHP Basic without Medicare	$2,993,046	$2,461,527	$2,270,622	$2,387,668	$2,532,198	$2,529,826	$3,429,246	$2,440,759	$2,441,705	$2,600,487	$2,120,459	$2,270,033	$30,477,574
ACA	$1,660,317	$2,033,686	$2,267,530	$2,626,395	$2,925,843	$3,053,679	$3,308,490	$3,165,076	$3,680,274	$4,277,813	$3,540,664	$4,555,709	$37,095,476

OHP = Oregon Health Plan
ACA = Affordable Care Act expansion

Last Updated: July 26, 2015

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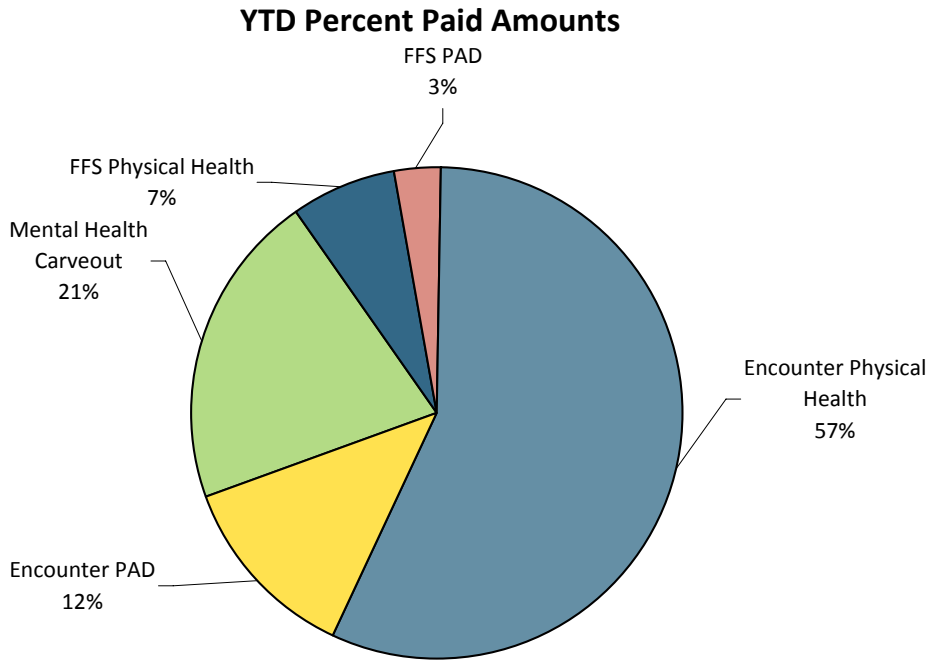
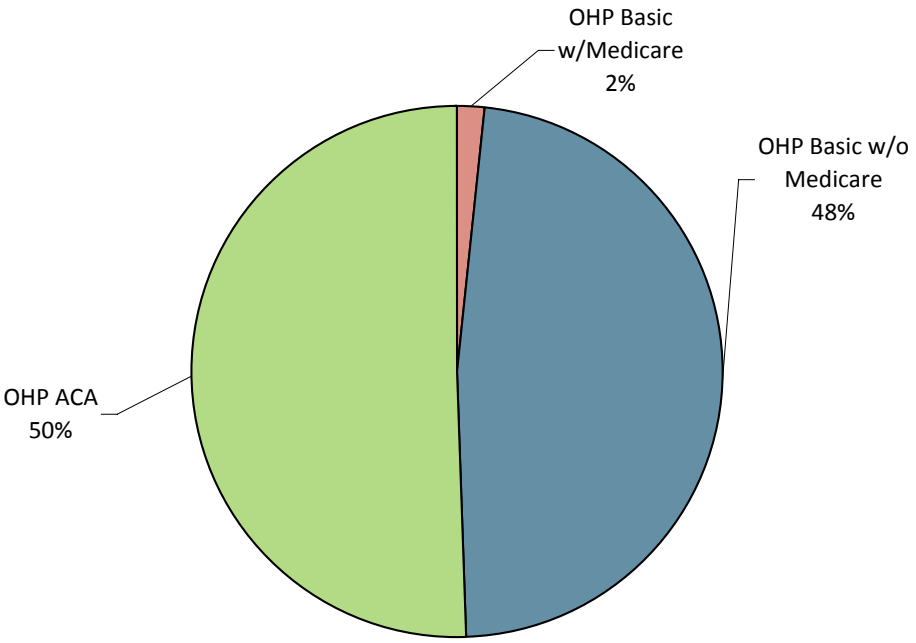
Pharmacy Utilization Summary Report: January 2014 - December 2014





OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
PAD = Physician-administered drugs

Last Updated: July 26, 2015

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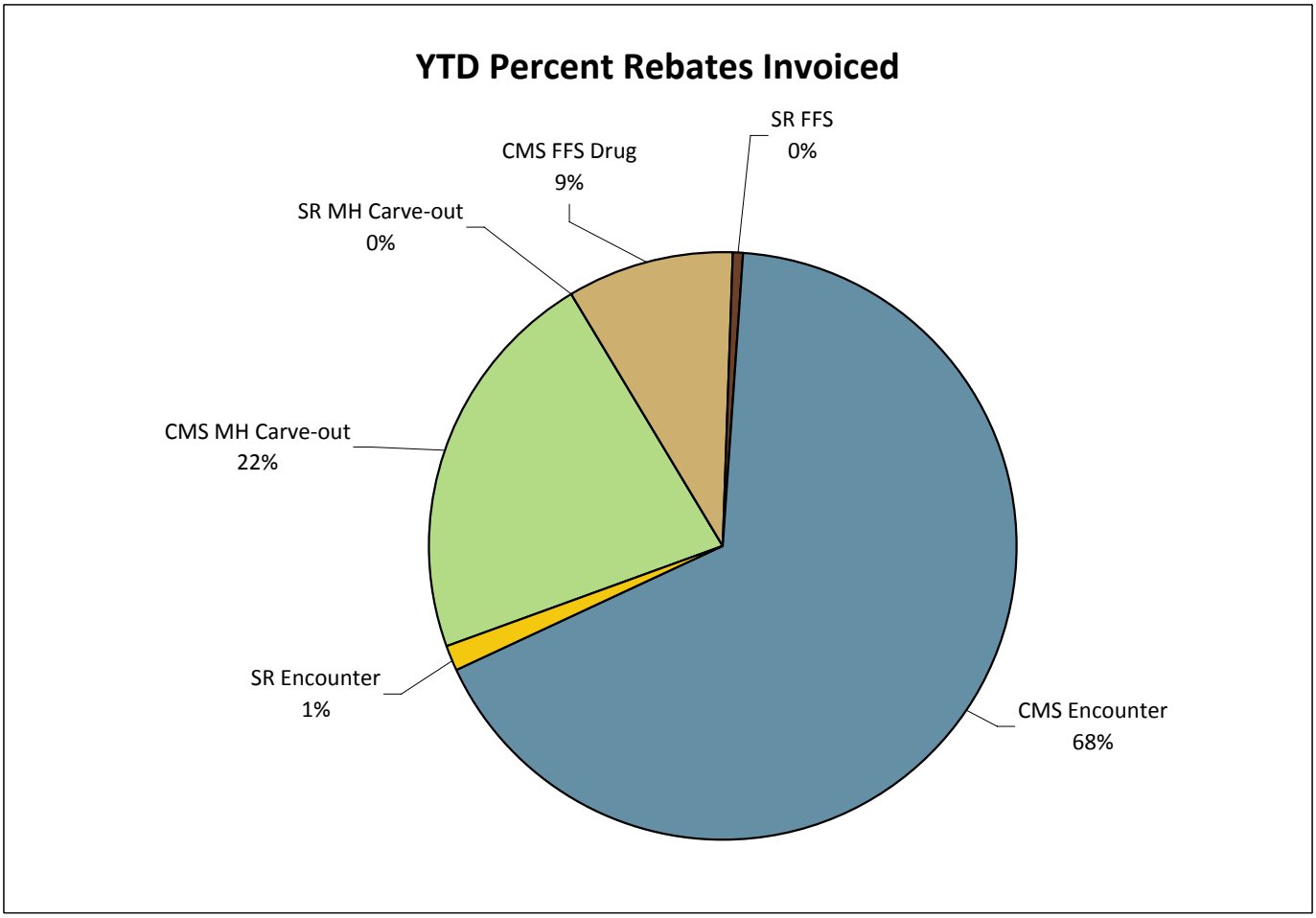
Pharmacy Utilization Summary Report: January 2014 - December 2014

Quarterly Rebates Invoiced	2014-Q1	2014-Q2	2014-Q3	2014-Q4	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$54,149,556	$67,019,848	$69,307,450	$75,634,200	$266,111,053
CMS MH Carve-out	$13,046,450	$14,644,358	$15,135,883	$15,228,555	$58,055,245
SR MH Carve-out		$62,641		$64,807	$127,447
CMS FFS Drug	$5,903,465	$6,059,538	$6,062,304	$6,560,269	$24,585,575
SR FFS	$495,250	$236,982	$229,999	$257,828	$1,220,059
CMS Encounter	$34,090,757	$45,109,954	$47,080,661	$52,460,278	$178,741,650
SR Encounter	$613,634	$906,375	$798,603	$1,062,464	$3,381,076

Quaterly Net Drug Costs	2014-Q1	2014-Q2	2014-Q3	2014-Q4	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$72,968,602	$73,247,227	$88,748,081	$90,116,236	$325,080,146
Mental Health Carve-Out Drugs	$13,700,215	$15,633,674	$17,446,790	$17,529,654	$64,310,333
FFS Phys Health + PAD	$8,393,922	$8,176,573	$8,555,877	$8,140,584	$33,266,956
Encounter Phys Health + PAD	$50,874,465	$49,436,980	$62,745,414	$64,445,998	$227,502,857



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

Last Updated: July 26, 2015

Drug Use Research & Management Program
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Pharmacy Utilization Summary Report: January 2014 - December 2014

PMPM Drug Costs (Excludes Rebate)	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$49.96	$48.03	$50.30	$46.20	$49.07	$51.53	$54.12	$50.87	$53.74	$55.78	$50.98	$59.01	$51.63
Mental Health Carve-Out Drugs	$10.87	$9.89	$10.46	$10.59	$10.58	$10.61	$11.12	$10.61	$10.98	$11.32	$10.47	$11.04	$10.71
FFS Physical Health Drugs	$25.64	$25.99	$22.06	$24.23	$23.60	$24.45	$25.64	$22.99	$25.86	$25.95	$23.58	$27.10	$24.76
FFS Physician Administered Drugs	$11.75	$9.22	$9.02	$10.91	$10.40	$11.54	$10.42	$10.89	$13.75	$12.56	$9.68	$9.89	$10.84
Encounter Physical Health Drugs	$31.25	$31.39	$34.85	$28.66	$31.96	$34.53	$35.64	$34.31	$35.77	$37.10	$34.60	$41.43	$34.29
Encounter Physician Administered Drugs	$8.19	$7.29	$6.84	$7.04	$7.29	$7.20	$8.43	$6.99	$7.47	$8.25	$7.13	$8.33	$7.54

Claim Counts	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Avg Monthly
Total Claim Count (FFS & Encounter)	756,249	755,906	864,161	879,470	903,745	914,248	944,871	914,947	958,673	1,008,538	874,488	978,481	896,148
Mental Health Carve-Out Drugs	113,660	109,878	124,571	130,358	134,503	134,086	140,589	136,822	142,387	148,426	132,301	151,810	133,283
FFS Physical Health Drugs	77,622	71,089	78,886	77,358	79,745	79,751	78,357	76,610	79,062	80,070	75,779	80,910	77,937
FFS Physician Administered Drugs	17,284	14,326	14,492	14,970	13,835	13,304	13,231	13,450	12,418	13,142	11,973	12,160	13,715
Encounter Physical Health Drugs	488,766	506,522	581,975	583,767	600,677	612,785	635,528	615,702	650,358	687,792	587,284	660,255	600,951
Encounter Physician Administered Drugs	58,917	54,091	64,237	73,017	74,985	74,322	77,166	72,363	74,448	79,108	67,151	73,346	70,263

Amount Paid per Claim (Excludes Rebate)	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$54.13	$54.16	$52.35	$49.03	$52.23	$54.63	$56.23	$55.46	$56.52	$56.48	$57.00	$60.24	$54.87
Mental Health Carve-Out Drugs	$78.39	$76.74	$75.50	$75.78	$75.69	$76.68	$77.69	$77.39	$77.77	$77.87	$77.37	$72.65	$76.63
FFS Physical Health Drugs	$46.28	$48.93	$43.56	$43.01	$41.07	$41.99	$43.32	$42.06	$43.99	$43.08	$43.63	$46.87	$43.98
FFS Physician Administered Drugs	$95.24	$86.13	$97.01	$100.13	$104.26	$118.81	$104.23	$113.45	$148.86	$127.02	$113.34	$113.83	$110.19
Encounter Physical Health Drugs	$43.43	$44.54	$44.52	$39.07	$43.80	$46.90	$47.64	$47.77	$48.06	$47.91	$49.34	$53.90	$46.41
Encounter Physician Administered Drugs	$94.45	$96.82	$79.12	$76.77	$79.97	$80.70	$92.83	$82.78	$87.72	$92.66	$88.91	$97.52	$87.52

Amount Paid per Claim - Multi Source Drugs (Excludes Rebate)	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$28.04	$27.71	$26.97	$25.20	$26.62	$26.85	$26.72	$26.88	$26.89	$26.87	$27.07	$27.03	$26.90
Mental Health Carve-Out Drugs	$62.58	$61.49	$60.20	$60.25	$60.42	$60.92	$61.73	$61.30	$61.38	$61.69	$60.78	$54.71	$60.62
FFS Physical Health Drugs	$22.39	$22.27	$21.67	$21.72	$21.92	$21.99	$22.26	$22.10	$21.97	$21.46	$21.68	$22.00	$21.95
Encounter Physical Health Drugs	$20.59	$20.90	$20.36	$17.59	$19.44	$19.80	$19.27	$19.56	$19.65	$19.67	$19.88	$21.07	$19.81

Amount Paid per Claim - Single Source Drugs (Excludes Rebate)	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$328.18	$364.88	$369.09	$336.45	$369.87	$400.73	$414.92	$405.47	$387.42	$371.19	$399.85	$451.42	$383.29
Mental Health Carve-Out Drugs	$438.69	$433.81	$432.24	$437.96	$437.83	$452.20	$461.31	$458.94	$457.61	$452.85	$461.02	$472.86	$449.78
FFS Physical Health Drugs	$314.59	$354.85	$303.74	$308.60	$283.71	$297.29	$308.82	$298.61	$309.90	$301.38	$313.54	$353.42	$312.37
Encounter Physical Health Drugs	$316.47	$357.76	$371.00	$326.97	$373.08	$408.24	$422.77	$412.14	$388.53	$369.94	$403.32	$460.65	$384.24

Multi-Source Drug Use Percentage	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Avg Monthly
Multi-Source Drug Use Percentage	92.8%	93.3%	93.5%	93.5%	93.5%	93.5%	93.4%	93.3%	92.9%	92.6%	92.9%	93.1%	93.2%
Mental Health Carve-Out Drugs	95.8%	95.9%	95.9%	95.9%	96.0%	96.0%	96.0%	96.0%	95.9%	95.9%	95.9%	95.7%	95.9%
FFS Physical Health Drugs	91.8%	92.0%	92.2%	92.6%	92.7%	92.7%	92.7%	92.8%	92.4%	92.3%	92.5%	92.5%	92.4%
Encounter Physical Health Drugs	92.3%	93.0%	93.1%	93.1%	93.1%	93.0%	93.0%	92.8%	92.3%	91.9%	92.3%	92.5%	92.7%

Preferred Drug Use Percentage	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Avg Monthly
Preferred Drug Use Percentage	85.97%	86.06%	86.28%	86.23%	85.96%	86.03%	86.13%	86.08%	86.40%	86.49%	86.42%	86.47%	86.2%
Mental Health Carve-Out Drugs	74.11%	74.36%	74.46%	74.46%	73.35%	73.24%	73.12%	73.05%	75.82%	77.03%	77.11%	76.83%	74.7%
FFS Physical Health Drugs	93.72%	93.56%	93.55%	93.57%	93.66%	93.88%	94.36%	94.57%	94.46%	94.60%	94.83%	94.63%	94.1%
Encounter Physical Health Drugs	87.97%	87.95%	88.21%	88.29%	88.19%	88.23%	88.15%	88.08%	87.91%	87.76%	87.57%	87.79%	88.0%

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	ABILIFY	Antipsychotics, 2nd Gen	$11,749,557	26.0%	12,430	$945	V
2	LATUDA	Antipsychotics, 2nd Gen	$2,177,624	4.8%	2,886	$755	V
3	SEROQUEL XR	Antipsychotics, 2nd Gen	$1,816,088	4.0%	3,085	$589	V
4	STRATTERA	ADHD Drugs	$1,612,252	3.6%	4,857	$332	Y
5	INTUNIV	ADHD Drugs	$1,442,348	3.2%	4,992	$289	V
6	INVEGA SUSTENNA	Antipsychotics, Parenteral	$1,049,112	2.3%	733	$1,431	V
7	INVEGA	Antipsychotics, 2nd Gen	$861,790	1.9%	925	$932	V
8	DULOXETINE HCL	Antidepressants	$673,057	1.5%	23,104	$29	V
9	FLUOXETINE HCL	Antidepressants	$556,148	1.2%	31,678	$18	Y
10	Factor Viii Recombinant Nos	Physican Administered Drug	$529,694	1.2%	19	$27,879	
11	BUPROPION XL	Antidepressants	$524,001	1.2%	16,042	$33	V
12	DIVALPROEX SODIUM ER	Antiepileptics (oral & rectal)	$465,644	1.0%	4,160	$112	Y
13	SERTRALINE HCL	Antidepressants	$424,770	0.9%	36,712	$12	Y
14	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$423,281	0.9%	589	$719	V
15	RISPERDAL CONSTA	Antipsychotics, Parenteral	$410,219	0.9%	593	$692	Y
16	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$394,495	0.9%	976	$404	V
17	SAPHRIS	Antipsychotics, 2nd Gen	$390,713	0.9%	762	$513	V
18	PRISTIQ ER	Antidepressants	$387,028	0.9%	1,553	$249	V
19	AMITRIPTYLINE HCL	Antidepressants	$372,916	0.8%	17,659	$21	Y
20	TRAZODONE HCL	Antidepressants	$335,059	0.7%	36,620	$9	
21	ABILIFY MAINTENA	Antipsychotics, Parenteral	$324,907	0.7%	219	$1,484	V
22	VENLAFAXINE HCL ER	Antidepressants	$289,148	0.6%	1,783	$162	V
23	LAMOTRIGINE	Antiepileptics (oral & rectal)	$283,585	0.6%	19,807	$14	Y
24	CITALOPRAM HBR	Antidepressants	$280,571	0.6%	31,864	$9	Y
25	HUMIRA	Targeted Immune Modulators	$269,933	0.6%	96	$2,812	Y
26	VENLAFAXINE HCL ER	Antidepressants	$261,175	0.6%	14,180	$18	Y
27	VIIBRYD	Antidepressants	$254,170	0.6%	1,288	$197	V
28	LANTUS	Diabetes, Insulins	$236,885	0.5%	752	$315	Y
29	ESCITALOPRAM OXALATE	Antidepressants	$222,060	0.5%	17,520	$13	Y
30	QUETIAPINE FUMARATE	Antipsychotics, 2nd Gen	$218,353	0.5%	11,474	$19	Y
31	BUPROPION HCL SR	Antidepressants	$215,528	0.5%	11,882	$18	Y
32	LORAZEPAM	Benzodiazepine Anxiolytics	$206,484	0.5%	21,567	$10	
33	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$204,887	0.5%	554	$370	Y
34	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$195,172	0.4%	12,094	$16	
35	NUVIGIL	ADHD Drugs	$194,060	0.4%	346	$561	V
36	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$190,568	0.4%	3,680	$52	Y
37	DIVALPROEX SODIUM	Antiepileptics (oral & rectal)	$181,986	0.4%	5,616	$32	Y
38	ENBREL	Targeted Immune Modulators	$180,580	0.4%	79	$2,286	Y
39	ZIPRASIDONE HCL	Antipsychotics, 2nd Gen	$165,852	0.4%	3,186	$52	V
40	MODAFINIL	ADHD Drugs	$165,436	0.4%	796	$208	V
		Top 40 Aggregate:	**$31,137,137**		**359,158**	**$1,115**	
		All FFS Drugs Totals:	**$45,156,621**		**690,813**	**$348**	

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

Last updated: July 26, 2015

ProDUR Report for April though June 2015

High Level Summary by DUR Alert

DUR Alert	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
DA (Drug/Allergy Interaction)	Set alert/Pay claim	45	21	0	24	0.00%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	2,104	500	0	1,602	1.77%
DD (Drug/Drug Interaction)	Set alert/Pay claim	244	53	0	191	0.17%
ER (Early Refill)	Set alert/Deny claim	78,814	14,019	134	64,656	68.03%
ID (Ingredient Duplication)	Set alert/Pay claim	21,271	5,191	3	16,069	18.27%
LD (Low Dose)	Set alert/Pay claim	922	159	0	759	0.73%
LR (Late Refill/Underutilization)	Set alert/Pay claim	118	75	0	43	0.03%
MC (Drug/Disease Interaction)	Set alert/Pay claim	1,557	734	0	822	1.30%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	1,108	297	2	807	0.90%
PG (Pregnancy/Drug Interaction)	Set alert/Deny claim	2,664	1,622	0	1,042	2.27%
TD (Therapeutic Duplication)	Set alert/Pay claim	7,008	2,026	1	4,975	6.00%
	Totals	**115,855**	**24,697**	**140**	**90,990**	**99.47%**

Clarification Code & Description	# of Paid Claims	# of Recipients	# of Drugs
None	1,247	809	169
2 - Other Override	93	55	61
3 - Vacation Supply	584	415	134
4 - Lost Prescription	725	558	123
5 - Therapy Change	3,764	3,256	311
6 - Starter Dose	85	69	48
7 - Medically Necessary	5,284	3,608	486
14 - Long Term Care Leave of Absenc	5	5	4
18 - Long Term Care Patien Admit/Re	11	8	11

Client	# of ER claims	Reason?	Notes
CO	8	Bend Pill Box-Vacation	LTC patient-early fills due to therapy changes. Pharmacy using wrong code.
IR	8	Central City Concern-Lost	Getting MH drug weekly per client request.
BR	7	Fred meyer-Vacation	3 MH prescriptions filled for 1 month supply 3 days in a row to get 3 month supply. In Hawaii
IK	6	Walmart-Vacation	3 MH prescriptions filled for 1 month supply 3 days in a row to get 3 month supply.
BL	5	Rite Aid-Vacation	5 meds filled same day for vacation
HE	5	Bi Mart-Lost	Client had meds stolen (MH, no control)
KB	5	Rite Aid-Vacation	5 meds filled same day for vacation
NX	5	Genoa-Lost	1 week supply filled
TR	5	OR University System-Vacatior	Birth control filled for 6 months-pharmacy billed 28 days each day for 6 days in a row.

ProDUR Report for April through June 2015						
Top Drugs in Early Refill						
DUR Alert	Drug Name	# Alerts	# Overrides	# Claims Screened	% Overrides	% Claims Screened Override ER
ER	Olanzapine (Zyprexa)	1,790	388	13,948	21.68%	2.78%
	Lithium Carbonate	1,281	245	9,256	19.13%	2.65%
	Divalproex Sodium (Depakote)	1,605	372	14,221	23.18%	2.62%
	Risperidone (Risperdal)	2,234	434	16,706	19.43%	2.60%
	Quetiapine (Seroquel)	2,949	541	21,705	18.35%	2.49%
	Ziprasidone (Geodon)	628	120	4,834	19.11%	2.48%
	Gabapentin	363	89	3,586	24.52%	2.48%
	Lamotrigine (Lamictal)	3,594	655	30,069	18.22%	2.18%
	Aripiprazole (Abilify)	2,378	437	21,375	18.38%	2.04%
	Fluoxetine (Prozac)	3,859	570	27,886	14.77%	2.04%
	Escitaloprim (Lexapro)	2,439	445	23,194	18.25%	1.92%
	Oxycodone HCl	281	128	7,418	45.55%	1.73%
	Sertraline (Zoloft)	4,938	810	49,087	16.40%	1.65%
	Trazodone	5,001	743	46,836	14.86%	1.59%
	Buspirone (Buspar)	1,578	250	16,193	15.84%	1.54%
	Diazepam	829	200	12,979	24.13%	1.54%
	Mirtazapine (Remeron)	1,081	144	9,441	13.32%	1.53%
	Lorazepam	1,768	418	27,952	23.64%	1.50%
	Duloxetine (Cymbalta)	3,005	480	32,355	15.97%	1.48%
	Bupropion (Wellbutrin)	3,947	573	42,445	14.52%	1.35%
	Amitriptyline	1,994	271	22,948	13.59%	1.18%
	Alprazolam	1,385	261	22,249	18.84%	1.17%
	Venlafaxine (Effexor)	2,135	292	25,569	13.68%	1.14%
	Citalopram (Celexa)	3,489	466	41,201	13.36%	1.13%
	Paroxetine (Paxil)	1,294	170	15,041	13.14%	1.13%
	Atomoxetine (Straterra)	672	80	7,347	11.90%	1.09%
	Hydrocodone Bit/APAP	210	59	8,082	28.10%	0.73%

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Retro-DUR Intervention History by Quarter FFY 2014 - 2015

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul-Sep
Pediatric Psychotropics	ADHD New Start with Follow Up In First 30 Days	Members Identified	25	28	20	10
		Profiles Sent	13	17	8	4
		Responses Received	4	1	2	2
		Response Rate	31%	6%	25%	50%
		Information Useful or Will Change Practice	2	1	0	1
		Patient Not With Office	1	0	0	0
		Already Scheduled	3	1	2	2
		Will Not Schedule	0	0	0	0
		Requested No Future Notifications	0	0	1	0
	Antipsychotic Metabolic Monitoring	Members Identified	639	0	703	0
		Profiles Sent	637	0	701	0
		Members With Response	144	0	173	0
		Response Rate	23%	0	25%	0
		Newly Scheduled	50	0	83	0
		Provider Contacted	265	0	244	0
		Provider Responses	68	0	73	0
		Provider Agreed with Recommendation	17	0	17	0
		Patient Not With Office	19	0	17	0
	Polypharmacy	Members Identified	0	254	0	0
		Profiles Sent	0	252	0	0
		Responses Received	0	23	0	0
		Response Rate	0	9%	0	0
		Information Useful or Will Change Practice	0	0	0	0
		Patient Not With Office	0	0	0	0

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Retro-DUR Intervention History by Quarter FFY 2014 - 2015

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul-Sep
Profile Review	Children under age 12 antipsychotic	Profiles Reviewed	158	134	64	33
	Children under age 18 on 3 or more psychotropics	Profiles Reviewed	30	24	10	13
	Children under age 18 on any psychotropic	Profiles Reviewed	128	113	58	32
	Children under age 6 on any psychotropic	Profiles Reviewed	8	7	9	6
	Lock-In	Profiles Reviewed	46	7	35	0
		Letters Sent To Providers	3	0	1	0
		Provider Responses	0	0	0	0
		Provider Agreed / Found Info Useful	0	0	0	0
		Locked In	19	2	11	0
	Polypharmacy	Profiles Reviewed	10	56	18	0
		Letters Sent To Providers	1	2	0	0
		Provider Responses	0	0	0	0
		Provider Agreed / Found Info Useful	0	0	0	0

Oregon State University
College of Pharmacy

Drug Use Research & Management Program

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Pediatric Psychotropic Quarterly Report

All OHP

Fiscal Year 2014 - 2015

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

7/27/2015

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

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

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Pediatric Psychotropic Quarterly Report

Fee For Service

Fiscal Year 2014 - 2015

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

7/27/2015

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

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

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Policy Update: Ivacaftor (Kalydeco®) for Cystic Fibrosis

Month/Year of Review: July 2015 **Last Reviewed**: May 2015

Proposed PA Criteria:
See **Appendix 3**. Prior authorization (PA) criteria are in place to ensure appropriate drug use and limit to patient populations in which ivacaftor has demonstrated to be effective and safe.

Research Questions:
- Does new evidence for efficacy or harms change previous conclusions regarding the effectiveness and safety of ivacaftor?
- Are there unique patients or situations where ivacaftor may be more effective or safer than currently available agents?

Conclusions:
- There is insufficient to low quality evidence that ivacaftor does not significantly improve lung function in patients with Cystic Fibrosis (CF) with the *R117H* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, as measured by lack of improvement in percent-predicted FEV_1 compared to placebo (2.6% vs. 0.5%, respectively; p=0.19) and does not improve body mass index based on one small, fair quality study. However, a post hoc subgroup analysis of adults 18 years of age or older showed a statistically significant improvement in FEV_1 compared to placebo (4.5% vs. -0.5%; p=0.01). However, a subgroup of patients aged 6 to 11 years demonstrated an unexplained negative effect, as absolute FEV_1 was significantly lower than placebo by 6.5% points (p=0.03). Based on this evidence alone, the FDA approved use of ivacaftor in adults with the *R117H* mutation based on this subgroup analysis. The FDA approved use of ivacaftor in pediatric patients 6 years of age and older based on an open-label extension study which subsequently showed a 6.4% improvement in mean change in FEV_1.
- There is insufficient to low quality evidence of no difference in patients experiencing a pulmonary exacerbations (RR 0.9; 95% CI 0.4 to 1.8) or body mass index (Treatment difference 0.26; 95% CI -1.57 to 2.10) in patients with the *R117H* mutation in the CFTR gene between ivacaftor and placebo.
- There is low quality evidence, based on one small pharmacokinetic study and one safety study in pediatric CF patients' aged 2 to 5 years (32 patients with the *G551D* mutation and 2 patients with the *S549N* mutation), that ivacaftor is relatively safe and improves sweat chloride concentrations. Based on this evidence, the FDA approved ivacaftor in patients aged 2 to 5 years with all of the following mutations: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R* or *R117H*.
- Evidence to support use of ivacaftor based on clinical outcomes remains very limited, with very small studies dealing with disease mutations that affect a small number of patients in the United States. It is difficult to determine the overall effectiveness and safety of ivacaftor for the treatment of CF and how it will affect disease progression. The strongest evidence remains in patients with the *G115D* mutation. Ivacaftor should not be used in CF patients homozygous for the *F508del* mutation (the most common mutation) due to evidence for lack of benefit in this population.

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- There is a need for new clinical endpoints, particularly in those with mild lung disease. 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 shown to correlate with improvement in FEV_1 and there is no threshold level for change in sweat chloride above which an improvement in FEV_1 is apparent.
- There are no identified adverse effects when ivacaftor is compared with placebo. However, although safety data are available for 60 weeks of treatment in trials, the long-term safety profile over a lifetime or in young children is unknown.

Recommendations:

- Approve use for and include those ages 2-5 years with gating mutations in the PA Criteria (Appendix 3).
- Approve updated PA criteria as presented in Appendix 3. Continue to adapt criteria as need be to monitor for an adequate clinical response and patient adherence as further data becomes available.
- Limited and inconsistent evidence at this time prohibits adequate and fair evaluation of ivacaftor for those with an *R117H* mutation in the *CFTR* gene. It is prudent to further await published data supporting improvements in clinically relevant outcomes before approving in this population.

Reason for Review:

Since the last P&T review of ivacaftor, the FDA approved ivacaftor for the treatment of CF in patients age 6 years and older who have an *R117H* mutation in the *CFTR* gene. In addition, the FDA approved ivacaftor for children aged 2 to 5 years who have one of the 10 FDA-approved mutations in the CFTR gene. Ivacaftor was already approved for people aged 6 years and older with these mutations. This review will evaluate the new indications and supporting evidence.

Previous Recommendations:

- There is low to moderate level of evidence to suggest that ivacaftor is superior to placebo in patients (≥12 years old) with the G551D mutation, as illustrated by an increase in forced expiratory flow rate at one second (FEV_1). There is also moderate evidence that ivacaftor is well tolerated with adverse effects resulting in discontinuations rates less than placebo. There are no head-to-head trials comparing ivacaftor to other CF treatments. Changes in FEV_1 with ivacaftor were similar to therapies used in the chronic management of CF. There is insufficient evidence to grade ivacaftor treatment in children under 12. Limited unpublished data suggests similar efficacy and safety as in patients over 12 years of age.
- The efficacy and safety evaluation of ivacaftor is limited by small study populations; study durations of only one year and unpublished data. Ivacaftor has been shown to be effective only in the CF population with the G551D mutation, making ivacaftor a treatment option in only a small percentage of patients with CF. The effects of ivacaftor on long term disease progression and important clinical outcomes including pulmonary exacerbations and hospitalizations are unknown.
- It is recommended to use clinical prior authorization criteria (**Appendix 3**) to limit the use of ivacaftor to patients that are six years and older, diagnosed with CF, have the G551D mutation in the CFTR gene, is prescribed by or in consultation with a pulmonologist or a practitioner at an accredited Cystic Fibrosis Center, and has had an adequate trial of standard medication therapy. Renewal criteria will be implemented to monitor for a clinical response and adherence.
- There is insufficient to low quality evidence based on one unpublished, phase III trial, that in addition to CF patients with the G551D mutation, ivacaftor is more effective than placebo in improving lung function as measured by FEV_1 in patients with 8 additional mutations. These include: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D. Evidence does not support use of the drug in patients with the G970R mutation.

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] Important outcomes for treatment include reducing mortality, pulmonary exacerbations, and respiratory symptoms. Forced expiratory volume in one second (FEV_1) is a commonly used outcome in clinical trials. The Cystic Fibrosis Questionnaire-revised (CFQ-R) is a validated patient-reported outcome questionnaire specific to CF which focused on respiratory health perception, quality of life, and clinically relevant respiratory symptoms. A minimally clinically important difference of 4 points was established for this domain.[3] Weight is also a commonly measured secondary outcome in trials of CF patients, as studies have shown that lower than average birth weights and poor growth are correlated with poorer lung function, increased morbidity and mortality in children with CF. [3] The nutritional status of patients with CF has been shown to be strongly associated with pulmonary function, respiratory status and survival. Sweat chloride levels is the gold standard for a diagnosis of CF. Normal individuals typically have levels < 40 mmol/L and patients with CF have elevated levels > 60 mmol/L.[4] More recently, endpoints such as sweat chloride, nasal potential difference, and intestinal current are proposed surrogate markers of CFTR function.[5] Sweat chloride has been used as a biomarker for evaluating changes in the CFTR activity in clinical trials of ivacaftor.[6] 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 shown to correlate with improvement in FEV_1. [4]

Many different mutations have been identified in the gene that causes CF. Ivacaftor is a CF transmembrane conductance regulator (CFTR) potentiator approved by the FDA in 2012 for the treatment of CF in patients 6 years and older with the G551D mutation in the CFTR gene (approximately 4% of CF patients) by demonstrating statistically superior improvement in FEV_1 compared to placebo.[7–10] The treatment effect in these trials was an increase in FEV1 of 10.6% which was seen within two weeks of treatment, a 55% decrease in respiratory exacerbations, a reduction in sweat chloride values of 50-60 mmol/L and a weight gain of 2.7 kg more than placebo. Ivacaftor is proposed to treat the underlying cause of CF, by influencing the basic gene defect, by normalizing airway surface liquid and helping to re-establish mucociliary clearance.[11,12] It is designed to increase the time that activated CFTR channels at the cell surface remain open. Over 1900 mutations have been identified in the CFTR gene, with different protein defects resulting from the mutation.[5] Ivacaftor is now indicated for the treatment of CF in patients in patients' aged 2 years and older who have one of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H.* Patients homozygous for the *F508*del CFTR mutation, the most common mutation in the CFTR gene accounting for approximately two thirds of mutations, do not receive benefit in lung function or patient-reported outcomes with ivacaftor and the drug should not be used in this population.[13] The F508del mutation results in misprocessing of CFTR resulting in failure of CFTR to traffic to the cell surface, while the G551D and other mutations result in failure of CFTR to open at cell surface, or gating mutations. Lastly, the R117H mutation affects chloride conductance in the pore region of the channel leading to poor conductance of chloride ion.[5] There are three common alleles at the poly-T locus of the *R117H* gene (5T, 7T, 9T), with the 5T variant associated with greater risk for CF.[14] Of the various clinical symptoms of CF, only pancreatic function has been shown to correlate well with CFTR genotype.

There are no head-to-head trials comparing ivacaftor to other CF treatments. Changes in FEV_1 observed with ivacaftor are similar to other therapies used in the chronic management of CF.

Elevated transaminases should be assessed prior to initiating ivacaftor and every 3 months during the first year of treatment. Patients who develop increased transaminase levels should be closely monitored. Therapy should be stopped if increases in ALT or AST greater than 5-times the upper limit of normal are observed.

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Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were 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, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
A Cochrane Collaboration Systematic Review was completed to evaluate the effects of CFTR potentiators on clinically important outcomes in children and adults with cystic fibrosis.[12] RCTs comparing CFTR potentiators to placebo were included in the review. At the time of this review, it had only been studied in those with the *G55aD* and *F508del* mutations, thus limiting the current relevance of the results. Primary outcomes were survival, quality of life, and change in FEV_1 from baseline. There were many secondary outcomes.

Four RCTs of parallel design (n=378) were included in the review, two of which have been published. Vertex Pharmaceuticals Incorporated sponsored all trials. Three trials included participants with the *G551D* mutation (one phase 2 and two phase 3) in adults and pediatrics, while one trial was in the *F508del* mutation. The primary endpoints in the trials were safety and/or FEV_1. There was a high risk of selective reporting bias and attrition bias in the included studies, with an overall moderate risk of bias across the included trials.[12]

No trial reported any deaths. Significantly higher quality of life scores in the respiratory domain were reported by the adult phase 3 G551D trial at 24 weeks, mean difference 8.10 (95% confidence interval (CI) 4.77 to 11.43) and 48 weeks, mean difference 8.60 (95%CI 5.27 to 11.93); but not by the pediatric phase 3 G551D trial. At 24 weeks in the 3 *G551D* trials, both children and adults in the ivacaftor group reported significant improvements in the change from baseline in FEV_1, with a mean difference of 16.8% (95% CI 13.5-20.1), or 0.37 liters at 48 weeks. At 16 weeks in the *F508* trial, there was no difference in FEV1 between ivacaftor and placebo (mean difference 2.4%; 95% CI -0.95 to 5.75). One study in adults with the *G551D* mutation reported significantly fewer episodes of pulmonary exacerbation requiring hospitalization in the ivacaftor group (OR 0.37; 95% CI 0.16 to 0.81).[12] Pooling data from the two of the G551D trials showed no statistical difference in number of pulmonary exacerbation (OR 0.64; 95% CI 0.36 to 1.12) or adverse effects requiring drug discontinuations (OR 0.25; 95% CI 0.04 to 1.56). [12]

The authors concluded that the *G551D* phase 3 trials demonstrated a clinically relevant impact at 24 and 48 weeks in adults and children but that there is no evidence to support ivacaftor in patients with the *F508del* mutation. [12]

New Guidelines:
No relevant guidelines were identified.

New FDA Approved Indications:

In December 2014, the FDA approved the use of ivacaftor for use in subjects with the *R117H* mutation in the CFTR gene. The *R117H* mutation is the third most common mutation, present in approximately 4% of people with CF, or approximately 700 people in the United States. This approval was based on the Phase 3, double-blind, randomized KONDUCT study in subjects aged 6 years and older.[10,15,14] The primary outcome was absolute change from baseline in percent (%)-predicted FEV_1 through week 24. Those with a %-predicted FEV_1 40-90% for subjects aged 12 years or older or 40-105% for subjects aged 6 to 11 years were included. A total of 69 subjects were randomized (34 in the ivacaftor group and 35 in the placebo group) and the majority of subjects were 18 years or older (72%). 70% of patients had the 5T variant, indicating more clinically significant disease and most patients (87%) were confirmed pancreatic sufficient. There was an absolute change from baseline in %-predicted FEV_1 of 2.6% in the ivacaftor group compared to 0.5% in the placebo with a least squares mean difference of 2.1% (95% CI -1.13 to 5.35%). This difference was not statistically significant (p=0.19) and therefore the study did not meet its primary endpoint. There was also no significant difference in time to first pulmonary exacerbation (p=0.8556) or change from baseline in body mass index (BMI) at week 24 (p=0.78). There was a statistically significant difference in change in FEV_1 relative to placebo in a subgroup of subjects aged 18 years and older (4.5% vs. -0.5%, respectively; p=0.01), which represented approximately 75% of subjects. In addition, there was a statistically significant difference in change in FEV_1 relative to placebo in subjects with the 5T poly-T status (6% vs. 0.7%; treatment difference 5.3; 95% CI 1.3 to 9.3), though subjects with 7T status only did not show a statistically significant difference in FEV_1 compared to placebo (-0.7% vs. -0.9%; treatment difference 0.2% [95% CI -8.1 to 8.5%]). However, the mean absolute change in FEV_1 in the subgroup of 17 subjects aged 6 to 11 years was significantly lower compared to placebo (-2.8% vs. 3.5%), demonstrating an unexplained negative effect in children. The company concluded that this was driven by the high baseline FEV_1 for these patients (95%) and the small sample size and that there was an overall neutral effect on lung function. There was a significantly greater decrease in sweat chloride in the ivacaftor group compared to placebo (-26.3 mmol/L vs. -2.3 mmol/L; p<0.0001)[15]; however there are no data available in patients aged 12 to 17 years. Although there was a significant improvement in quality of life, as measured by the CFQ-R domain, in the ivacaftor group versus placebo, there was no statistically significant difference in the number of patients achieving the minimal clinically important difference of at least 4 percentage points for respiratory domain (RR 1.44; 95% CI 0.7 to 3.1).[14] An unpublished, open-label extension period study (KONTINUE) showed an improvement in FEV_1 of 6.4% in the subgroup of 6 to 11 year olds and overall, a mean increase of 5.5 percentage points. The initial decrease in the controlled trial should be taken into consideration and more evidence is needed to demonstrate an improvement. Results for KONTINUE were not available on clinicaltrials.gov.

Although the study did not meet the primary endpoint, adult approval was based on subgroup analysis from the trial and expected clinical benefit based on secondary outcomes in pediatric patients.

In March 2015, the FDA approved ivacaftor for use in children ages 2 to 5 years with CF who have one of the 10 mutations in the CFTR gene already approved in adults (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, and R117H*).[10] The expanded use in this population is based on results of an open-label, non-controlled, phase 3 study (KIWI) that evaluated the safety and pharmacokinetics of weight-based dosing of ivacaftor (50 mg or 75 mg twice daily) for 24 weeks. A total of 9 patients, all with the *G551D* mutation in the CFTR gene, were enrolled in the initial pharmacokinetic stage of the study. Pharmacokinetic properties for both doses were similar to that reported in adults in previous studies. The second part of the study, which included 32 patients with the *G551D* mutation and 2 patients with the *S549N* mutation, assessed safety outcomes over 24 weeks. Overall, 88.9% of patients experienced at least one adverse event; the most common being pyrexia, vomiting, ecchymosis, and rhinorrhea. Five patients experienced elevations in liver transaminases and there were a total of 7 serious adverse events. There was a decrease in the sweat chloride concentration through week 24 (-46.86 mmol/L) but statistical analysis compared to placebo was not provided and other clinical efficacy outcomes, such as lung function, were not included.[16]

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Pulmonary Exacerbations
2) Hospitalizations
3) Disease Progression
5) Quality of life

Primary Study Endpoint:

1) Absolute change from baseline in % predicted FEV_1 through week 24

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
KONDUCT[14] RCT, DB, PC	1. Ivacaftor 250 mg Q12 H (I) 2. Placebo (P)	Demographics: Men: 81% Age: 31 years %pred FEV1 73% Key Inclusion Criteria: Patients over 6, FEV1% predicted 40-105 if 6-11 y/o or 40-90 if 12 or older Key Exclusion Criteria: Pulmonary exacerbation within 4 weeks, abnormal liver function, colonization with organisms associated with a rapid decline in pulmonary status, history of alcohol or illicit drug abuse within 1 year, use of any inhibitors or inducers of CYP4503A	N=34 N=34	Absolute change from baseline in %pred FEV_1: I: 2.6% P: 0.5% Treatment difference 2.1 (95% CI -1.13 to 5.35; p=0.20) Pulmonary Exacerbations I: 11 (32%) P: 13 (37%) RR 0.9; (95% CI 0.4 to 1.8) Change from baseline BMI: I: 0.23 kg/m^2 P: 0.49 kg/m^2 Treatment difference 0.26 (95% CI -1.57 to 2.10) Quality of Life (CFQ-R): achieved MCID for respiratory domain: I: 14 (41.2%) P: 10 (28.6%) RR 1.44 (05% CI 0.7 to 3.1) Decrease in Sweat chloride concentrations: I: -26.3 mmol/L P: -2.3 mmol/L Treatment difference -24.0 (954% CI -28.01 to -19.93; p<0.001)	NS NS NS NS NA	Serious Adverse Events: I: 6 (17%) P: 4 (12%) RR 1.5; 95% CI 0.4 to 6.2 Adverse Events Leading to Discontinuations: I: 0 P: 0	NS NS	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: Selection: Interactive web response system vendor; randomization specification and dummy randomization code produced by masked study biostatistician Performance: Double-blind design Detection: Unclear if outcome assessors blinded Attrition: Average Attrition (15%) and similar between groups; ITT analysis done. **Applicability**: Patient: Majority of patients (70%) with the 5T variant, indicating more clinically significant disease and greater than 18 y/o Intervention: Ivacaftor 150 mg twice daily Comparator: Placebo Outcomes: Spirometry done according to the American Thoracic Society guidelines. Unclear of clinical utility of sweat chloride Setting: Unclear **Analysis**: In a small study of patients with mild to moderate CF there was no benefit seen in overall population in lung function, pulmonary exacerbations, or BMI. FDA approval was based on approval of subgroup analysis in patients > 18 y/o who had a lower baseline FEV1 compared to patients ages 6-11 who experienced an unexplained negative effect from ivacaftor. Further analysis of clinical important outcomes with therapy on CFTR gene needed.

Abbreviations [alphabetical order]: ARR = absolute risk reduction; BMI= body mass index; CI = confidence interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised; DB: double blind; FEV1: forced expiratory volume; ITT = intention to treat; mITT = modified intention to treat; MCID: minimally clinical important difference; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; RCT: randomized controlled trial

Randomized Controlled Trials:

The only relevant RCT identified was the KONNECTION trial.[17] This trial data were previously presented and reviewed by the P&T committee to support the expanded indication; however, it was unpublished at the time. A summary of the trial can be found below, with the abstract presented in **Appendix 1**.

Table 1. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results	Quality*
KONNECTION[17] Randomized, Crossover study	Ivacaftor 150 mg BID vs. placebo	Patients with CF ≥6 years old with non-*G551D* gating mutations (*G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P,* or *G1349D.* (N=39)	Absolute change in %-predicted FEV_1 through 8 weeks of treatment	Ivacaftor: 7.5% Placebo: -3.2% Mean difference: 10.7% (95% CI 7.3 to 14.1; P<0.0001) There was high variability among and within subgroups of genotypes; in many groups, FEV_1 did not significantly change from baseline and the number of patients in each subgroup was extremely small.	Poor

Abbreviations: BID = twice daily; CF = Cystic Fibrosis; FEV1 = Forced expiratory volume in 1 second;
*Quality of each study is ranked as "Good", "Fair" or "Poor" based on DURM Standard Methods for Quality Assessment and Grading the Evidence.

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Appendix 1: Abstracts of Clinical Trials

1. De Boeck K1, Munck A2, Walker S3, Faro A4, Hiatt P5, Gilmartin G6, Higgins M6. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *J Cyst Fibros*. 2014 Dec;13(6):674-80. doi: 10.1016/j.jcf.2014.09.005. Epub 2014 Sep 26.

BACKGROUND:
Ivacaftor is used to treat patients with CF and a G551D gating mutation; the KONNECTION study assessed the efficacy and safety of ivacaftor in patients with CF and a non-G551D gating mutation.

METHODS:
Patients with CF ≥6-years- old with non-G551D gating mutations received ivacaftor 150mg q12h or placebo for 8weeks in this 2-part, double-blind crossover study (Part 1) with a 16-week open-label extension (Part 2). The primary efficacy outcome was absolute change in FEV1 through 8 and 24weeks of ivacaftor treatment; secondary outcomes were changes in BMI, sweat chloride, and CFQ-R and safety through 8 and 24weeks of treatment.

RESULTS:
Eight weeks of ivacaftor resulted in significant improvements in percent predicted FEV1, BMI, sweat chloride, and CFQ-R scores that were maintained through 24weeks. Ivacaftor was generally well tolerated.

CONCLUSIONS:
Ivacaftor was efficacious in a group of patients with CF who had selected non-G551D gating mutations.

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions
1 ivacaftor.mp 65
2 Kalydeco.mp 11
3 cystic fibrosis.mp. or Cystic Fibrosis/ 23507
4 1 or 2 65
5 3 and 4 65
6 limit 5 to yr="2014-Current" 21
7 Limit 6 to (clinical trial or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews) 2

Both of the resulting two studies were published in March 2014 and were included in the previous update.

Appendix 3: Proposed PA Criteria

Ivacaftor (Kalydeco®)

Goal:

- To ensure appropriate drug use and limit to patient populations in which ivacaftor has demonstrated to be effective and safe.

Length of Authorization: 30 days

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the client have a diagnosis of cystic fibrosis and is 2 years of age or older?	Yes: Go to #3	No: Pass to RPH; Deny (medical appropriateness)
3. 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 #4	No: Pass to RPH; Deny (medical appropriateness) If unknown, there needs to be a FDA cleared CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation)
4. Is the request from a practitioner at an accredited Cystic Fibrosis Center or a pulmonologist?	Yes: Go to #5	No: Pass to RPH; Deny (medical appropriateness)
5. Is the patient on ALL the following drugs, or has had an adequate trial of each drug, unless contraindicated or not appropriate based on age (<6 y/o) and normal lung function: - Dornase alfa, AND - Hypertonic saline, AND - Inhaled or oral antibiotics (if appropriate)	Yes: Go to #6	No: Pass to RPH; Deny (medical appropriateness)
6. Is the patient on concomitant therapy with a strong CYP3A4 inducer (rifampin, St. John's wort)?	Yes: Pass to RPH; Deny (medical appropriateness)	No: Go to #7.
7. Does the patient have decreased liver function, defined as elevated levels (i.e., ≥3x the upper limit of normal) in ≥3 of the	Yes: Pass to RPH; Deny (medical appropriateness)	No: Go to #8

following levels: ALT, AST, AP, GGT, total bilirubin? Note: This was an additional exclusion criteria from the trials		
8. Is ivacaftor dosed appropriately based on age, weight, and co-administered drugs (See dosing and administration below)?	Yes: Approve for 30 days	No: Pass to RPH; Deny (medical appropriateness)

Renewal Criteria		
1. Is this the first time the patient is requesting a renewal?	Yes: Go to #2	No: Go to #3
2. Does the patient have a documented response to therapy as defined as below? • Sweat chloride test below 60 mmol/L or decreased by 30% if the baseline was less than 60 mmol/L OR • Lack of decline in FEV_1	Yes: Go to #4	No: Pass to RPH; Deny (medical appropriateness)
3. Does the patient have documented response to therapy as defined as below? For patients ≥ 6 y/o • a sustained absolute improvement in FEV_1 of ≥5%, OR • A reduction in the incidence of pulmonary exacerbations by 50% For patients 2-5 y/o (cannot complete lung function tests) • Significant improvement in BMI, OR • Improvement in exacerbation frequency or severity If no improvement in either of above, repeat sweat chloride test: • Sweat chloride test below 60 mmol/L or decreased by 30% IF the baseline was less than 60 mmol/L	Yes: Go to #4	No: Pass to RPH; Deny (medical appropriateness)
4. Has the patient been compliant with therapy, as determined by refill claims history?	Yes: Go to #5	No: Pass to RPH; Deny
5. If within first year of treatment, are liver function tests (AST/ALT) within normal limits in the past 3 months? If after 1 year of	Yes: Go to #6	No: Pass to RPH; Deny (medical appropriateness)

treatment, are liver function tests (AST/ALT) within normal limits in past 1 year? Note: Monitoring LFTs is recommended every 3 months for the first year, followed by once a year.		
6. Is ivacaftor dosed appropriately based on age, weight, and co-administered drugs (See dosing and administration below)?	Yes: Approve for 6 months	No: Pass to RPH; Deny (medical appropriateness)

Limitations of Use:

• Ivacaftor is not effective in patients with Cystic Fibrosis who are homozygous for the *F508del* mutation in the *CFTR* gene.

Dosage and Administration:

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

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

Rifabutin Phenobarbital Phenytoin Carbamazepine St. John's wort		recommended

P&T/DUR Review: *7/15 (MH); 5/15; 5/14; 6/12*
Implementation: *8/12*

Initial Pediatric SSRI Antidepressant – Daily Dose Limit

Goals:

- Approve only for covered OHP diagnoses.
- Limit risk of new-onset of deliberate self-harm thoughts and behaviors, or suicidality associated with initiation of antidepressant therapy at above recommended doses

Length of Authorization:

- Up to 12 months

Requires PA:

- Any SSRI in children 0-4 years of age.
- Any daily SSRI dose higher than maximum dose in the table below for patients <25 years of age on date of first antidepressant claim (i.e. no claim for any antidepressant in Specific Therapeutic Classes H2H, H2S, H2U, H7B, H7C, H7D, H7E, H7J, H8P or H8T in the 102 days prior)

GSN	SSRI	Age-specific Maximum Initial Dose (mg)			
		Age range (years)			
		5-9	10-15	16-19	20-24
70991, 46206, 46204, 46203, 46205	citalopram	10	10	20	20
50712, 51642, 51698, 50760	escitalopram	5	10	10	10
46219. 46216, 46217, 47571, 46215, 46214, 46213	fluoxetine	10	10	20	20
46222, 46224. 46225, 46223, 46226, 53387, 53390, 53389, 53388,	paroxetine (immediate release)	10	10	20	20
46229, 46228, 46227, 46230	sertraline	25	25	50	50

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the patient under 5 years of age?	Yes: Go to #3	No: Go to #5
3. Is the request from a child psychiatrist or was the regimen developed in consultation with a child psychiatrist?	Yes: Approve for 12 months	No: Pass to RPH; Deny Recommend provider seek a consultation with a child psychiatrist, such as the no-cost/same-day consultation service of OPAL-K. www.ohsu.edu/OPALK

Approval Criteria		
4. Is the client being treated for funded diagnoses on the OHP List of Prioritized Services?	Yes: Go to #5	No: Pass to RPH; Deny, (Diagnosis not funded by OHP)
5. Has the patient been treated previously with antidepressants and is the dose below the maximum recommended dose?	Yes: Approve for 12 months.	No: Go to #6
6. Is the requested dose above the recommended initial dose for the patient's age (i.e. was the days' supply entered correctly, is the patient's age accurate)?	Yes: Pass to RPh. Go to #7.	No: Approve 12 months
7. Are there clinical circumstances that justify an increased dose?	Yes: RPh to evaluate on a case-by-case basis.	No: Deny for medical appropriateness Recommend provider consider lowering the initial dose and/or seek a consultation with a child psychiatrist, such as the no-cost/same-day consultation service of OPAL-K. www.ohsu.edu/OPALK

P&T/DUR Review: *7/15 (TW); 5/15; 11/14*
Implementation: ***TBD***

Rifaximin (Xifaxan®)

Goal:

- Optimize appropriate pharmacological management hepatic encephalopathy.

Length of Authorization:

- ~~6 months to~~ L~~L~~ifetime

Requires PA:

- Rifaximin

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the treating diagnosis prevention or treatment of hepatic encephalopathy (572.2)?	**Yes:** Go to ~~4~~3	**No:** Pass to RPh. Deny; not funded by OHP or for medical appropriateness~~Go to 3~~
3. Is the patient currently managed with a~~n adequate~~ regularly scheduled daily ~~dose~~regimen of lactulose?	**Yes:** Go to 5	**No:** Go to ~~7~~4
4. Does the patient have a contraindication to lactulose?	**Yes:** Go to 5	**No:** Pass to RPh Deny; medical appropriateness Note: studies demonstrate effectiveness of rifaximin as add-on therapy to lactulose.
~~4.~~5. Is the patient currently prescribed a benzodiazepine drug?	**Yes:** Go to 6	**No:** Approve for lifetime
~~5.~~6. Is the patient tapering off the benzodiazepine? Note: tapering process may be several months	**Yes:** Approve for ~~1 year~~lifetime	**No:** Pass to RPh. Deny; medical appropriateness Note: studies explicitly excluded use of benzodiazepines and benzodiazepine-like drugs because of their risk for precipitating an episode of hepatic encephalopathy.~~ If justification is given for not tapering off the benzodiazepine, approve for 6 months.~~

Approval Criteria		
~~6. Does the patient have a contraindication to lactulose?~~	~~**Yes:** Approve for lifetime~~	~~**No:** Inform prescriber studies demonstrate effectiveness of rifaximin as add-on therapy to lactulose. If justification is given for not treating with lactulose, approve for 6 months.~~

P&T/DUR Review: *7/15; 5/15 (AG)*
Implementation *TBD*

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Prior Authorization Review: Codeine

Background:
During the May Pharmacy and Therapeutics (P&T) Committee meeting, the Committee voted to establish Prior Authorization (PA) for use of codeine in children. A safety review of codeine was therefore conducted to determine appropriate criteria for safe use.

Codeine is commonly used to manage moderate pain and reduce cough, but has its limitations as an unpredictable analgesic. Codeine is a prodrug that requires conversion into morphine by cytochrome P450 2D6 (CYP2D6), but its conversion is subject to wide genetic variation leading to either poor pain control in some patients, or at the opposite spectrum, high risk for morphine overdose in others. Codeine is available as a single-ingredient product or in combination with acetaminophen or aspirin and in some cough and cold medications. During 2011, 1.7 million pediatric patients (0-17 years of age) received a prescription for a codeine product from U.S. outpatient retail pharmacies.[1] Interestingly, prescriptions for codeine-containing products only slightly decreased in frequency between 2001 and 2010, despite convincing studies documenting their lack of benefit and serious adverse effects.[2] Indeed, claims for codeine products are commonly encountered for pediatric patients covered under the Oregon Health Plan (OHP).

Fifteen deaths (n=12) or overdoses (n=3) of children (ages 21 months to 12 years) who received standard doses of codeine have been reported in the U.S.[1,3] Many of these children had obstructive sleep apnea and received codeine post-operatively after tonsillectomy and/or adenoidectomy.[1,3] Children who died were found to have very elevated levels of morphine in their blood, which likely further compromised their respiratory function after these particular surgeries.[1,3] Most of these children were also found to have an inherited genetic variant of CYP2D6, the enzyme that metabolizes codeine to morphine.[1,3] Patients with this enzyme variant very rapidly metabolize codeine, resulting in increased risk of developing life-threatening or fatal amounts of morphine in the body. These patients are considered "ultra-rapid metabolizers" of CYP2D6. Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine.[1]

The prevalence of the ultra-rapid CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not currently available for other ethnic groups.[1]

The U.S. Food and Drug Administration (FDA) issued its strongest warning (Boxed Warning) of risk for respiratory failure and death in children who are ultra-rapid metabolizers of codeine due to the CYP2D6 variant.[4] However, routine CYP2D6 genotype testing is not recommended because patients with normal metabolism may, in some cases, convert codeine to morphine at levels similar to ultra-rapid metabolizers.[1] Therefore, the FDA issued a Contraindication, which is a formal means for the FDA to make a strong recommendation against use of a drug in certain patients, to restrict any codeine product from being used for post-operative pain in any child who has undergone tonsillectomy and/or adenoidectomy.[4] For management of other types of pain in children, the FDA advises codeine should only be used if the benefits are anticipated to outweigh the risks.[4]

The European Medicines Agency,[5] the United Kingdom's Medicines and Healthcare Products Regulatory Agency,[6] and Health Canada[7] have also issued warnings regarding use of codeine in pediatric patients; but these agencies also provide guidance for use of codeine in children. Briefly, these agencies advise to restrict codeine use for acute moderate pain only (not cough) in children older than 12 years of age, and only if pain is not relieved by acetaminophen or ibuprofen.[5-7] Similar to FDA labeling, these agencies also state codeine is contraindicated in all children younger than 18 years who undergone tonsillectomy or adenoidectomy (or both) for obstructive sleep apnea.[5-7] In children aged 12-17 years, codeine should not be prescribed for more than 3 days at a maximum daily dose of 240 mg.[5]

Recommendations:
Establish PA, as recommended by the P&T Committee, by implementing the following criteria outlined in the proposed PA (see **Appendix 1**) to promote safe use of codeine and codeine-containing products in children under 18 years of age.

References:

1. FDA Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy [2-20-13]. U.S. Food and Drug Administration. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm . Accessed 9 June 2015.

2. Racoosin JA. Death and respiratory arrest related to ultra-rapid metabolism of codeine to morphine. U.S. Food and Drug Administration, FDA Advisory Committee presentation. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/pediatricadvisorycommittee/ucm343601.pdf . Accessed 9 June 2015.

3. Kaiser S, Asteria-Penaloza R, Vittinghoff E, et a.. National patterns of codeine prescriptions for children in the emergency department. Pediatrics. Pediatrics. 2014;133:e1139-e1147. doi:10.1542/peds.2013-3171.

4. Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER). U.S. Food and Drug Administration. Available at: http://www.fda.gov/safety/medwatch/safetyinformation/ucm356221.htm . Accessed 9 June 2015.

5. Pharmacovigilance Risk Assessment Committee recommends restricting use of codeine when used for pain relief of children [6-14-13]. The European Medicines Agency. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001813.jsp&mid=WC0b01ac058004d5c1 . Accessed 9 June 2015.

6. Drug Safety Update: Codeine for analgesia: restricted use in children because of reports of morphine toxicity [7-10-13]. Medicines and Healthcare Products Regulatory Agency, United Kingdom. https://www.gov.uk/drug-safety-update/codeine-for-analgesia-restricted-use-in-children-because-of-reports-of-morphine-toxicity . Accessed 9 June 2015.

7. Health Canada's review recommends codeine only be used in patients aged 12 and over. Health Canada. Availabe at: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/33915a-eng.php . Accessed 9 June 2015.

Codeine

Goal(s):

- Promote safe use of codeine

Length of Authorization:

Up to 3 days

Requires PA:

- All patients under 18 years of age
- All drug products containing codeine

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the prescription for common cold or cough? (460; 786.2)	Yes: Pass to RPh. Deny; not funded by the OHP	No: Go to 3
3. What is the age of the patient?	Ages 0-12 years: Pass to RPh. Deny; medical appropriateness	Ages 13-17 years: Go to 4
4. Has the patient recently undergone tonsillectomy or adenoidectomy?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to 5
5. Does the dose exceed 240 mg per day?	Yes: Pass to RPh. Deny; medical appropriateness	No: Approve for up to 3 days' supply

3

P&T / DUR Review: *7/15*
Implementation: *TBD*

Leuprolide Hormone Therapy

Goal:

- Approve for OHP-funded conditions in children and adolescents up to 16 years of age.

Length of Authorization:

Precocious puberty: through age 12 years in females, age 13 years in males.
Gender dysphoria: through age 16 years.

Requires PA:

- Leuprolide in children and adolescents through 16 years of age.

Approval Criteria		
1. What diagnosis is being treated and what is the age and gender of the patient?	Record ICD9 code and age/gender.	
2. Is the patient female and aged <13 years or male and aged <14 years?	Yes: Go to #3	No: Go to #4
3. Is the diagnosis central precocious puberty (CPP)? [precocious sexual development and puberty, ICD-9 259.1] • Note CPP is often associated with hydrocephalus, cranial irradiation, Silver-Russell syndrome, hypothalamic tumor, or hamartoma. • All above diagnoses and conditions are rare in children and adolescents.	Yes: Approve through: • Age 12 years for females • Age 13 years for males	No: Go to #4
4. Is the diagnosis gender dysphoria (ICD-9 302.6, 302.85)?	Yes: Go to #5	No: Pass to RPH; deny for medical appropriateness

Approval Criteria		
5. Does the request meet all of the following criteria? • Diagnosis of gender dysphoria made by a mental health professional with experience treating gender dysphoria. • At least 6 months of counseling and psychometric testing for gender dysphoria. • Prescribed by, or in consultation with, a pediatric endocrinologist. • Confirmation of puberty (physical changes and hormone levels) no earlier than Tanner Stages 2-3 (bilateral breast budding or doubling to tripling testicular volume).	Yes: Approve through • Age 16 years	No: Pass to RPH; deny for medical appropriateness
RPH only: All other indications need to be evaluated as to whether it is an OHP-funded condition. Refer unique situations to Medical Director of DMAP.		

P&T / DUR Review: *7/15; 5/15; 9/07*
Implementation: *TBD; 11/07; 7/09*

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Class Review: HIV Antiretroviral Agents

Month/Year of Review: July 2015

Research Questions:

- What are the current antiretroviral recommendations in the United States (U.S.) for management of Human Immunodeficiency Virus type 1 (HIV-1, or HIV)?
- What antiretroviral agents and formulations are currently available?
- What are the current challenges with antiretroviral therapy?

Conclusions:

- There is high quality evidence that antriretroviral agents (ARV) should be initiated in all HIV-infected patients with a CD4 T-lymphocyte cell count (CD4) less than 350 cells/µL; there is low to moderate quality evidence to suggest ARV should be initiated in HIV-infected patients with CD4 counts between 350 and 500 cells/µL; however, evidence to support initiating ARV in HIV-infected patients with CD4 counts greater than 500 cells/µL is limited to expert opinion but is common in clinical practice.[1] The U.S. guidelines recommend treating all HIV-infected patients regardless of CD4 counts,[1–4] while European[5] and international[6] guidelines suggest it may be appropriate to wait for CD4 counts to decrease below 500 cells/µL, or even 350 cells/µL, depending on resources avaiable.
- The U.S. Department of Health and Human Services (HHS)[1] and the International Antiviral Society-USA (IAS-USA)[2] publish the two primary evidence-based guidelines for management of HIV in the U.S. Both guidelines are largely congruent in their recommendations for initial ARV in treatment-naïve HIV-infected persons. There is high quality evidence the type of ARV regimen should be determined by baseline resistance testing and patient characteristics, with consideration for patient preference. The IAS-USA recommend an ARV regimen consisting of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) with either an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) pharmacokinetically enhanced (i.e., boosted) with ritonavir or cobicistat. The HHS makes similar recommendations but have preferential recommendations for an INSTI-based regimen or a ritonavir-boosted PI regimen (i.e., with darunavir) because of less drug-drug interactions (i.e., with dolutegravir or raltegravir), tolerability and lower genetic barrier to develop resistance.
- Specific considerations for special populations in both U.S. guidelines are largely based on observational data and clinical experience:
    - Pregnancy: Pregnancy should not preclude the use of an optimal ARV regimen initiation as the rate of congenital birth defects following exposure to ARV during pregnancy is not higher than that reported in the general population. However, a regimen of zidovudine/lamivudine plus either ritonavir-boosted lopinavir or ritonavir-boosted atazanavir in treatment-naïve patients is commonly used.[4]
    - Pediatrics: ARV for children should generally consist of two NRTIs plus one active drug from the following classes: NNRTI or PI, generally boosted with low-dose ritonavir. Although INSTIs may be considered first-line treatment in adults, there are insufficient data to recommend these agents as preferred agents for initial therapy in children.[3]

- Patients with significant cardiovascular risk factors: low-quality evidence suggests abacavir, ritonavir-boosted lopinavir, and ritonavir-boosted fosamprenavir may be associated with higher rates of cardiovascular events than other agents.[2]
- Hepatitis B virus (HBV): emtricitabine, lamivudine and tenofovir have activity against HBV. If HIV treatment is needed, fully suppressive ARV initiated with the NRTI backbone combination of emtricitabine plus tenofovir or lamivudine plus tenofovir is recommended.[2]
- Hepatitis C virus (HCV): selection of optimal ARV is determined by potential drug interactions if concomitant HCV treatment is being given.[2]
- Immunosuppression/Cancer: because of their favorable drug interaction profiles, dolutegravir- or raltegravir-based regimens are recommended in patients receiving immunosuppressants or chemotherapy for malignancies.[2]

- In adherent patients presenting with virological failure, drug-resistance testing should be performed while the patient is taking the failing ARV regimen or within 4 weeks of treatment discontinuation, if possible. A new regimen should include at least two, and preferably three, fully active agents.[1,2]
- Primary challenges specific to ARV includes improving access to HIV care to vulnerable populations and minority populations; choosing a tolerable and convenient regimen that maximizes adherence in order to reduce morbidity, mortality and drug resistance; reducing fraud, waste and abuse of antiretroviral drugs; and continued research to improve efficacy and safety of ARV, understanding of HIV and development of a cure.

Recommendations:

- Create a *voluntary* Preferred Drug List (PDL) for all HIV antiretroviral drugs and combination products, including NRTIs, NNRTIs, INSTIs, PIs, Fusion Protein Inhibitors, CCR5 Antagonists, and ARV-specific CYP P450 Inhibitors.
- Designate all drugs as *preferred* at this time.

Background:

The advancement of management of HIV since the initial outbreaks of opportunistic infections and Kaposi's sarcoma reported in California and New York are among the greatest accomplishments in modern medicine.[7] Once a universally fatal disease associated with complete CD4 cell loss, ARV today is not only potent and reduces morbidity and mortality, but is also convenient and well tolerated. Treatment initiated before advanced disease develops reduces plasma HIV RNA concentrations to undetectable values in most motivated patients who have access to these drugs.[8] The degree of immunological recovery varies, but patients treated before onset of advanced immunodeficiency (i.e., CD4 <200 cells/µL) have significantly sustained CD4 count gains after ARV is initiated.[8]

The average CD4 count in adults without HIV is about 900 cells/µL.[9] However, in HIV-infected persons, the infection will eventually develop progressive immunosuppression without treatment, as evident by CD4 cell depletion, leading to AIDS-defining illnesses and premature death.[1] Symptomatic disease often emerges as the peripheral CD4 count falls to lower than 350 cells/µL.[8] The risks of most AIDS-defining opportunistic infections (e.g., *Pneumocystis jirovecii* pneumonia) and cancers (e.g., Kaposi's sarcoma) increase as the CD4 count falls below 200 cells/µL.[8] Thus, a CD4 count of 350 cells/µL is generally the threshold at which the benefits of starting ARV clearly outweigh the risk of delaying treatment. However, the U.S. guidelines[1,2] make stronger recommendations to starting HIV treatment earlier (i.e., CD4 count >350 cells/µL) than recommendations made by European and international guidelines,[5,6] which is strengthened by new evidence to suggest that starting ARV earlier leads to significantly increased CD4 normalization rates,[9] as well as the premise that suppressing HIV earlier reduces risk of viral transmission and reduces chronic inflammation thought to contribute to cardiovascular complications and other end-organ damage leading to liver disease, kidney disease, neurologic complications, and malignancies reported in HIV-infected cohorts.[1,8]

The immediate goal of therapy is to reduce HIV viral load to a threshold less than 200 copies of RNA/mL, but preferably less than 50 copies of RNA/mL, an "undetectable" range for most commercial assays and below which the virus does not evolve and drug resistance does not emerge.[8] Ultimately, however, the goal is to restore immune function early in order to reduce HIV-associated morbidity and mortality and prevent HIV transmission.[1]

Quantitative viral load, which is the concentration of plasma HIV RNA, is measured before ARV begins, but its primary value is in monitoring treatment response or failure.[8] Chronic established HIV infection is often associated with a stable HIV RNA set point, which varies between individuals, but which is associated with the rate of CD4 decline and with the risk of AIDS and death.[1] Current ARV therapy in treatment-naïve persons suppress plasma viral loads below assay detection limits in over 90% of clinical trial participants – rates that are often also seen in real world clinical use.[8] Once viremia is controlled for 1-2 years, virological failure is uncommon.[8] Predictors of virologic success include:

- High potency ARV regimen,
- Strict adherence to the ARV regimen,
- Low baseline viremia,
- Higher baseline CD4 count (>200 cells/μL), and
- Rapid reduction of viremia in response to treatment.[1]

At present, ARV therapy is considered lifelong. Sustained viral suppression is the foundation for immune recovery, optimal health and prevention of resistance and viral transmission.[2] Thus, it is paramount to maximize adherence and minimize toxicity by treating HIV-infected patients with an effective therapy that is well tolerated and convenient, and has limited drug interactions and little effect on comorbid conditions.[2] In resource-rich countries like the U.S., individualization of therapy is common and best managed by healthcare providers with HIV expertise where individualized care can be provided.[2,8]

Antiretroviral therapy consists of a combination of drugs targeting the HIV life cycle with the aim of stopping HIV replication. Because of the high replication and mutation rates of HIV-1, usually three antiretroviral agents from two or more drug classes must be taken simultaneously to suppress replication and prevent the development of resistance.[10] Individual drugs are generally classified by the viral life cycle step they inhibit, which currently includes six classes that target five unique steps: binding, fusion, reverse transcription, integration and proteolytic cleavage (see **Figure in Appendix 1**). Extracellular virions enter the cell through a complex three-step process, which is (1) attachment to the CD4 receptor, (2) binding to the CCR5 or CXCR4 co-receptors, or both, and (3) membrane fusion.[8] CCR5 antagonists block CCR5 binding and fusion inhibitors block fusion of the virion. The HIV reverse transcriptase enzyme catalyzes transcription of HIV RNA to double-stranded DNA, a step inhibited by nucleoside (or nucleotide) and nonnucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs, respectively). The HIV integrase enzyme facilitates incorporation of HIV DNA into host chromosomes, a step inhibited by integrase strand transfer inhibitors (INSTI). After transcription and translation of the HIV genome, immature virions are produced and bud from the cell surface. The HIV protease enzyme cleaves polypeptide chains, allowing the virus to mature, a step inhibited by HIV protease inhibitors (PIs).[8] HIV enters its preferred target cells by binding to one or both of the chemokine receptors CCR5 and CXCR4. Nearly all patients with primary HIV infection harbor a virus that binds to CCR5, but as the disease progresses over time, many untreated individuals develop a virus that also binds to CXCR4. Since one therapeutic drug class specifically targets CCR5, testing is needed if this class is utilized to define which tropism of the virus (CCR5 vs. CXCR4) is present.[8]

Antiretroviral agents listed by drug class are described in **Table 1**. The exception is the addition of two pharmacokinetic enhancers, or boosters, used solely to improve the pharmacokinetic profiles of the PIs and the INSTI elvitegravir.[1] Several well tolerated and highly effective regimens are available for treatment-naïve patients. The differences in terms of virological outcomes for the available regimens are subtle.[8] Therefore, baseline resistance testing and patient characteristics should guide design of the specific regimen, with convenience, pill burden, tolerability and long-term toxic effects important factors to consider when decisions are made between the various therapeutic options.[1,8] In general, ARV therapy is initiated as a regimen consisting of two NRTIs (the "backbone") combined with a third agent (the "anchor"), which consists of an NNRTI, a boosted PI, or an INSTI.

Table 1. Antiretroviral Agents by Class.[2,8]

Antiretroviral Class	Drug	Comments
Nucleoside Reverse Transcriptase Inhibitors (NRTI)	Abacavir* Didanosine Emtricitabine* Stavudine Lamivudine*^ Zidovudine Tenofovir*^	A combination of 2 NRTIs (often tenofovir and emtricitabine) is the foundation of recommended ARV therapy. Abacavir and lamivudine had lower rates of viral suppression than tenofovir and emtricitabine when combined with ritonavir-boosted atazanavir or efavirenz when baseline HIV-1 RNA levels were >100,000 copies/mL. However, there is no difference if these drugs are combined with INSTIs dolutegravir or raltegravir. Abacavir should only be used in HLA-B*5701-negative persons to reduce risk of hypersensitivity reactions. Evidence whether abacavir increases risk for myocardial infarction is conflicting. Long-term use of tenofovir is associated with increased risk of kidney injury, which is accentuated by concomitant use of boosted PIs. Tenofovir is more strongly associated with early and non-progressive decrease in bone mineral density.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)	Efavirenz* Delavirdine Rilpivirine* Etravirine Nevirapine	Efavirenz has long-term efficacy and safety data but has inferior tolerability to some INSTI-based regimens. There is conflicting evidence whether efavirenz may be associated with increased risk of suicidality or not. Rilpivirine is only an option for persons with HIV-1 RNA levels <100,000 copies/mL.
Integrase Strand Transfer Inhibitors (INSTI)	Dolutegravir* Elvitegravir* Raltegravir*	Compared with NNRTI-based or boosted PI-based regimens, INSTI-based regimens have consistently shown higher rates of viral suppression. Elvitegravir requires boosting with cobicistat. Elvitegravir boosted with cobicistat has similar rates of resistance as raltegravir; variants of HIV resistant to one drug should be considered cross-resistant with the other drug, though dolutegravir may be active against HIV strains resistant to raltegravir or elvitegravir. Raltegravir was the first INSTI approved and has demonstrated durable efficacy since coming to market in 2007; this durability is likely a class effect.
Protease Inhibitors (PI)	Atazanavir* Fosamprenavir Darunavir* Indinavir (ritonavir)** Lopinavir Nelfinavir Saquinavir Tipranavir	PIs are commonly used in combination with 2 NRTIs for initial ARV therapy. Most PIs are extensively metabolized by cytochrome P450 CYP3A system; ritonavir is generally given at low doses (100-200 mg/day) to inhibit CYP3A4 enzymes and boost the co-administered PIs. Cobicistat may also be used as a booster. Most PIs are associated with hyperlipidemia and other metabolic abnormalities such as insulin resistance. Long-term PI exposure has been associated with increased risk of cardiovascular disease. Newer PIs are less frequently associated with these adverse effects. Atazanavir blocks bilirubin conjugation, which can cause jaundice in some people but does not represent hepatotoxicity. Atazanavir may also be associated with cholelithiasis, nephrolithiasis and renal impairment. Atazanavir may be inferior to darunavir and raltegravir due to increased discontinuation rates observed with increased bilirubin levels. Darunavir contains a sulfa moiety and results in rash in about 10% of patients; incidence/severity of rash are similar in patients with or without a documented sulfa allergy.
CCR5 Inhibitors	Maraviroc	Maraviroc is only active in patients who do not have virions that use CXCR4 for cell entry. A specialized assay is therefore needed to screen for co-receptor tropism. Drug interactions may affect dosing.
Fusion Inhibitors	Enfuvirtide	Enfuvirtide must be given subcutaneously twice daily.

*These drugs are recommended as part of an initial ARV regimen in treatment-naïve HIV-infected patients by the IAS-USA and/or HHS guidelines.[1,2]
**Ritonavir is generally given at low doses to inhibit the P450 CYP3A system to boost co-administered PIs, which would otherwise be extensively metabolized by these enzymes.
^NRTI used as part of an ARV regimen for HIV or for Hepatitis B.

There are still several challenges with management of HIV infection:

- First, ARV therapy cannot eliminate HIV and only suppresses the virus, which still persists in reservoirs found in specialized immune cells and tissues.[10] Continued research is needed to better understand HIV and evaluate ARV therapy. Historically, many of the sentinel studies used to make policy decisions on when and how to treat HIV infection used endpoints such as suppression of virus replication in the peripheral blood, increases in peripheral blood CD4 count, or progression to AIDS.[11] Despite success using these outcomes, significant immunologic abnormalities were documented in these studies: CD4 cells continued to be dysfunctional, lymphoid tissues remained depleted of CD4 cells, markers of immune activation remained elevated, the CD8 T-cell responses remained abnormal, and responses to vaccines continued to be suboptimal.[11]

- Second, rapid development of drug resistance is the major cause of therapeutic failure.[1] High adherence to ARV is not achieved in many patients though it is necessary to maintain adequate viral control and reduce resistance and viral transmission.[8] Incomplete adherence leads to ongoing HIV replication, which, in the presence of suboptimal drug exposure, can select for viral strains with mutations conferring resistance to those agents.[10] A number of factors are associated with lower levels of adherence, including the stigma associated with HIV infection, depression, alcohol or drug use, young age, adverse effects of ARV, and pill burden.[10,12] A recent meta-analysis of 19 randomized controlled trials (n=6321) found that once-daily ARV regimens were associated with a modestly higher rate of adherence than twice-daily regimens, though the difference in adherence between the two groups were not associated with a difference in viral suppression.[12] Each antiretroviral drug, and to some degree each drug class, varies in its ability to generate drug resistance.[8] For example, the NRTIs and NNRTIs are more susceptible to development of resistance, while the PIs have a higher threshold for development of resistance and may be more forgiving in terms of non-adherence.[8] Transmission of drug-resistant variants can also occur, so a baseline genotypic resistance test is recommended once HIV infection is diagnosed.[8] The genotypic characterization of these mutations is now a routine part of clinical management and has improved outcomes.[8] Once resistance mutations are selected, they can persist indefinitely in infected cells, increasing the risk of treatment failure if the affected drug is used at later point of time.[8]

- Third, access to HIV care remains limited in marginalized communities in the U.S.[8] The U.S. Centers for Disease Control and Prevention estimates that only 50% of the people living with HIV in the U.S. receive regular HIV care and that among individuals receiving ARV, only 76% have suppressed viral loads.[13] Moreover, rates of adherence to ARV tend to decline over time, even when ARV therapy is provided at no cost.[10] Among the estimated 1.1 million persons living in the U.S. with HIV in 2009, 18.1% were undiagnosed, 45.2% were aware of their infection but not retained in care, 4.1% were retained in care but not prescribed ARV, 7.2% were prescribed ARV but not virally suppressed, and 25.3% were virally suppressed.[14] Forty-four percent were black; 19% were Hispanic; and 33% were white.[15] Most patients living with HIV (61%) were 35 to 54 years of age; 15% were 25 to 34 years of age; and 7% were 13 to 24 years of age.[15] Male individuals constituted 76% of the HIV population.[15] The percentages of black and Hispanics who were aware of their infection were lower than whites; the percentages linked to care, retained in care, prescribed ARV, and with a suppressed viral load were also lower among blacks and Hispanics compared with whites.[15] Persons who had undiagnosed HIV or diagnosed HIV but not retained in care accounted for 63.3% of the population infected with HIV in 2009 but were responsible for 91.5% of the estimated HIV transmissions during that time.[14] In contrast, persons who were virally suppressed were 94.0% (0.4 transmissions per 100 person-years) less likely to transmit HIV.[14] Fortunately, there are positive trends in some populations. The annual rate of HIV diagnoses during the last decade decreased by more than 33.2%, from 24.1 per 100,000 persons in 2002 to 16.1 in 2011.[16] The annual number of HIV diagnoses decreased the most in persons with infection attributed to injection drug use or heterosexual contact. Diagnoses attributed to male-to-male sexual contact, however, increased among males aged 13-24 years and 45 years and older.[16]

- Other, non-clinical challenges also exist. Recently the Community Access National Network (CANN), a group that supports access to HIV care, and the Partnership for Safe Medicines, a non-profit organization targeting counterfeit medication, published a document alerting clinicians and patients to evidence that HIV medications are being resold illegally.[17] In some cases, counterfeit medications were sold to patients or pharmacies; in other cases, fraudulently acquired medications were repackaged and sold to pharmacies. An August 2014 report by the HHS Office of Inspector General (OIG) also highlighted potential fraud involving prescription medications paid for by Medicare's Part D program.[18] According to the OIG, the high cost of ARV and the potential for the drugs to be abused may make them a target for fraud.[18] Data from the Centers for Medicare & Medicaid Services (CMS) between 2011 and 2012 included records of 135,554 patients who allegedly received ARV during a 1-year span costing the Part D program $2.8 billion.[18] Of these patients, 1,600 patients had no evidence of an HIV diagnosis in their Medicare records, used an unusually high number of pharmacies or prescribers, received excessive amounts of the drugs, or received simultaneous prescriptions for drugs that should not be used together.[18] The OIG also found evidence of "doctor shopping" in which 179 beneficiaries received prescriptions from at least 6 different prescribers.[18] Although the numbers of potentially fraudulent cases are relatively small and the data has some limitations, the OIG has recommended that CMS take further steps to monitor prescription fraud with these drugs.[19] From a clinical perspective, fraud involving ARV poses special risks to patients because it can contribute to the development of resistant strains of the virus.[19]

Purpose for Class Review:
The purpose of this guideline-centered review is to establish preferred drug lists of classes of HIV antiretroviral agents for the Oregon Health Plan (OHP) population, establish a basis to monitor for appropriate utilization and, if necessary, provide future evidence-based recommendations for the management of these agents as treatments evolve and more options become available.

Methods:
The two primary sources of practice guidelines utilized in the U.S. to guide management of HIV were reviewed: the IAS-USA guidelines and the HHS guidelines.[1–4] The World Health Organization (WHO) HIV/AIDS guidelines for key populations[6] were also consulted.

Guidelines:

International Antiviral Society-USA
Recommendations of the IAS-USA Panel on antiretroviral treatment of adult HIV infection were recently updated in 2014.[2] The recommendations were developed by a volunteer, international panel of experts in HIV research and patient care selected by the IAS-USA and vetted for suitability, expertise, conformance to the group's conflict of interest criteria, and ability to work toward consensus.[2] Strength of recommendations were graded as **A** (strong support), **B** (moderate support) or **C** (limited support). Quality of evidence was graded as **Ia** (≥1 RCT published in peer-reviewed literature), **Ib** (≥1 RCT published as an abstract), **IIa** (case-controls or cohorts published in peer-reviewed literature), **IIb** (case-controls or cohorts published in abstract) or **III** (panel analysis and opinion).

Initiating ARV Therapy:
In patients with HIV infection willing and ready to start therapy, ARV is recommended regardless of CD4 cell count.[2] Baseline genotypic testing for resistance should be performed in all treatment-naïve patients (**A IIa**).[2] The strength of recommendations and the quality of the evidence increase as the CD4 cell counts decrease and in the presence of certain concurrent conditions:

- For CD4 cell counts ≤500/µL: **A Ia**
- For CD4 cell counts >500/µL: **B III**
    - Except pregnancy (**A Ia**); chronic hepatitis B virus co-infection (**A IIa**); or HIV-associated nephropathy (**A IIa**)[2]

During the acute phase of primary HIV infection, ARV is recommended and should be offered, regardless of symptoms (**B III**) to reduce viral load, lower viral set-point, induce robust immune reconstitution and increase in CD4 cell counts. It should be started as soon as possible, preferably within the first 2 weeks of diagnosis, in patients with opportunistic infections (**A Ia**) and AIDS-defining illnesses (**A Ia**). An exception is in the setting of cryptococcal meningitis, where data on when best to initiate ARV are still unknown but should be considered when expert management of both cryptococcal and HIV infection is available (**B III**). ARV is recommended in all HIV-infected persons with tuberculosis (TB) and should be started within 2 weeks of TB treatment when the CD4 cell counts is <50/µL, and by 8 to 12 weeks for those with higher CD4 cell counts (**A Ia**).[2]

Monitoring ARV Therapy:
HIV RNA levels should be monitored at about 4 weeks after treatment is initiated or changed, and then every 3 months thereafter to confirm viral suppression is below the detectable limit of sensitive commercial assays (**A Ia**). Once HIV RNA level is suppressed at 1 year and CD4 cell count is stable at ≥350/µL, viral load and CD4 cell count can be monitored at intervals of ≤6 months in patients with good adherence (**C III**). Once viral load is suppressed consistently for more than 2 years and CD4 cell counts are consistently >500/µL, monitoring CD4 cell counts is optional unless virological failure occurs or there are concurrent immunosuppressive treatments or conditions (**C III**). HIV-1 RNA level >200 copies/mL should prompt evaluation of factors leading to failure and consideration of switching ARV (**A IIa**). Genotypic testing for resistance should also be performed in cases of virologic failure (**A Ia**). Laboratory monitoring for ARV toxicity is also recommended. After 16 weeks of successful treatment, the frequency of monitoring is generally decreased to between every 3 to 6 months (**C III**).[2]

Recommended ARV Regimens:
Initial ARV therapy is based on baseline resistance testing and patient characteristics but also involves consideration for patient preference.[2] Recommended first-line ARV is based on the combination of two NRTIs with either an INSTI, a NNRTI or a PI boosted with ritonavir or cobicistat.[2] Recommended and alternative regimens are listed in **Table 2** and **Table 3**.

Table 2. Recommended Initial ARV Regimens Equally Recommended by the International Antiviral Society-USA.[2]

Type of Regimen	Antiretroviral Drug Combination	Rating
Integrase Strand Transfer Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Dolutegravir plus tenofovir/emtricitabine	A Ia
	Dolutegravir plus abacavir/lamivudine**	A Ia
	Elvitegravir/cobicistat*/tenofovir/emtricitabine	A Ia
	Raltegravir plus tenofovir/emtricitabine	A Ia
Non-nucleoside Reverse Transcriptase Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Efavirenz/tenofovir/emtricitabine	A Ia
	Efavirenz plus abacavir/lamivudine**	A Ia
	Rilpivirine^/tenofovir/emtricitabine	A Ia
Protease Inhibitor (boosted) + 2 Nucleoside Reverse Transcriptase Inhibitors	Atazanavir (boosted with ritonavir) plus tenofovir/emtricitabine	A Ia
	Atazanavir (boosted with ritonavir) plus abacavir/lamivudine**	A Ia
	Darunavir (boosted with ritonavir) plus tenofovir/emtricitabine	A Ia

*Cytochrome P450 3A4 inhibitor without antiretroviral activity used to increase exposure of certain antiretroviral agents. Cobicistat has less drug interactions as ritonavir and is not interchangeable with ritonavir. Concomitant use of cobicistat and tenofovir is recommended only in patients with an estimated creatinine clearance ≥70 mL/min.
**Abacavir/lamivudine may perform less well with baseline HIV-1 RNA >100,000 copies/mL, unless combined with dolutegravir.
^Rilpivirine-based regimens recommended only in patients with pre-treatment HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/µL.

Table 3. Alternative Initial Regimens Recommended by the International Antiviral Society-USA.[2]

Type of Regimen	Antiretroviral Drug Combination	Rating
Integrase Strand Transfer Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Raltegravir plus abacavir/lamivudine**	B Ia
Non-nucleoside Reverse Transcriptase Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Nevirapine plus 2 NRTIs	B Ia
	Rilpivirine^ plus abacavir/lamivudine**	A Ia
Protease Inhibitor (boosted) + 2 Nucleoside Reverse Transcriptase Inhibitors	Atazanavir/cobicistat plus 2 NRTIs[#]	B Ia
	Lopinavir (boosted with ritonavir) fixed-dose combination with 2 NRTIs	B Ia
	Darunavir (boosted with ritonavir) plus abacavir/lamivudine**	B Ib
	Darunavir/cobicistat plus 2 NRTIs[#]	B III
Nucleoside Reverse Transcriptase Inhibitors-limiting* or Nucleoside Reverse Transcriptase Inhibitors-sparing*	Lopinavir (boosted with ritonavir) plus lamivudine	B Ia
	Lopinavir (boosted with ritonavir) plus raltegravir	B Ia
	Darunavir (boosted with ritonavir) plus raltegravir	B Ib

* Appropriate in clinical situations in which minimizing or eliminating NRTI exposure is desired (e.g., high risk of cardiovascular disease; positive HLA-B*5701 assay who also has chronic kidney disease or osteoporosis).[2]
^ Rilpivirine-based regimens recommended only in patients with pre-treatment HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/µL.
** Abacavir/lamivudine may perform less well with baseline HIV-1 RNA >100,000 copies/mL.
[#] Concomitant use of cobicistat and tenofovir is recommended only in patients with an estimated creatinine clearance ≥70 mL/min.

Specific Populations:

Pregnancy: The rate of congenital birth defects following exposure to ARV during pregnancy is not higher than that reported in the general population and is not greater with exposure during the first trimester than later during pregnancy.[2] Clinical experience supports initiation with zidovudine/lamivudine plus either ritonavir-boosted lopinavir or ritonavir-boosted atazanavir. Efavirenz is no longer contraindicated in pregnancy but is still generally avoided in clinical practice, especially during the first trimester. Pharmacokinetic changes during pregnancy may necessitate dose modification of ritonavir-boosted atazanavir when given with either tenofovir or acid suppressant drugs.[2]

Cardiovascular, Renal and Bone Diseases: Consideration should be given to avoiding use of abacavir, ritonavir-boosted lopinavir, and ritonavir-boosted fosamprenavir in persons at high risk for cardiovascular disease because these regimens have been associated with increased risk of cardiovascular events in some studies. Patients with reduced renal function should generally avoid tenofovir, especially in combination with a boosted PI. Initiation of ARV therapy generally results in a 2% to 6% loss of bone mineral density (BMD) over the following 1 to 2 years. Loss of BMD is greater with tenofovir than with abacavir, and less with raltegravir than with ritonavir-boosted atazanavir or ritonavir-boosted darunavir when combined with tenofovir/emtricitabine.[2]

HBV Infection: Recommended ARV therapy includes tenofovir and emtricitabine (or lamivudine) as the backbone NRTI regimen.[2]

HCV Infection: Drug interactions between ARV and direct-acting antivirals for HCV are common because many of these drugs are substrates for CYP P450 or P-glycoprotein. Therefore, selection of an optimal ARV regimen is determined by potential drug interactions.[2]

Malignancy and Immunosuppressive Therapy: Because of their favorable drug interaction profiles, dolutegravir- or raltegravir-based regimens are recommended in patients receiving anticancer or immunosuppressive agents.[2]

Treatment-Experienced Patients:

Consideration of a new ARV regimen in the setting of virologic failure should always include consideration for the potential reasons for failure, such as adverse effects, exacerbation of comorbidities, drug interactions, pill burden, dosing frequency, and food requirements, all of which can affect adherence. Interpretation of mutations and cross-resistance can be complex and consideration for a new ARV regimen is done with expert advice. Rates of virologic failure are comparable at 1 year for NNRTI and boosted PI regimens; however, NNRTI-based regimens are associated with more NNRTI and NRTI mutations than PI-based regimens. Higher rates of treatment failure are also reported in patients receiving alternative recommended ARV, which may suggest patients receiving alternative recommended ARV are more non-adherent to the regimen. The second regimen used after initial virologic failure should generally include a boosted PI because of the high barrier to resistance, especially if there is evidence of a compromised NRTI backbone. If there is initial failure with an NNRTI-based regimen, there is evidence for a boosted PI with at least one other active agent (NRTI, NNRTI or INSTI). In the setting of multidrug resistance, inclusion of a potent boosted PI (e.g., darunavir) in the new regimen is recommended because of its higher barrier to resistance. ARV typically used with a boosted PI in regimens for multidrug-resistant HIV include ertravirine, dolutegravir, maraviroc, and in exceptional circumstances, the fusion inhibitor enfuvirtide.[2]

U.S. Department of Health and Human Services

The HHS guideline on use of antiretroviral agents in HIV-1-infected adults and adolescents was last updated April 2015.[1] Pre-treatment genotypic resistance testing should guide selection of the most optimal initial ARV regimen since 6-16% of HIV drug resistance is found in ARV-naïve patients and the presence of transmitted drug-resistant viruses may lead to suboptimal virologic response.[1] Suboptimal adherence may result in reduced treatment response. Patient factors such as active substance abuse or depression, the complexity of the ARV regimen, access to medication, and inadequate treatment education and support should all be considered and addressed in order to improve adherence to the ARV.[1] Initial patient characteristics that should be considered when choosing an ARV regimen are:

- Pre-treatment HIV RNA level (viral load);
- Pre-treatment CD4 cell count;
- HIV genotypic drug resistance testing results;
- HLA-B*5701 status;
- Patient preferences; and
- Patient's anticipated adherence/motivation.[1]

The Panel on Antiretroviral Guidelines for Adults and Adolescents graded strength of recommendations as **A** (strong support), **B** (moderate support) or **C** (optional). Quality of evidence was graded as **I** (data from RCTs), **II** (data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes) or **III** (expert opinion).

Deferring ARV therapy until the CD4 count declines places a person at risk for AIDS-defining conditions and has been associated with higher risk of morbidity and mortality. In addition, the magnitude of CD4 recovery is directly correlated with CD4 count at ARV initiation, and many individuals who start treatment with CD4 counts <350 cells/µL never achieve counts >500 cells/µL until up to 6 years after initiating ARV therapy. Therefore, initiating ARV in treatment-naïve patients is recommended for all HIV-infected persons if pretreatment CD4 count <350 cells/µL to reduce risk of disease progression (**A I**). Initiating ARV in patients with CD4 counts between 350-500 cells/µL is also recommended (**A II**), but the recommendation is based on observational data showing a statistically significant increase in progression to AIDS, but with unclear effect on mortality, if ARV is delayed. The panel moderately recommends initiation of ARV in patients with a CD4 count >500 cells/µL (**B III**), recognizing there is inconclusive evidence early initiation with high CD4 counts decreases morbidity or mortality but is beneficial from a public health perspective.[1]

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An ARV regimen for treatment-naïve patients generally consists of two NRTIs (one of which is emtricitabine/tenofovir or abacavir/lamivudine) in combination with a third active antiretroviral drug from one of three drug classes: an INSTI, an NNRTI, or a PI boosted with cobicistat or ritonavir. The choice of the NRTI combination is typically guided by differences between tenofovir and abacavir because emtricitabine and lamivudine have similar safety and efficacy profiles. The choice between an INSTI, NNRTI or PI as the third drug in an initial ARV regimen should be guided by the regimen's efficacy, genetic barrier to resistance, adverse effects profile, patient convenience, the patient's comorbidities, and drug-drug interactions. The panel classifies the regimens in **Table 4** as *recommended* regimens for antiretroviral-naïve patients.[1]

Table 4. Recommended Initial ARV Regimens in Treatment-naïve Patients.[1]

Type of Regimen	Antiretroviral Drug Combination	Rating
Integrase Strand Transfer Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Dolutegravir/abacavir/lamivudine*	A I
	Dolutegravir plus tenofovir/emtricitabine	A I
	Elvitegravir/cobicistat/tenofovir/emtricitabine^	A I
	Raltegravir plus tenofovir/emtricitabine	A I
Protease Inhibitor (boosted) + 2 Nucleoside Reverse Transcriptase Inhibitors	Darunavir/ritonavir plus tenofovir/emtricitabine	A I

*Recommended only in patients who are HLA-B*5701 negative.
^Concomitant use of cobicistat and tenofovir is recommended only in patients with an estimated creatinine clearance ≥70 mL/min.

The INSTI-based regimens are recommended because of their high virologic efficacy, excellent safety and tolerability profiles and, with dolutegravir and raltegravir, low number of drug-drug interactions. For patients who are at high risk for intermittent therapy because of poor adherence or have transmitted NRTI drug resistance, a ritonavir-boosted PI-based regimen is preferred given the PIs high genetic barrier to resistance.[1]

Alternative regimens are also recommended on the basis of individual patient characteristics and needs. These regimens are effective and tolerable, but have potential disadvantages when compared with the recommended regimens, have limitations for use in certain patient populations, or have less supporting data from randomized clinical trials. The panel classifies the regimens in **Table 5** as *alternative* regimens for antiretroviral-naïve patients.[1]

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Table 5. Alternative Initial ARV Regimens in Treatment-naïve Patients.[1]

Type of Regimen	Antiretroviral Drug Combination	Rating
Non-nucleoside Reverse Transcriptase Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Efavirenz/tenofovir/emtricitabine	B I
	Rilpivirine/tenofovir/emtricitabine*	B I
Protease Inhibitor (boosted) + 2 Nucleoside Reverse Transcriptase Inhibitors	Atazanavir/cobicistat plus tenofovir/emtricitabine**	B I
	Atazanavir with ritonavir plus tenofovir/emtricitabine	B I
	Darunavir with ritonavir plus abacavir/lamivudine^	B II
	Darunavir/cobicistat plus tenofovir/emtricitabine**	B II
	Darunavir/cobicistat plus abacavir/lamivudine^	B III

* Rilpivirine-based regimens recommended only in patients with pre-treatment HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/µL.
** Concomitant use of cobicistat and tenofovir is recommended only in patients with an estimated creatinine clearance ≥70 mL/min.
^ Abacavir/lamivudine may perform less well with baseline HIV-1 RNA >100,000 copies/mL. Recommended only in patients who are HLA-B*5701 negative.

Other regimen options are regimens that, in comparison to *recommended* and *alternative* regimens, may have reduced virologic activity, limited supporting data from large comparative clinical trials, or other factors such as more toxicities, higher pill burden, poor drug interaction profile, or limitations for use in certain patients populations.[1] The panel classifies the regimens in **Table 6** as *other optional* regimens for antiretroviral-naïve patients.

Table 6. Other Optional Initial ARV Regimens in Treatment-naïve Patients.[1]

Type of Regimen	Antiretroviral Drug Combination	Rating
Integrase Strand Transfer Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Raltegravir plus abacavir/lamivudine*	C II
Non-nucleoside Reverse Transcriptase Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Efavirenz plus abacavir/lamivudine*	C I
Protease Inhibitor (boosted) + 2 Nucleoside Reverse Transcriptase Inhibitors	Atazanavir with ritonavir plus abacavir/lamivudine*	C I
	Lopinavir/ritonavir plus abacavir/lamivudine*	C I
	Lopinavir/ritonavir plus tenofovir/emtricitabine	C I
	Atazanavir with cobicistat plus abacavir/lamivudine*	C III
Other Regimens When Tenofovir or Abacavir Cannot be Used	Darunavir with ritonavir plus raltegravir	C I
	Lopinavir/ritonavir plus lamivudine	C I

* Abacavir/lamivudine may perform less well with baseline HIV-1 RNA >100,000 copies/mL. Recommended only in patients who are HLA-B*5701 negative.

HIV/HCV Co-infection:
All HIV-infected patients should be screened for HCV. ARV may slow the progression of liver disease by preserving and restoring immune function and reducing HIV-related immune activation and inflammation. For most HIV/HCV-coinfected patients, including those with cirrhosis, the benefits of ARV therapy outweigh concerns regarding drug-induced hepatotoxicity. Therefore, ARV should be initiated in most HIV/HCV-coinfected patients, regardless of the CD4 count (**B II**). However, combined treatment of HIV and HCV can be complicated by drug-drug interactions, increased pill burden and toxicities; therefore, in patients with CD4 counts >500 cells/µL, ARV therapy may be deferred until HCV treatment is completed (**C III**). In patients with lower CD4 counts (e.g., <200 cells/µL), ARV therapy should be initiated promptly (**A I**) and HCV therapy may be delayed until the patient is stable on HIV treatment (**C III**). Initial ARV regimens recommended for most HIV/HCV-coinfected patients are the same as those recommended for patients without HCV infection. However, the ARV regimen should be selected with consideration for potential drug-drug interactions and overlapping toxicities if given concurrently with the HCV treatment regimen.[1]

HIV/HBV Co-infection:
Prior to initiation of ARV therapy, all patients who test positive for hepatitis B surface antigen should be tested for HBV DNA using a quantitative assay to determine the level of activity of HBV replication (**A III**). Emtricitabine, lamivudine and tenofovir have activity against HBV. If HIV treatment is needed, fully suppressive ARV initiated with the NRTI backbone combination of emtricitabine plus tenofovir or lamivudine plus tenofovir is recommended (**A I**). If HBV treatment is needed and tenofovir cannot be safely used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen (**B I**). Other HBV treatment regimens include peginterferon alfa monotherapy or adefovir in combination with lamivudine or emtricitabine or telbivudine in addition to a fully suppressive ARV regimen (**B II**). Discontinuation of agents with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV.[1]

Pregnancy:
The use of ARV therapy and the resultant reduction of HIV RNA levels decrease perinatal transmission of HIV. Thus, ARV therapy is recommended for all HIV-infected pregnant women, regardless of virologic, immunologic or clinical parameters (**A I**).[4] Genotypic resistance testing is recommended for all pregnant women before ARV initiation (**A III**) and for pregnant women with detectable HIV RNA levels while on ARV (**A I**). Pregnancy should not preclude the use of an optimal ARV regimen.[4]

Pediatrics:
Few randomized, Phase 3 clinical trials of ARV in pediatric patients exist that provides direct comparison of different treatment regimens. Most pediatric drug data come from Phase I/II safety and pharmacokinetic trials and non-randomized, open-label studies. ARV for children should generally consist of two NRTIs plus one active drug from one of the following classes: a NNRTI or a PI boosted with low-dose ritonavir. Limited evidence indicates INSTIs may have also be effective in pediatric patients, but there are still insufficient data to prefer an INSTI-based regimen over the other commonly used pediatric regimens at this time. Selection of an initial regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing (**A III**).[3] The panel recommends initiating combination ARV in treatment-naïve children using one of the following preferred agents in combination with **2 NRTIs**:

- For neonates/infants aged ≥42 weeks postmenstrual and ≥14 days postnatal and children <3 years: lopinavir/ritonavir (**A I**);
- For children aged 3 years to <6 years: efavirenz or lopinavir/ritonavir (**A I**);
- For children aged ≥6 years: atazanavir/ritonavir or efavirenz or lopinavir/ritonavir (**A I**).

The panel recommends the following preferred 2-NRTI combinations:

- For infants <3 months: zidovudine plus (lamivudine or emtricitabine) (**A I**);
- For children aged ≥3 months: abacavir plus (lamivudine or emtricitabine) (**A I**) or zidovudine plus ((lamivudine or emtricitabine) (**A I**);
    - HLA-B*5701 genetic testing should be performed before initiating abacavir-based therapy, and abacavir should not be given to a child who tests positive for HLA-B*5701 (**A II**);
- For children aged ≥12 years: abacavir plus lamivudine or plus emtricitabine (**A I**).
- For adolescents at Tanner Stage 4 or 5: abacavir plus lamivudine or plus emtricitabine (**A I**) or tenofovir plus lamivudine or plus emtricitabine (**A I**).[3]

HIV-2 Infection:
HIV-2 infection is endemic in West Africa. It has had only limited spread outside this area and should be considered in persons of West Africa origin or in those who have had sexual contact or shared needles with persons of West Africa origin. Like HIV-1, HIV-2 infection can progress to AIDS but is generally characterized by a longer asymptomatic stage, lower plasma HIV-2 viral loads, and lower mortality rate relative to HIV-1 infection. There have been no randomized trials addressing the question of when to start ARV or the choice of initial or second-line therapy. Although the optimal CD4 count threshold for initiating ARV in HIV-2 is unknown, ARV therapy should be started before there is clinical progression. However, NNRTIs and enfuvirtide should be avoided as HIV-2 is intrinsically resistant to these drugs. Pending more data, an initial ARV regimen for HIV-2 infected patients, or HIV-1/HIV-2 co-infected patients, should include two NRTIs plus a boosted PI or an INSTI.[1]

Virologic Failure:
ARV regimens currently recommended for initial therapy of HIV-infected patients have a high likelihood of achieving and maintaining plasma HIV RNA levels below the limits of detection of currently used assays. Patients on ARV who do not achieve this treatment goal or who experience virologic rebound often develop resistance mutations to one or more components of their regimen. Many patients with detectable viral loads are non-adherent to treatment. Once virologic failure is confirmed, every effort should be made to assess whether suboptimal adherence or drug-drug interactions may be contributing to inadequate virologic response to ARV. If virologic failure persists after these issues have been addressed, resistance testing should be performed, and the regimen should be changed as soon as possible to avoid progressive accumulation of resistance mutations. In all cases, expert advice is critical. Drug-resistance testing should be performed while the patient is taking the failing ARV regimen (**A I**) or within 4 weeks of treatment discontinuation (**A II**). A new regimen should include at least two, and preferably three, fully active agents (**A I**). A fully active agent is one that is expected to have uncompromised activity on the basis of the patient's treatment history and drug-resistance testing results. In general, adding a single ARV agent to a virologically failing regimen is not recommended because this may increase the risk of development of resistance to all drugs in the regimen (**B II**). For some highly ARV-experienced patients, maximal virologic suppression is not possible. In these cases, ARV therapy should be continued (**A I**) with regimens designed to minimize toxicity, preserve CD4 counts, and delay clinical progression.[1]

World Health Organization
The WHO recently published guidelines on HIV prevention, diagnosis, treatment and care for key populations in 2014.[6] The guidelines aim to increase awareness of the needs and issues important to five key populations, and provide a comprehensive package of evidence-based HIV-related recommendations for these groups: men who have sex with men, people who inject drugs, people in prisons and other closed settings, sex workers, and transgender people. Recommendations largely encompass all facets of HIV prevention and care in these populations. However, there are no clinical ARV recommendations specific to these populations except to note that because of stigma, discrimination and marginalization, these populations frequently present late for treatment and will require immediate initiation of ARV therapy. The WHO guidelines primarily differ from the U.S. guidelines in that they make no specific recommendation to start ARV therapy when CD4 counts are higher than 500 cell/μL.[6]

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Appendix 1: HIV Life Cycle

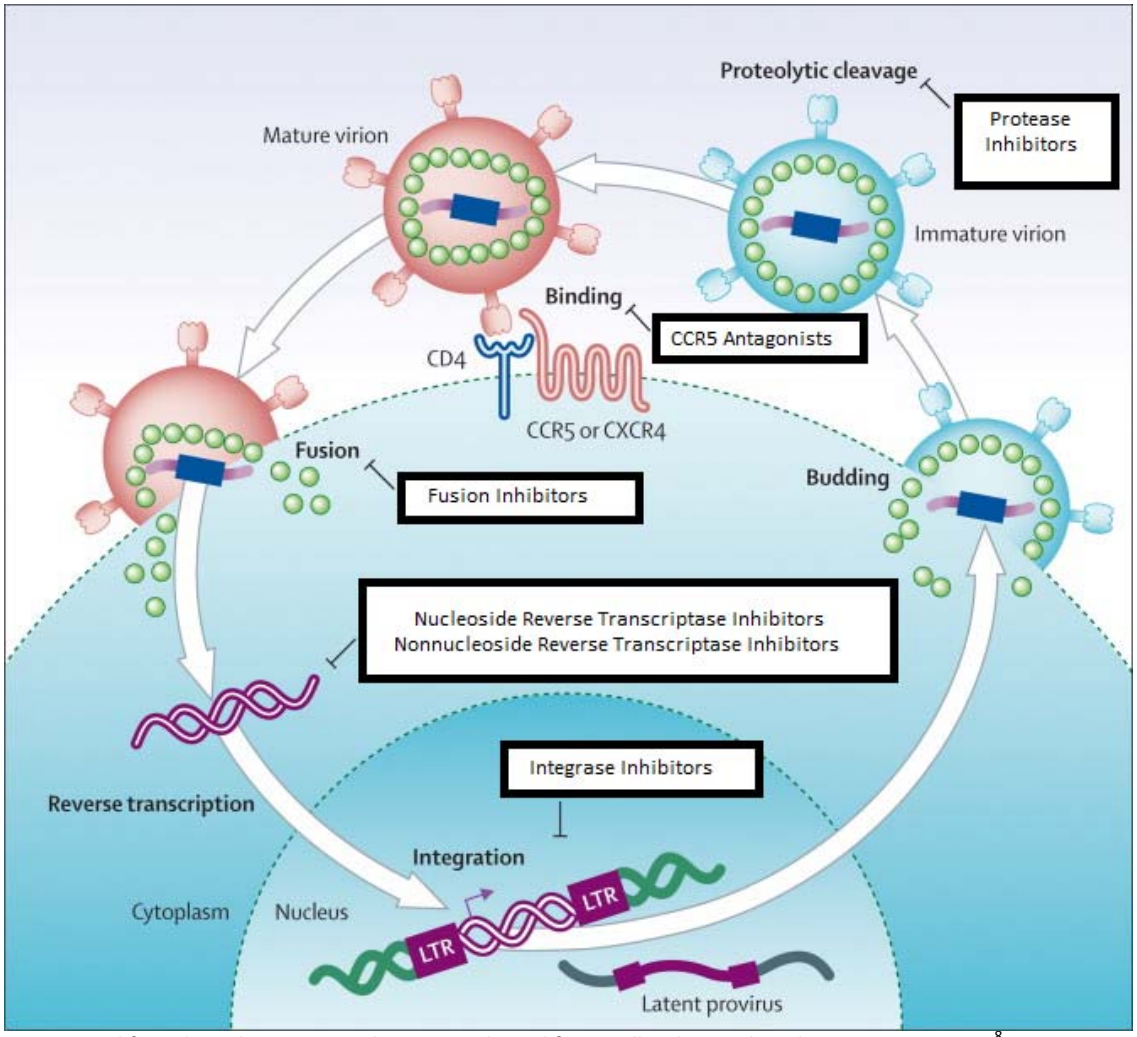

Figure. HIV life cycle and antiretroviral targets. *Adapted from Volberding and Deeks. Lancet 2010;376.*[8]

Appendix 2. Drug Information of FDA-Approved Antiretroviral Therapy and Pharmacokinetic Enhancers

Table 1. Antiretroviral Therapy Formulations

Drug Name	Mechanism/Class	Oral Formulation(s)	Dosing Frequency
ZIAGEN (abacavir)	NRTI	Solution; Tablet*	Daily – BID
EPZICOM (abacavir/lamivudine)	NRTI	Tablet	Daily
TRIUMEQ (abacavir/dolutegravir/lamivudine)	NRTI/INSTI	Tablet	Daily
TRIZIVIR (abacavir/lamivudine/zidovudine)	NRTI	Tablet*	BID
EMTRIVA (emtricitabine)	NRTI	Capsule; Solution	Daily
TRUVADA (emtricitabine/tenofovir)	NRTI	Tablet	Daily
ATRIPLA (efavirenz /emtricitabine/tenofovir)	NRTI/NNRTI	Tablet	Daily
COMPLERA (emtricitabine/rilpivirine/tenofovir)	NRTI/NNRTI	Tablet	Daily
STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir)	NRTI/INSTI/CYP P450 Inhibitor	Tablet	Daily
EPIVIR (lamivudine)	NRTI	Solution*; Tablet*	Daily – BID
COMBIVIR (lamivudine/zidovudine)	NRTI	Tablet*	BID
VIDEX EC; VIDEX (didanosine)	NRTI	Capsule*; Solution	Daily – BID
ZERIT (stavudine)	NRTI	Capsule*; Solution*	BID
RETROVIR (zidovudine)	NRTI	Capsule*; Syrup*; Tablet*	BID – TID
SUSTIVA (efavirenz)	NNRTI	Capsule; Tablet	Daily
EDURANT (rilpivirine)	NNRTI	Tablet	Daily
RESCRIPTOR (delavirdine)	NNRTI	Tablet	TID
INTELENCE (etravirine)	NNRTI	Tablet	BID
VIRAMUNE; VIRAMUNE XR (nevirapine)	NNRTI	Suspension*; Tablet*; Tablet ER*	Daily – BID
TIVICAY (dolutegravir)	INSTI	Tablet	Daily – BID
VITEKTA (elvitegravir)	INSTI	Tablet	Daily
ISENTRESS (raltegravir)	INSTI	Chew Tablet; Packet; Tablet	BID
REYATAZ (atazanavir)	PI	Capsule; Packet	Daily
EVOTAZ (atazanavir/cobicistat)	PI/CYP P450 Inhibitor	Tablet	Daily
PREZISTA (darunavir)	PI	Suspension; Tablet	Daily – BID
PREZCOBIX (darunavir/cobicistat)	PI/CYP P450 Inhibitor	Tablet	Daily
LEXIVA (fosamprenavir)	PI	Suspension; Tablet	Daily – BID
CRIXIVAN (indinavir)	PI	Capsules	BID – TID
KALETRA (lopinavir/ritonavir)	PI/CYP P450 Inhibitor	Solution; Tablet	Daily – BID

VIRACEPT (nelfinavir)	PI	Tablet	BID – TID
INVIRASE (saquinavir)	PI	Capsule; Tablet	BID
APTIVUS (tipranavir)	PI	Capsule; Solution	BID
NORVIR (ritonavir)	CYP P450 Inhibitor	Capsule; Solution; Tablet	w/ PI
TYBOST (cobicistat)	CYP P450 Inhibitor	Tablet	Daily
SELZENTRY (maraviroc)	CCR5 Antagonist	Tablet	BID
FUZEON (enfuvirtide)	Fusion Inhibitor	Solution (subcutaneous inj)	BID

*generic formulation available

Table 2. Drug Characteristics (adapted from the HHS HIV Guideline for Adults and Adolescents[1])

Drug Name	Metabolism/Elimination/Dose Adjustments	Adverse Events
Nucleoside Reverse Transcriptase Inhibitors		
Abacavir (ABC) Fixed Combinations: ABC/ZDV/3TC ABC/3TC ABC/3TC/DTG	• Metabolized by alcohol dehydrogenase and glucuronyl transferase • Renal excretion of metabolites: 82% • Dose adjustment for ABC recommended with mild hepatic insufficiency • Only NRTI to not require renal dose adjustment	• Hypersensitivity Reactions: patients positive for HLA-B*5701 at highest risk; symptoms may include: fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, fatigue, or respiratory symptoms (sore throat, cough or shortness of breath) • Initial cohort studies suggest increased risk of MI with recent/current use of ABC, but the risk has not been substantiated in other studies
Didanosine (ddI)	• Renal excretion: 50% • Dose adjustment for ddI recommended with renal insufficiency	• Pancreatitis • Peripheral neuropathy • Retinal changes, optic neuritis • Lactic acidosis with hepatic steatosis w/ or w/o pancreatitis (rare but life-threatening) • Nausea, vomiting • Insulin resistance; diabetes mellitus • Potential association w/ non-cirrhotic portal hypertension • One cohort suggested increased risk of MI with recent/current use of ddI, but the risk has not been substantiated in other studies
Emtricitabine (FTC) Fixed Combinations: FTC/EFV/TDF FTC/RPV/TDF FTC/EVG/c/TDF FTC/TDF	• Renal excretion: 86% • Dose adjustment for FTC recommended with renal insufficiency	• Minimal toxicity • Hyperpigmentation/skin discoloration
Lamivudine (3TC) Fixed Combinations: 3TC/ZDV 3TC/ABC 3TC/ZDV/ABC 3TC/ABC/DTG	• Renal excretion: 71% • Dose adjustment for 3TC recommended with renal insufficiency	• Minimal toxicity • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue 3TC
Stavudine (d4T)	• Renal excretion: 50% • Dose adjustment for d4T recommended with renal	• Peripheral neuropathy • Hyperlipidemia; lipoatrophy

	insufficiency	• Pancreatitis • Lactic acidosis/severe hepatomegaly w/ hepatic steatosis (rare but life-threatening) • Insulin resistance; diabetes mellitus • Rapidly progressive ascending neuromuscular weakness (rare)
Tenofovir (TDF) Fixed Combinations: TDF/EFV/FTC TDF/RPV/FTC TDF/EVG/c/FTC TDF/FTC	• Renal excretion is primary route of elimination • Dose adjustment for TDF recommended with renal insufficiency	• Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy • Osteomalacia, decrease in bone mineral density • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF • Asthenia, headache, diarrhea, vomiting and flatulence
Zidovudine (ZDV) Fixed Combinations: ZDV/3TC ZDV/3TC/ABC	• Metabolized to azidothymidine glucuronide • Renal excretion of azidothymidine glucuronide • Dose adjustment for ZDV recommended with renal insufficiency	• Bone marrow suppression; macrocytic anemia or neutropenia • Nausea, vomiting, headache, insomnia, asthenia • Nail pigmentation • Lactic acidosis/severe hepatomegaly w/ hepatic steatosis (rare but life-threatening) • Hyperlipidemia; lipoatrophy • Insulin resistance; diabetes mellitus • Myopathy
Non-Nucleoside Reverse Transcriptase Inhibitors		
Efavirenz (EFV) Fixed Combinations: EFV/TDF/FTC	• Metabolized by CYP 2B6 (primary), 3A4 and 2A6 • CYP 3A4 mixed inducer/inhibitor (primarily inducer) • CYP 2C9 and 2C19 inhibitor, 2B6 inducer	• Rash • Neuropsychiatric symptoms • Increased transaminase levels • Hyperlipidemia • False-positive results w/ some cannabinoid and benzodiazepine screening assays reported • Teratogenic in primates; potentially teratogenic during first trimester in pregnant women
Etravirine (ETR)	• Metabolized by CYP 3A4, 2C9 and 2C19 • Induces CYP 3A4 • Inhibits 2C9 and 2C19	• Rash, including Stevens-Johnson syndrome (rare) • Hypersensitivity reactions, characterized by rash, sometimes organ dysfunction (hepatic failure) • Nausea
Nevirapine (NVP)	• Metabolized by CYP P450s • Induces CYP 3A4 and 2B6 • 80% excreted in urine (glucuronidated metabolites; <5% unchanged); 10% in feces	• Rash, including Stevens-Johnson syndrome (rare) • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported o Rash reported in about 50% of cases o ARV-naïve females w/ CD4 counts >250 cells/µL and ARV-naïve males w/ CD4 counts >400 cells/µL are at significantly higher risk. Do not initiate NVP in these patients.
Rilpivirine (RPV) Fixed Combinations: TDF/RPV/FTC	• Metabolized by CYP 3A4	• Rash • Depression, insomnia, headache • Hepatotoxicity
Protease Inhibitors		
Atazanavir (ATV) Fixed Combinations: ATV/c	• Metabolized by CYP 3A4 • Inhibits CYP 3A4 • Dose adjustment for ATV recommended with hepatic insufficiency • With cobicistat: metabolized and inhibits CYP 3A4	• Indirect hyperbilirubinemia • Prolongs PR interval; reports of first degree symptomatic AV block • Hyperglycemia • Cholelithiasis • Nephrolithiasis • Renal insufficiency • Serum transaminase elevations

		• Hyperlipidemia, especially w/ RTV boosting; fat maldistribution • Skin rash • Increase in serum creatinine w/ cobicistat
Darunavir (DRV) Fixed Combinations: DRV/c	• Metabolized by CYP 3A4 • Inhibits CYP 3A4 • Induces CYP 2C9 • With cobicistat: metabolized and inhibits CYP 3A4	• Skin rash (10%); contains a sulfonamide moiety; Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia; fat maldistribution • Serum transaminase elevation • Hyperglycemia • Increase in serum creatinine w/ cobicistat
Fosamprenavir (FPV)	• Metabolized by CYP 3A4 • Inhibits and induces CYP 3A4 • Dose adjustment for FPV recommended with hepatic insufficiency	• Skin rash (12%); contains a sulfonamide moiety • Diarrhea, nausea, vomiting • Headache • Hyperlipidemia; fat maldistribution • Serum transaminase elevation • Hyperglycemia • Nephrolithiasis
Indinavir (IDV)	• Metabolized by CYP 3A4 • Inhibits CYP 3A4 • Dose adjustment for IDV recommended with hepatic insufficiency	• Nephrolithiasis • GI intolerance, nausea • Hepatitis; indirect hyperbilirubinemia • Hyperlipidemia; fat maldistribution • Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia and hemolytic anemia • Hyperglycemia
Lopinavir/Ritonavir (LPV/r)	• Metabolized by CYP 3A4 • Inhibits CYP 3A4	• GI intolerance, nausea, vomiting, diarrhea • Pancreatitis • Asthenia • Hyperlipidemia (esp. hypertriglyceridemia); fat maldistribution • Serum transaminase elevation • Hyperglycemia • Insulin resistance; diabetes mellitus • PR interval and QT interval prolongation
Nelfinavir (NFV)	• Metabolized by CYP 2C19 and 3A4 to M8 metabolite • Inhibits CYP 3A4 • Only PI not boosted with RTV	• Diarrhea • Hyperlipidemia; fat maldistribution • Hyperglycemia • Serum transaminase elevation
Ritonavir (RTV) Fixed Combinations: LPV/r	• Metabolized primary by CYP 3A4 and 2D6 • Potently inhibits CYP 3A4 and 2D6 • Induces CYP 1A2, 2C8, 2C9 and 2C19 and UGT1A1	• GI intolerance, nausea, vomiting, diarrhea • Paresthesia (circumoral and extremities) • Hyperlipidemia (esp. hypertriglyceridemia); fat maldistribution • Hepatitis • Asthenia • Hyperglycemia

Saquinavir (SQV)	• Metabolized by CYP 3A4	• GI intolerance, nausea, and diarrhea • Headache • Serum transaminase elevation • Hyperlipidemia; fat maldistribution • Hyperglycemia • PR interval and QT interval prolongation
Tipranavir (TPV)	• Metabolized by CYP 3A4 • Induces CYP 3A4, 1A2, 2C19 • Inhibits CYP 2D6 • Net effect when combined w/ RTV: inhibits CYP 3A4 and 2D6	• Hepatotoxicity: clinical hepatitis (including hepatic decompensation and hepatitis-associated fatalities) has been reported • Skin rash (3% to 21%); TPV has a sulfonamide moiety • Rare cases of fatal and nonfatal intracranial hemorrhages; risks include brain lesion, head trauma, recent neurosurgery, coagulopathy; hypertension; alcoholism; use of anticoagulants/antiplatelets • Hyperlipidemia; fat maldistribution • Hyperglycemia
Integrase Strand Transfer Inhibitors		
Dolutegravir (DTG) Fixed Combinations: DTG/ABC/3TC	• UGT1A1-mediated glucuronidation, and to a lesser extent CYP3A	• Hypersensitivity reactions including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported • Insomnia • Headache
Elvitegravir (EVG) Fixed Combinations: EVG/c/FTC/TDF	• Metabolized by CYP 3A, UGT1A1 and 1A3	• Nausea • diarrhea
Raltegravir (RAL)	• UGT1A1-mediated glucuronidation	• Rash, including Stevens-Johnson syndrome, hypersensitivity reactions, toxic epidermal necrolysis • Nausea; diarrhea • Headache • Pyrexia • CPK elevation, muscle weakness and rhabdomyolysis • Insomnia
Fusion Inhibitor		
Enfuvirtide (T20)	• Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool	• Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in almost 100% of patients • Increased incidence of bacterial pneumonia • Hypersensitivity reactions (<1%); symptoms include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Re-challenge is not recommended.
CCR5 Antagonist		
Maraviroc (MVC)	• Metabolized by CYP 3A4	• Abdominal pain • Cough; Upper respiratory tract infections • Dizziness • Musculoskeletal symptoms • Pyrexia • Rash • Hepatotoxicity, which may be preceded by severe rash or signs of systemic allergic reactions • Orthostatic hypotension, especially in patients with severe renal insufficiency

Abbreviations: c = cobicistat; r = ritonavir

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Drug Use Evaluation: Human Immunodeficiency Virus (HIV) Antiretrovirals

Research Questions:

1) What antiretroviral therapies (ARVs) are used by Oregon Health Plan (OHP) patients, are the ARVs used recommended by guidelines and what is the relative net cost?
2) What is the prevalence of OHP patients who are treated prophylactically for HIV transmission?
3) What is the level of adherence to ART by OHP patients?
4) What is the prevalence of OHP patients using ARV regimens that are recommended to be always avoided by United States Department of Health and Human Services (HHS)?[1]
5) What is the prevalence of OHP patients meeting fraud and misuse indicators developed by the HHS Office of Inspector General?[2]

Conclusions:

1) There was approximately a 17% increase in the amount paid to pharmacies per member per month and 8% decrease in claim count per 1000 members per month over the calendar year. This trend was driven by increased use of more expensive combination products resulting in fewer claims but higher costs. Complera™ and Stribild™ cost increased about 50% during this time. The most commonly prescribed ARVs are highly recommended or alternative options according to guidelines.[3] The net cost of the most common ARV regimens varied from a low of about $12,410/year to a high of about $32,850/year. Integrase strand transfer inhibitor (INSTI) therapies are some of the least expensive and have fewer potential drug interactions whereas protease inhibitor (PI) based therapies are some of the more expensive with more potential drug interactions.
2) There is rare use of HIV transmission prophylaxis at this time. Only 12 patients (2.1%) met the definition of post-exposure ARV and 4 patients (0.7%) met the definition of pre-exposure ARV.
3) Adherence to ARV remains a primary concern as just 59.5% of patients were more than 90% adherent to one or more of their ARV drugs. One combination product is significantly more expensive than other competing combination products. Identifying this poor value to prescribers could both improve OHP cost structure while maintaining access to multiple combination products to improve adherence.
4) No OHP patients were using ARVs that are recommended to avoid.
5) Using HHS Office of Inspector General devised criteria; there is little indication of fraud or abuse of ARV drugs in the FFS program. Three patients met the excessive dose indicator but service dates indicate lower doses were likely used by the patient. There were no patients accessing excessive numbers of pharmacies or prescribers. Four patients (0.7%) had exactly 480 “Days Supply” of several drugs each during the year.

Recommendations:

1) Work with established, high Medicaid volume HIV clinics to identify high value (i.e. preferred) regimens and low value (non-preferred) regimens.
2) Work with established, high Medicaid volume HIV clinics to determine the best way to educate prescribers of least and best value drugs.
3) Work with established, high Medicaid volume HIV clinics to determine opportunities to collaborate and assist with improving adherence to antiretroviral therapy.

Background:
In Oregon, the prevalence of HIV in 2013 was 5.0 per 100,000 persons (9.2 per 100,000 in men and 0.8 per 100,000 in women).[4] The prevalence was highest for Hispanic men (14.8 per 100,000) and black men (12.3 per 100,000).[4] Oregon counties with HIV rates above the state average included Multnomah (13.4), Polk (10.4), Malheur (6.6) and Washington (5.8) counties.[4] The OHP fee-for-service (FFS) program spent about $500,000 (net of rebate) in the first quarter of 2015 on ARV. The HIV ARV drug class ranks first among the non-mental health carve-out classes for the FFS program and is the highest net cost drug class for coordinating care organizations ($2.5 million). There are 36 unique drugs currently marketed as ARV (Appendix 1). Branded combination drugs currently dominate market share (>50% by net cost) for the entire OHP. Generic formulations are emerging: 4 nucleoside reverse transcriptase inhibitors (NRTIs) and 2 NRTI combination products are now available.

Antiretroviral therapy is recommended for all patients with confirmed HIV infection.[5] An optimal ARV regimen for a treatment-naïve persons consists of 2 NRTIs in combination with a third drug from one of 3 drug classes: an non-nucleoside/nucleotide reverse transcriptase inhibitor (NNRTI), a boosted PI, or an INSTI.[3] A more detailed presentation of particular ARV options is included in the accompanying HIV Antiretroviral Class Review.[6]

The Centers for Disease Control and Prevention (CDC) also recommends pre-exposure prophylaxis or PrEP (specifically Truvada™) as one option for HIV prevention.[7] However, the recommendations also include the caution that: "When PrEP is prescribed, clinicians should provide access, directly or by facilitated referral, to proven effective risk-reduction services. Because high medication adherence is critical to PrEP efficacy but was not uniformly achieved by trial participants, patients should be encouraged and enabled to use PrEP in combination with other effective prevention methods." [7] The CDC suggests to consider prescribing no more than 90-day supply which can be refilled after confirmatory negative HIV test, that the use for coitally timed or other noncontinuous daily use is not recommended and that patients should be seen in routine follow-up to assess HIV status, adverse effects, change in risk behaviors, adherence and social support.[7]

Non-adherence to ARV can negatively impact viral response and can lead to drug resistance.[8] It is documented that patients that have less than 95% adherence have higher rates of viral response failure.[9,10] However, these studies do not reflect the newer ARVs. Pill burden, drug adverse events and complex psycho-social situations can all reduce adherence.[8] The HHS guidelines also note that prior authorization programs promoting use of generic drugs may reduce drug costs but can lead to increased pill burden and lower adherence rates.[8] In response, new formulations containing 3 or 4 antiretroviral drugs have been developed to address potential pill burden.

The HHS Office of Inspector General published an audit of ARV drug use in Medicare Part D patients in August 2014.[2] The audit found 1,578 patients with questionable ARV utilization patterns in 2012[2] including several combinations the HHS guidelines identified as those to always avoid in order to prevent adverse events and resistance development.[1] The audit does not report the total number of Part D patients receiving ARV in 2012 but, the number of patients associated with the most common drug combinations were 72,183 patients.[2] The audit created 6 criteria of questionable use: 1) no record of HIV or HIV indication (n=888); 2) dose exceeding 2-times the recommended dose (n=226); 3) supply exceeding 480 days in the calendar year (n=206); 4) persons accessing more than 6 pharmacies (n=213); 5) persons accessing more than 6 prescribers (n=179); and 6) concurrent use of contraindicated drugs for more than 60 days (n=10).[2] Medicare Part D paid $2.8 billion for HIV drugs and $32 million for questionable use in 2012.[2] The Office of Inspector General recommended expansion of drug utilization review programs, expansion of fraud, waste and abuse monitoring and expansion of beneficiary lock-in programs, among other recommendations.[2]

Methods: All patients with a paid FFS drug claim for an ARV drug in Appendix 1 during the 2014 calendar year were included. Patients with claims for only lamivudine or tenofovir (hierarchical ingredient code list sequence number (HSN) = 010215 OR 022937) in 2014 and no other FFS or encounter claims for ARV drugs from January 1, 2013 to March 31, 2015 were excluded as this indicates hepatitis B treatment in the absence of an HIV diagnosis. Patients with Medicare Part D coverage (BMM or BMD) and patients with less than 274 days (75%) eligible (FFS or CCO combined) during the 2014 calendar year were also excluded as the claims history for these patients is incomplete. For the remaining patients, all encounter and FFS claims from January 1, 2013 to March 31, 2015 were queried for medical and drug history. The

"HIV Population" includes all patients with a FFS claim for an ARV drug in 2014. The "Study Population" is a subset of the HIV Population that also met the 75% eligibility requirement and did not have Part D coverage.
Gross drug cost and utilization trends for the entire HIV Population were calculated using pharmacy reimbursed costs (excluding confidential rebates) and claim counts for ARV drugs per eligible member per month from both FFS and encounter drug claims. Total number of OHP eligible persons, including Part D patients, was used as the denominator to allow similar comparison to the other drug utilization evaluations previously reviewed by the Pharmacy and Therapeutics Committee.

A snap shot of the most current ARV therapy for each patient in the Study Population was identified by using the last ARV claim end date in 2014 (claim end date = claim dispense date + "Days Supply"). Looking back 60 days from the end date, any ARV drug initiated or with active "Days Supply" from a previous fill within the 60-day period was considered part of the patient's current ARV therapy for 2014. Unique final ARV regimens were identified and the number of patients for each unique regimen was counted. Drug cost was calculated using the average net price per day of each agent in the regimen; cost was not based on actual paid claims.

Post-exposure prophylaxis was quantified by identifying patients with claims for HSN 026515 (emtricitabine/tenofovir) plus HSN 035072 (raltegravir) within 5 days of each other, with less than 35 "Days Supply" for each claim and with no other claim for those two HSNs in the 90 days before or after. Pre-exposure prophylaxis was quantified by identifying patients taking no other ARV drugs except those in HSN 026515 (emtricitabine/tenofovir) in 2014, and who have no HIV ICD9 code (042xx, V08, 079.53 or 795.71) on any medical claim from January 1, 2013 to March 31, 2015.

The length of therapy ("Therapy Length") in "days" was calculated for each HSN component for each patient using the last claim date in 2014 plus the "Days Supply" entry and subtracting the first claim date in 2014. The medication possession rate (MPR) was calculated for each patient and HSN component using the formula: Total Days Supply / Therapy Length. The combined therapy length for each patient was determined using the last claim date in 2014 of any ARV drug plus the "Days Supply" entry and subtracting the first claim date of any ARV drug in 2014.

Results: Figure 1 displays the overall ARV drug cost and claim count trend per 1000 OHP members per month during 2014. There was approximately a 17% increase in the amount paid to pharmacies per member per month and 8% decrease in claim count per 1000 members per month over the calendar year.

Figure 1: Oregon Health Plan ART Pharmacy Reimbursed Cost and Claim Count, Calendar Year 2014

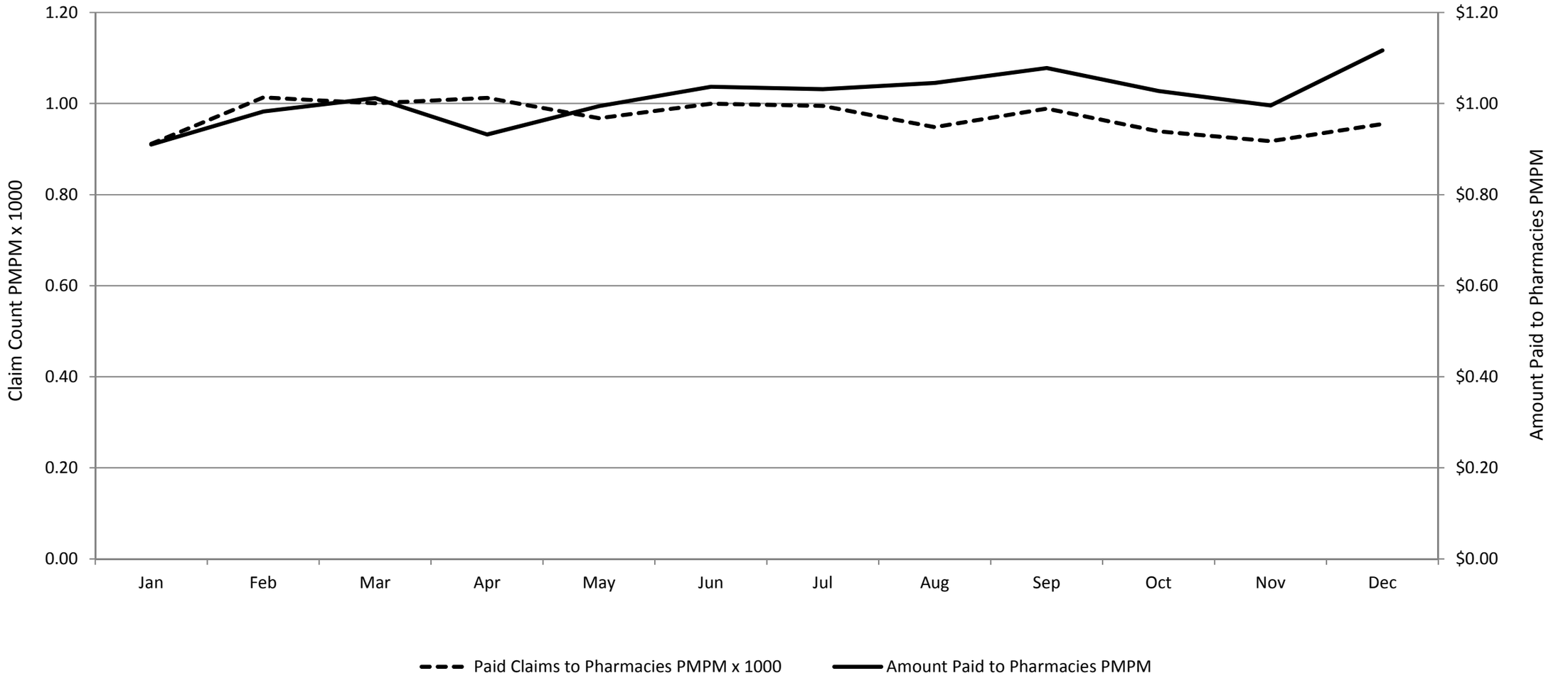
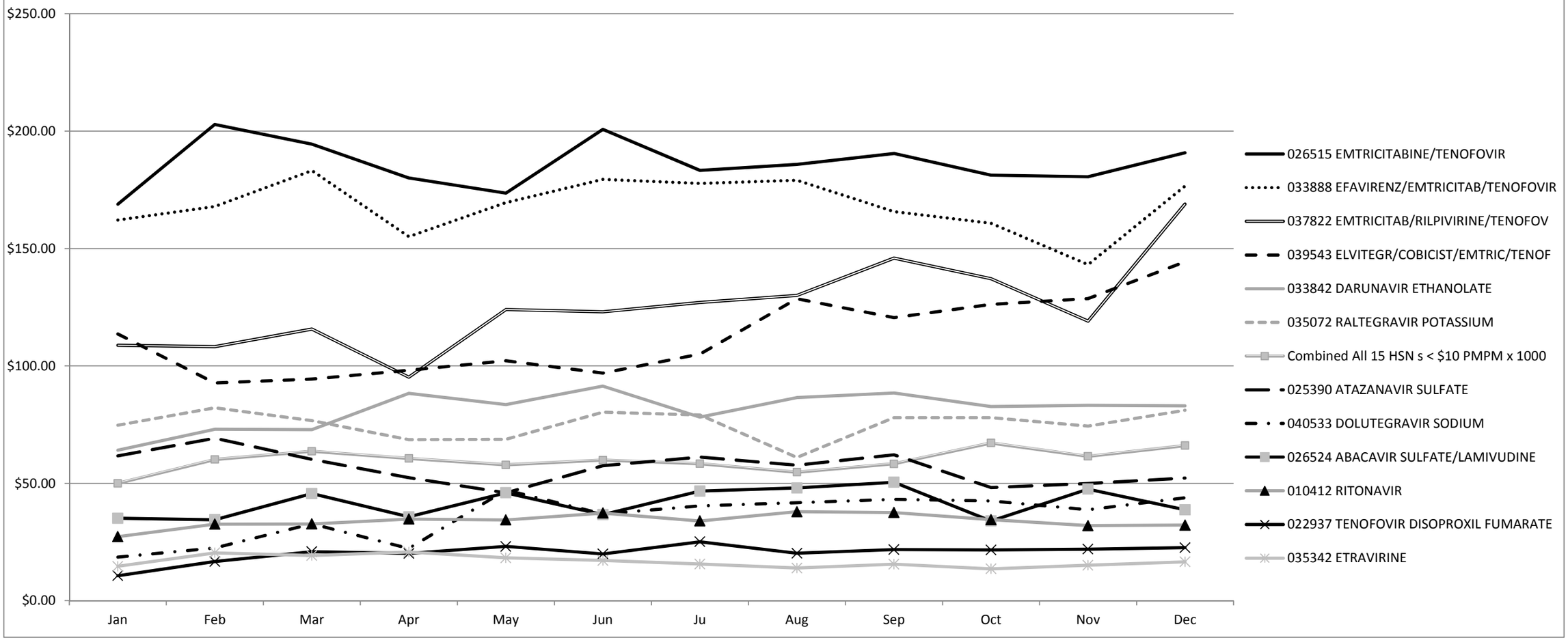


Figure 2 shows an increasing trend in the use of combination drugs, which are generally more expensive but result in fewer pharmacy claims. The combination of emtricitabine/tenofovir (Truvada™) ranks first by cost, averaging $186.05 PMPM x 1000; the combination of efavirenz/emtrictabine/tenofovir (Atripla™) ranks second at $168.35 PMPM x 1000; the combination of emtriactabine/rilpivirine/tenofovir (Complera™) ranks third at $125.24 PMPM x 1000; and the combination of elvitegravir/cobicistat/emtricitabine/tenofovir (Stribild™) ranked fourth at $112.60 PMPM x 1000. The cost of Complera™ and Stribild™ increased about 50% over the last 6 months of 2014; all other ARV drug costs remained grossly unchanged.

Figure 2: Unique ART Drug by Reimbursed Pharmacy Costs PMPM x 1000, Calendar Year 2014



There were 672 patients identified with a paid FFS drug claim for an ARV drug identified in Appendix 1. Eight patients were excluded as patients only receiving hepatitis B therapy, leaving 664 patients as the OHP HIV Population. After exclusions for less than 75% of eligible days in calendar year 2014 (n=78) and Medicare Part D (n=15), the final HIV Study Population for this drug use evaluation is 571 patients. Table 1 displays the demographic characteristics of the Study Population which is similar to the characteristics of the HIV Population. The Study Population were primarily male (n=486, 84.1%) and ethnically diverse, with 224 (39.2%) identified as non-white. Significantly, most (n=542, 94.9%) patients had an HIV diagnosis of record during the study period.

Table 1 - Demographics

	OHP HIV Population		**HIV Study Population**	
N=	664	%	571	%
Mean age in years (range)	41.4	(0-64)	41.5	(0-64)
< 19 years	10	1.5%	7	1.2%
19-64 years	654	98.5%	564	98.8%
> 64 years	0	0.0%	0	0.0%
Female	99	14.9%	85	14.9%
White	401	60.4%	347	60.8%
HIV ICD9 Code (042xx, V08, 079.53 or 795.71) on any claim from CY2013-Q12015	623	93.8%	542	94.9%

Table 2 displays a snap shot of the "last" (i.e. most current drug) therapy each patient received in 2014. The top 10 ARV regimens account for 75.9% of therapies. There were 66 patients (11.6%) who received unique regimens and another 71 patients (12.4%) who received regimens shared by less than 5 patients. Eight of the top 10 ARV regimens are identified as highly recommended therapy by HHS for treatment-naïve patients.[3] The most commonly identified regimens consisted of the NRTI/NNRTI branded combination products Atripla™ (n=107, 18.7%) and Complera™ (n=79, 13.8%). Truvada™ was included in 5 of the top 10 ARV regimens. The net cost of the most common regimens varied from a low of about $34/day to a high of about $90/day. PI based therapies are some of the most expensive and INSI based therapies are some of the least expensive. Comparative net prices will be disclosed in executive session.

Table 2 - Incidence of Final Drug Therapy

Patient counts by drug combinations.
Combinations defined as mix of drugs in each patient's final 60 days of therapy in CY2014

HHS[1] Evidence grade*	Drug 1	Drug 2	Drug 3	Study Population 571	%
BI (Alternative Initial)^	EMTRICITAB/TENOFOVIR/EFAVIRENZ			107	18.7%
BI (Alternative Initial)^	EMTRICITAB/TENOFOV/RILPIVIRINE			79	13.8%
AI (Recommended Initial)	EMTRICITABINE/TENOFOVIR	RITONAVIR	DARUNAVIR ETHANOLATE	56	9.8%
AI (Recommended Initial)	EMTRIC/TENOF/*ELVITEGR*/COBICIST			55	9.6%
BI (Alternative Initial)	EMTRICITABINE/TENOFOVIR	RITONAVIR	ATAZANAVIR SULFATE	46	8.1%
AI (Recommended Initial)	EMTRICITABINE/TENOFOVIR	*RALTEGRAVIR POTASSIUM*		41	7.2%
AI (Recommended Initial)	EMTRICITABINE/TENOFOVIR	*DOLUTEGRAVIR SODIUM*		20	3.5%
	EMTRICITABINE/TENOFOVIR	NEVIRAPINE		15	2.6%
AI (Recommended Initial)	ABACAVIR SULFATE/LAMIVUDINE	*DOLUTEGRAVIR SODIUM*		8	1.4%
CI (Optional Initial)	ABACAVIR SULFATE/LAMIVUDINE	*RALTEGRAVIR POTASSIUM*		7	1.2%
	Other Combinations - Patient counts per unique combination of >1 and <=5			71	12.4%
	Other Combination - Only 1 patient per unique combination			66	11.6%

Nucleoside Reverse Transcriptase Inhibitors (NRTI); Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI); **Protease Inhibitor (PI),** *Integrase Inhibitor (INSTI)*

***A** (strong support), **B** (moderate support), **C** (optional), **I** (data from RCTs)

^ Previously "Recommended"

Table 3 displays the number of patients meeting the definition of post-exposure and pre-exposure prophylaxis. There were 12 patients (2.1%) with single claims in 2014 for the HHS recommended post-exposure therapy and no other ARV therapy in the 90-days prior or after. Only 4 patients (0.7%) received only claims for Truvada™ in 2014 and none had an HIV diagnosis during the study period.

Table 3 - HIV Prophylaxis in Study Population

	Study Population	
N=	571	%
Post-exposure prophylaxis	12	2.1%
Pre-exposure prophylaxis	4	0.7%

Table 4 summarizes the patient medication possession rate (MPR) by drug component. There were 231 patients (40.5%) with less than 90% MPR and 4 patients (0.7%) with exactly 480 days of several drugs each during the year. There were no patients using therapies identified as therapies to avoid by the HHS.

Table 4 - Length of Therapy in 2014

	Study Population	
	571	%
Average total length of therapy any ARV drug (min-max)	306	(4-425)*
Patients with all drugs MPR >= 90%	340	59.5%
Patient with any drug MPR < 90%	231	40.5%
Patients $\geq$ 480 Days Supply for any drug	4	0.7%

* *Can exceed 365 because the day supply of the last claim filled in 2014 is added to the total*

Table 5 displays the number of patients that met the HHS Office of Inspector General Indicators of drug diversion. Only 3 patients met the criteria for excessive dose and these are likely errors in the data entry of "Days Supply" by the pharmacy. The service dates indicate lower doses were likely used by the patient. There were no patients accessing excessive numbers of pharmacies and prescribers.

Table 5 – Office of Inspector General - Indicators of Diversion

	Study Population	
	571	%
Count of patients with ARV claim exceeding 2x recommended dose *	3	0.5%
Patient with >= 6 unique pharmacies for ARV claims, 2014 **	0	0.0%
Patient with >= 6 unique prescribers for ARV pharmacy claims, 2014 ***	0	0.0%
Unique patients meeting any of the above:	3	0.5%

*Note: Possibly to be day supply entry errors

** Note: Ten patients had 4 pharmacies. All the rest had 3 or less.

*** Note: One patient had 5 prescribers. Three patients had 4 prescribers. All the rest had 3 prescribers or less.

Limitations: Net drug cost estimates are based upon the most recent rebate rates used for invoicing, not collected rebates, and is expected to be an optimistic representation of net price. Furthermore, Invoices are prepared using federal rebate rates reported after claim payment, they are subject to dispute by manufacturers and are frequently missing.

Reporting the last ARV for each patient was used to capture the most current utilization patterns while still maintaining a single patient as the unit of analysis. The methods used to define the last ARV may have included drugs that have been discontinued in the current therapy and may have contributed to the multiple unique therapies reported. These methods may also have contributed to the low adherence rates found. It is recognized that patients that have failed prior ARV may be using ARV that is specifically directed by their own unique resistance patterns. This DUE is not focused on assessing the individual appropriateness of an individual's ARV but merely documenting the most common ARV prescribed at a point in time.

It is possible patients could be using clinic samples or paying cash for ARV that would not be captured in this analysis. Limiting the Study Population to those with 75% eligibility during the study period is an attempt to draw conclusions from a sample where these practices would be less likely. Interpretation of the low adherence rate and low prophylaxis rates are most affected by alternate drug sources.

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Appendix 1 – Unique Antiretroviral Drugs Marketed in United States (HIC3 = W5C, W5I, W5J, W5K, W5L, W5M, W5N, W5O, W5P, W5Q, W5T, W5U, W5X)

Class	Generic Name	Brand Name	ABBR	Forms / Dose Frequency	Generic?
Cellular Chemokine Receptor 5 Antagonist (CCR5)	MARAVIROC	SELZENTRY	MVC	Tablet / BID	N
Fusion Inhibitor (FI)	ENFUVIRTIDE	FUZEON	T20	Subcutaneous / BID	N
Integrase Inhibitor (INSTI)	*DOLUTEGRAVIR SODIUM*	TIVICAY	DTG	Tablet / BID	N
Integrase Inhibitor (INSTI)	*ELVITEGRAVIR*	VITEKTA	EVG	Tablet / QD	N
Integrase Inhibitor (INSTI)	*RALTEGRAVIR POTASSIUM*	ISENTRESS	RAL	Tablet; Chew; Packet / BID	N
Nucleoside Reverse Transcriptase Inhibitors (NRTI)	ABACAVIR SULFATE	ZIAGEN	ABC	Solution; Tablet* / QD - BID	*Y
Nucleoside Reverse Transcriptase Inhibitors (NRTI)	DIDANOSINE	VIDEX	ddI	Capsule*; Solution / QD - BID	*Y
Nucleoside Reverse Transcriptase Inhibitors (NRTI)	EMTRICITABINE	EMTRIVA	FTC	Capsule; Solution / QD	N
Nucleoside Reverse Transcriptase Inhibitors (NRTI)	LAMIVUDINE	EPIVIR	3TC	Solution; Tablet / QD – BID	Y
Nucleoside Reverse Transcriptase Inhibitors (NRTI)	STAVUDINE	ZERIT	d4T	Capsule; Solution / BID	Y
Nucleoside Reverse Transcriptase Inhibitors (NRTI)	TENOFOVIR DISOPROXIL FUMARATE	VIREAD	TDF	Tablet; Powder / QD	N
Nucleoside Reverse Transcriptase Inhibitors (NRTI)	ZIDOVUDINE	RETROVIR	ZDV	Capsule; Syrup; Tablet; Intravenous/ BID – TID	Y
2 NRTI COMBO	EMTRICITABINE/ TENOFOVIR	TRUVADA		Tablet / QD	N
2 NRTI COMBO	LAMIVUDINE/ ZIDOVUDINE	COMBIVIR		Tablet / QD	Y
2 NRTI COMBO	ABACAVIR SULFATE/LAMIVUDINE	EPZICOM		Tablet / QD	N
3 NRTI COMBO	ABACAVIR/LAMIVUDINE/ ZIDOVUDINE	TRIZIVIR		Tablet / QD	Y
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	DELAVIRDINE MESYLATE	RESCRIPTOR	DLV	Tablet / QD	N
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	EFAVIRENZ	SUSTIVA	EFV	Capsule; Tablet / QD	N
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	ETRAVIRINE	INTELENCE	ETR	Tablet / BID	N
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	NEVIRAPINE	VIRAMUNE	NVP	Suspension; Tablet; Tablet ER / QD - BID	Y
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	RILPIVIRINE HCL	EDURANT	RPV	Tablet / QD	N
2 NRTI- 1 NNRIT COMBO	EMTRICITAB/ TENOFOVIR /RILPIVIRINE	COMPLERA		Tablet / QD	N
2 NRTI- 1 NNRIT COMBO	EMTRICITAB/ TENOFOVIR /EFAVIRENZ	ATRIPLA		Tablet / QD	N
2 NRTI – *1 INSTI* COMBO	ABACAVIR SULFATE/LAMIVUDINE *DOLUTEGRAVIR SODIUM*	TRIUMEQ*		Tablet / QD	N
2 NRTI – *1 INSTI* – CYP P450 Inhibitor COMBO	EMTRIC/ TENOF /*ELVITEGR*/COBICIST/	STRIBILD		Tablet / QD	N
Protease Inhibitor (PI)	SAQUINAVIR MESYLATE	INVIRASE	SQV	Capsule; Tablet / BID	N
Protease Inhibitor (PI)	NELFINAVIR MESYLATE	VIRACEPT	NFV	Tablet	N
Protease Inhibitor (PI)	INDINAVIR SULFATE	CRIXIVAN	IDV	Capsules / BID - TID	N
Protease Inhibitor (PI)	FOSAMPRENAVIR CALCIUM	LEXIVA	FPV	Suspension; Tablet / QD	N
Protease Inhibitor (PI)	ATAZANAVIR SULFATE	REYATAZ	ATV	Capsule; Packet / QD	N
Protease Inhibitor (PI)	TIPRANAVIR	APTIVUS	TPV	Capsule; Solution / BID	N
Protease Inhibitor (PI)	DARUNAVIR ETHANOLATE	PREZISTA	DRV	Suspension; Tablet / QD	N
PI + CYP P450 Inhibitor COMBO	ATAZANAVIR / COBICISTAT	EVOTAZ		Tablet / QD	N
PI + CYP P450 Inhibitor COMBO	DARUNAVIR / COBICISTAT	PREZCOBIX		Tablet / QD	N
PI + CYP P450 Inhibitor COMBO	LOPINAVIR/ RITONAVIR	KALETRA	LPV/r	Solution; Tablet / QD -BID	N
CYP P450 Inhibitor	RITONAVIR	NORVIR	RTV	Capsule; Solution; Tablet / BID	N
CYP P450 Inhibitor	COBICISTAT	TYBOST		Tablet / QD	N

*Not included in analysis. One patient identified after study completed.

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Class Update: Antiplatelet Drugs

Month/Year of Review: July 2015 **Last Review:** July 2014

Current Status of PDL Class:

- See Appendix 1

Research Questions:

- Is there new comparative evidence that antiplatelet drugs differ in effectiveness or safety for adult patients with acute coronary syndromes (ACS) or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack (TIA), or symptomatic peripheral arterial disease (PAD)?
- Is there evidence of a difference in effectiveness or harms for the length of dual antiplatelet therapy (aspirin plus a $P2Y_{12}$ receptor antagonist) after drug-eluting stent (DES) implantation?

Conclusions:

- There is moderate quality evidence that prasugrel is associated with a lower rate of major adverse cardiovascular events (MACEs) compared to clopidogrel in patients with coronary artery disease (CAD) (OR 0.86; 95% CI 0.78 to 0.94), but also a high risk of major bleeding (OR 1.33; 95% CI 1.09 to 1.61). However, a recent meta-analysis demonstrated that the risk of MACEs far outweighed that of major bleeding (OR 7.48; 95% CI 3.75 to 14.94, p<0.0001) and of minor bleeding (OR 3.77; 95% CI 1.73 to 8.22; p=0.009).[5]
- There is no other new comparative effectiveness evidence for clopidogrel, prasugrel, ticagrelor ticlopidine, aspirin, dipyridamole or dipyridamole ER/aspirin (D-ER/ASA) other indications.
- Dual antiplatelet therapy (DAPT) consisting of aspirin plus a $P2Y_{12}$ receptor antagonist is recommended after drug-eluting stent (DES) implantation for at least 12 months by the American College of Cardiology/American Heart Association (ACC/AHA) and for six to 12 months by European guidelines, followed by aspirin monotherapy.
- There is low quality evidence that short-term DAPT (less than 12 months) compared to-12 month therapy is associated with a similar rate of stent thrombosis and MI, with a reduced risk of major bleeding, while extended therapy (>12 months) compared with 12-month therapy is associated with reduction in stent thrombosis (NNT 100-250) and MI (NNT 50-125), but increased risk of major bleeding (NNH 111-325).[1–3] Studies have also demonstrated an increase in all-cause mortality with extended DAPT beyond one year (2.0% vs. 1.5%; OR 1.36; 95% CI 1.00-1.85; NNH 200), driven by non-cardiovascular events.[1] Further studies are needed to evaluate this risk and define the optimal duration of therapy. At this time, DAPT should be recommended for a year in most patients receiving a DES with high risk patients considering longer term use (up to 30 months) and patients at high risk of bleeding considering therapy for less than 6 months.
- There is moderate quality evidence that long term use (> 1 year) of ticagrelor may reduce risk of myocardial infarction (MI) (NNT 118) and stroke (NNT 303), but increase risk of major bleeding (NNH 65) in patients with prior MI (more than 1 year previously) taking aspirin, based on the PEGASUS-TIMI 54 trial.[4]

- New recommendations from the AHA for the primary prevention of stroke do not recommend antiplatelet regimens other than aspirin (and cilostazol for patients with PAD) be used for prevention of stroke due to a lack of evidence from relevant clinical trials. Primary prevention of stroke with aspirin is recommended for high risk individuals (10-year risk >10%), for persons with chronic kidney disease, and as a reasonable treatment option for patients with heart failure who do not have Atrial Fibrillation (AF) or a previous thromboembolic event.

Recommendations:

- Continue to list aspirin and clopidogrel as preferred drugs due to high level evidence of benefit for multiple indications (Coronary Artery Disease [CAD], ACS, stroke and PAD).
- Evaluate comparative costs of other antiplatelet drugs in executive session for PDL changes.
  Continue the prior authorization policy with minor modifications consistent with updated treatment guidelines

PA Criteria:

Current PA criteria is in place for platelet inhibitors (Appendix 3) to approve platelet inhibitors for covered diagnoses which are supported by medical literature

Reason for Review:

Routine update of class and evaluation of new comparative evidence.

Previous P&T Conclusions (July 2014[6]):

- There is no new comparative effectiveness evidence for clopidogrel, prasugrel, ticagrelor, ticlopidine, aspirin, dipyridamole or D-ER/ASA.
- There is moderate quality evidence that vorapaxar produces lower rates of a composite of cardiovascular (CV) deaths, myocardial infarction (MI) or stroke at 3 years versus placebo when added to standard antiplatelet therapy for secondary prevention in patients experiencing a stroke, PAD or MI patients who have not undergone percutaneous coronary intervention (PCI) (HR 0.87 95% CI 0.80 - 0.94, ARD 1.1%, NNT 91). Significance was driven primarily by the MI component (HR 0.83 95% CI 0.74 – 0.90, ARD 0.8%, NNT 125). There is moderate quality evidence that vorapaxar does not prevent cardiovascular complications in patients with unstable angina or non-ST elevated MI (UA/NSTEMI).
- There is no new comparative safety evidence for clopidogrel, prasugrel, ticagrelor ticlopidine, aspirin, dipyridamole or D-ER/ASA.
- There is moderate quality evidence that vorapaxar increases moderate to severe bleeding rates at 3 years compared to placebo (HR 1.35 95% CI 1.16 -1.58, ARD 1.6%, NNH 63). The trial was stopped 6 months early because of more hemorrhagic stroke for vorapaxar (HR 2.73 95% CI 1.22 – 6.14, ARD 0.2%, NNH 500).

Background:

Antiplatelet drugs are recommended to prevent cardiovascular (CV) events and premature death in patients who have experienced Acute Coronary Syndrome (ACS), transient ischemic attacks (TIA), noncardioembolic stroke, MI or symptomatic peripheral arterial disease (PAD).[7] Prasugrel and vorapaxar are contraindicated in patients with prior TIA or stroke. The FDA approved indications are represented in Table 1 below.

Table 1: FDA Approved Indications.

	2^o Stroke	2^o PAD	2^o MI	ACS	
				No PCI	PCI
ASA/DP ER	x				
clopidogrel	x	x	x	x	x
prasugrel	CI				x
ticagrelor				x	x
vorapaxar	CI	x	x		

Abbreviations: 2^o = secondary prevention; x = FDA-indicated; CI=contraindication; PCI= percutaneous coronary intervention

Ticlopidine, clopidogrel, and prasugrel irreversibly block $P2Y_{12}$, a key adenosine phosphate receptor on the platelet surface. Ticlopidine causes rare, but serious, neutropenia and is rarely prescribed. [6] Clopidogrel is the only generically available $P2Y_{12}$ inhibitor but is limited by a slower onset of action, incomplete platelet inhibition and poor response in some patients. Variability in responsiveness to clopidogrel has been documented, but there are no guideline recommendations for testing or how to manage this unknown risk. Cangrelor and ticagrelor are reversible inhibitors of $P2Y_{12}$. Cangrelor is a rapid acting injectable drug intended for percutaneous coronary interventions (PCI) and will not be covered in this review. Vorapaxar is unique because it is a selective antagonist of the protease-activated receptor-1 (PAR-1), the primary thrombin receptor. Vorapaxar has not been studied alone and should only be used with aspirin and/or clopidogrel according to their indications or standard of care.[8]

The multiple guidelines for treatment of CAD recommend aspirin 75-162 mg daily for all patients[9–11] and clopidogrel 75 mg daily as an alternative for patients intolerant to aspirin. Recently, the U.S. Food and Drug Administration recommended against routine use of aspirin for primary prevention but stated it may still be appropriate when prescribed by a healthcare provider to higher-risk patients.[12,13] Conversely, various clinical guidelines, including the American Diabetes Association guidelines do recommend aspirin for primary prevention in certain high risk individuals (those with a 10-year risk > 10%).[14]

Dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor plus aspirin is recommended for ACS, following PCI, for certain high risk patients with stable ischemic heart disease or peripheral artery disease, and for minor ischemic stroke or transient ischemic attack.[9,15] The recommendation of which $P2Y_{12}$ inhibitor to use concomitantly with ASA in various ACS patient types is evolving and varies depending on the guideline source.[15] The duration of DAPT has also been debated in the literature. Finding the duration that appropriately balances the risk of ischemic complications and bleeding risk has remained a challenge and guidelines have differing recommendations for use.[15,16] The ACCF/AHA/SCAI guideline recommends DAPT for at least 12 months for patients with ACS receiving a stent, with a consideration for greater than 12 months with a drug-eluting stent. However, the recent ESC/EACTS guideline recommends DAPT for 12 months only for patients at high-risk of thrombosis with ACS, with a consideration for less than 6 months if the patient is at high risk for bleeding. While guidelines have recommended 12 months with DAPT following ACS (with or without stent placement), some evidence has shown shorter durations (3-6 months) may be sufficient. None of these trials, however, were powered for ischemic endpoints; all were open-label and the time from stenting to randomization varied. The first large RCT powered to detect differences in ischemic outcomes was the DAPT study,[17] which demonstrated decreased rates of stent thrombosis and major CV events with extending DAPT up to 30 months, with an unexplainable increase in overall mortality, primarily driven by non-cardiovascular mortality. This has been editorialized as due to cancer, bleeding, and trauma-related deaths.[18] In addition, results seemed to be more significant in the subgroup of 'older generation' stents which may not be as effective in preventing thrombosis as the newer generation drug-eluting stents. A cohort of patients from the DAPT trial

with bare metal stents (BMS) showed insufficient evidence to evaluate DAPT for 30 months compared to 12 months as the trial was not powered to assess differences in this group.[19]

Either aspirin (50-325 mg daily) or D-ER/ASA is recommended over anticoagulants for secondary prevention of non-cardioembolic ischemic stroke.[9,20] Clopidogrel is an option for aspirin-intolerant patients. [9,20]

Aspirin 75-325 mg daily or clopidogrel 75 mg daily is recommended for symptomatic PAD patients to reduce the risk of myocardial infarction, stroke or vascular death.[9,21] Neither prasugrel or ticagrelor have evidence to support their use for PAD or stroke patients. [6]

Methods:
The DERP scan searched Ovid MEDLINE from January 2014 through January 2015 for new systematic reviews and randomized controlled trials (RCTs) comparing any of the antiplatelet agents.[22] An additional search through June 2015 was done. Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
The DERP Scan identified no new potentially relevant comparative effectiveness reviews. Since the literature search done by the DERP scan, the following systematic reviews were identified. They are tabulated by indication and population.

<u>Acute Coronary Syndrome</u>

Extended duration dual antiplatelet therapy

Since the release of the DAPT study, systematic reviews and meta-analyses have further evaluated extended duration DAPT after coronary stenting, particularly its effect on overall mortality due to the difference in all-cause mortality seen in the DAPT trial.[23] The first systematic review included a literature search identifying 14 relevant articles, including the DAPT trial. While this review did not limit studies to patients with ACS, the majority of the trials (10) evaluated DAPT following ACS. All studies included DAPT with aspirin and a thienopyridine, the majority being clopidogrel. Thirty two percent of patients in the DAPT study received prasugrel with aspirin. Meta-analysis using a random-effects model of study results found no difference in all-cause mortality (HR 1.04; 95% CI 0.96 – 1.14) or cardiovascular mortality (HR 1.01; 95% CI 0.93 – 1.12) with extended duration DAPT (at least 6 months) compared with a short duration (less than 6 months) or aspirin alone. While this review did not show an overall difference in mortality, it included a heterogeneous population including patients with PAD, Atrial Fibrillation, and CAD managed medically and those undergoing PCI. Thus, it is unknown whether the effects of DAPT on cardiac mortality might be disease-specific.

A similar systematic review was conducted but only included trials in patients post-PCI with a DES.[2] Ten trials (n=31,666) were included in the meta-analysis comparing different durations of DAPT; shorter duration being 6 months or less and longer duration being longer than 1 year. As the DAPT trial resulted in an

unexpected increase in all-cause mortality, the goal of this review was to further evaluate the risk of mortality with longer duration of DAPT. Overall, shorter DAPT (1 year) was associated with significantly lower rates of mortality compared with longer DAPT (≥1 year) (HR 0.82; 95% CI 0.69-0.98). The results were primarily driven by a reduction in non-cardiac mortality as there was no difference in cardiac mortality. There was no significant difference in all-cause death comparing ≤6 months vs. ≥1 year duration of DAPT (HR 0.87; 95% CI 0.64 to 1.19). Similar to the DAPT study, there was a significantly lower rate of stent thrombosis with 1 year and longer of DAPT compared to shorter durations. However, shorter DAPT duration was associated with significantly lower rates of major bleeding and any bleeding compared with longer DAPT.

Lastly, a meta-analysis of RCTs assessed the benefits and risks of short term (< 12 months) or extended (> 12 months) DAPT versus standard 12 month therapy following PCI with DES.[3] A total of 10 RCTs (n=32,287) were included in the meta-analysis, including the DAPT trial. Clopidogrel and aspirin was the most frequent drug combination; prasugrel or ticagrelor were available in three and two studies, respectively. The majority of patients in the trials had either stable angina or non-ST elevation MI (NSTEMI) ACS. Cardiovascular mortality between short-term and 12-month DAPT did not differ significantly (OR 0.95; 95% CI 0.68 to 1.33). Similarly, CV mortality did not significantly differ between extended DAPT and 12-month therapy (OR 1.09; 95% CI 0.79 to 1.50). There was a significant reduction in the odds of a MI with extended DAPT compared with 12-month therapy (OR 0.53; 95% CI 0.42 to 0.66), as well as in stent thrombosis (OR 0.33; 95% CI 0.21 to 0.51). There was no difference in MI or stent thrombosis between shorter duration of DAPT and 12-month therapy. As expected, the risk of bleeding increased as the duration of therapy increased with the highest risk in the extended DAPT therapy and a reduction in risk in the short term therapy. There was no difference seen in all-cause mortality between short-term and 12-month DAPT; with a higher risk of all-cause death in extended therapy versus 12-month therapy (OR 1.30; 95% CI 1.02 to 1.66; NNH 238).

CADTH summarized the evidence for clinical effectiveness, cost effectiveness and recent guidelines for clopidogrel, prasugrel and ticagrelor in adults with ACS.[17] The literature search extended from January 2007 through May 2012 and was limited to RCTs, systematic reviews, technology assessments, meta-analyses, economic evaluations and guidelines that were appraised for quality. Aspirin plus clopidogrel was found to reduce the risk of CV events and was cost-effective compared to aspirin alone in ACS patients with UA/NSTEMI or STEMI whether patients were medically managed or revascularized. Prasugrel (TRITON-TIMI 38[24]) and ticagrelor (PLATO[25]) were more effective than standard clopidogrel doses but with a higher risk of bleeding. It was noted that the PLATO[25] trial had no difference for the composite primary outcome in the North American subpopulation, though it is unknown whether this was due to higher aspirin doses observed in this population. CADTH authors concluded that clopidogrel and aspirin remain the recommended therapy for ACS patients but that ticagrelor or prasugrel may be considered in STEMI patients that have not received antiplatelet therapy prior to arrival to the catheterization lab, or in high risk NSTEMI patients where quick onset of action is a priority.

Current guidelines recommend the use of proton pump inhibitors (PPIs) with DAPT in individuals at high risk for gastrointestinal ulceration or bleed. However, studies have noted a drug-drug interaction between PPIs and clopidogrel, which may reduce activation of clopidogrel when used concomitantly. A recent systematic review evaluated the comparative effectiveness and safety of concomitant use of PPIs and DAPT among patients with unstable angina and NSTEMI. [26] Results from this review conflicted with the original observational studies that demonstrated an association between concomitant administration of PPIs and poor clinical outcomes. Four RCTs included in this review demonstrated use of omeprazole resulted in no differences in ischemic events versus the control group but led to a greater reduction in upper GI bleeds. Evidence from RCTs should be weighted heavier compare to observational data.

A high quality meta-analysis of RCTs compared major adverse cardiac events (MACEs) and bleeding in patients with prasugrel versus clopidogrel to help determine if the increased risk of bleeding associated with prasugrel is outweighed the decreased risk of MACEs compared to clopidogrel.[5] All studies in patients

with CAD were included through a literature search up to December 15, 2014. Nine studies (n=25,214) were included in the meta-analysis and MACEs were defined as a composite outcome of CV deaths, MI, and ischemic stroke. As expected, the incidence of MACEs was lower in the prasugrel group than in the clopidogrel group (OR 0.86; 95% CI 0.78 to 0.94; p<0.0001) and the incidence of major bleeding was higher in the prasugrel group (OR 1.33; 95% CI 1.09 to 1.61; p=0.004). The risk of MACEs outweighed that of major bleeding (OR 7.48; 95% CI 3.75 to 14.94, p<0.0001) and of minor bleeding (OR 3.77; 95% CI 1.73 to 8.22; p=0.009). Results using a fixed effect model were of the same conclusion. In double-dose clopidogrel trials, there was no difference in the incidence of MACEs, major bleeding, and minor bleeding between prasugrel group and clopidogrel group. Sensitivity analysis suggested the presence of publication bias for the outcome of major bleeding only. [5]

Stroke

A review by the Cochrane Collaboration assessed the efficacy and safety of immediate oral antiplatelet therapy in people with acute ischemic stroke, including RCTs comparing oral antiplatelet therapy started within 14 days of stroke, with control (placebo or no treatment) in people with definite or presumed ischemic stroke.[27] A total of 8 trials with a low risk of bias were identified, but two trials evaluating aspirin 160-300 mg daily accounted for 98% of the data. The review found treatment with aspirin led to a significant decrease in death or dependent on help from other people for their activities of daily living (OR 0.95; 95% CI 0.91 to 0.99)and a nominally significant reduction in death (OR 0.92; 95% CI 0.85 to 1.00; p=0.05), with a small increased risk of intracranial hemorrhage (OR 1.23; 95% CI 1.00 to 1.50). The authors concluded that this small risk was outnumbered by the benefit, including a reduction in recurrent stroke (OR 0.77; 95% CI 0.69 to 0.87) and pulmonary embolism (OR 0.71; 95% CI 0.53 to 0.96). In addition, the indirect comparisons of different agents showed no evidence of significant heterogeneity of effect between the different agents tested (aspirin alone, ticlopidine alone, the combination of aspirin and dipyridamole). However, the data from the non-aspirin regimens were extremely limited.

New Guidelines:

Acute Coronary Syndrome

NICE recommends ticagrelor as a treatment alternative to clopidogrel post-MI for up to 12 months. The recommendation is based on a technology assessment of ticagrelor that estimated a decreased cost per Quality Adjusted Life Year gained over clopidogrel for the treatment of ACS in Great Britain.[28] A separate technology assessment from NICE also provided guidance for prasugrel for ACS and recommends prasugrel in combination with aspirin as a possible option for preventing atherothrombotic events in adults with ACS having PCI.[29]

The American College of Chest Physicians recommends ticagrelor over clopidogrel for patients the first year after ACS (2B recommendation, based upon unclear or close risk/benefit balance and moderate quality evidence) and recommend against prasugrel for patients less than 60 kg, over 75 years of age or with a previous history of stroke. Clopidogrel plus aspirin are recommended for 6-12 months in patients undergoing elective PCI and stent placement.[9]

The 2014 American Heart Association/American College of Cardiology (AHA/ACC) guidelines for the management of patients with NSTEMI ACS recommends aspirin 162-325 mg be given as soon as possible after presentation with a maintenance dose of 81 to 325 mg per day continued indefinitely.[30] Clopidogrel is recommended for those who cannot tolerate aspirin. For those undergoing early invasive therapy, the guidelines recommend a P2Y12 inhibitor (clopidogrel or ticagrelor) with aspirin for up to 12 months of therapy, but ticagrelor is preferred over clopidogrel (Class IIa). Ticagrelor and prasugrel are preferred over clopidogrel in post-PCI patients (Class IIa), but prasugrel should be avoided in patients who are at a high risk of bleeding.

The European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) also released 2014 guidelines on myocardial revasculrization.[31] In patients with NSTE-ACS or STEMI undergoing PCI, the guideline recommends prasugrel or ticagrelor in combination with aspirin for 12 months if there is no excessive risk of bleeding (Class 1; Level B). Clopidogrel is recommended only when prasugrel or ticagrelor are not available or are contraindicated. In those with stable CAD undergoing PCI, the guidelines recommend clopodgrel for elective stenting with DAPT for at least 1 month after BMS and at least 6 months after DES implantation (Class I; Level B), with shorter DAPT considered (< 6 months) in patients at high bleeding risk (Class IIB; Level A) and longer therapy in patients at high ischemic risk and low bleeding risk.

Noncardioembolic Ischemic Stroke or Transient Ischemic Attack

The AHA/ACCF published updated guidelines for secondary prevention of stroke in 2014.[11] The guidelines state that aspirin 50 to 325 mg daily monotherapy or D-ER/ASA twice daily are indicated as initial therapy for TIA or ischemic stroke for prevention of future stroke. Clopidogrel 75 mg daily as monotherapy is a reasonable option for secondary prevention, especially for patients allergic to aspirin. The update includes a new recommendation to consider DAPT with aspirin and clopidogrel within 24 hours of a minor ischemic stroke or TIA for 90 days (Level B). This recommendation is based on the results of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, which enrolled patients within 24 hours of a minor ischemic stroke or TIA.[24] Patients were assigned aspirin plus clopidogrel or aspirin plus placebo for 90 days. There were fewer ischemic or hemorrhagic stroke events in the combination group (8.6%) compared to the aspirin group (11.7%) [HR 0.68; 95% CI 0.57 -0.81] and rates of bleeding were similar. Initiation of aspirin and clopidogrel days to years after a stroke increases the risk of hemorrhage compared to either agent alone and is not routinely recommended. Additionally, Level C evidence highlights the uncertainty of adding antiplatelet therapy to a vitamin K antagonist (i.e., warfarin) in patients with a history of ischemic stroke, TIA, AF or CAD.[11] For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit.

The guidelines for the primary prevention of stroke were also updated in 2014.[32] The majority of the recommendations regard controlling modifiable risk factors to prevent stroke and for antithrombotic therapy for the prevention of stroke in AF, with aspirin as a consideration for patients with nonvalvular AF and a CHA_2DS_2-VAS_c score of 1. A new recommendation lists anticoagulants or antiplatelet agents as reasonable treatment options for patients with heart failure who do not have AF or a previous thromboembolic event (CLASS IIa; Level of Evidence A). This recommendation comes from the WARCEF trial which showed no difference in the primary outcome of ischemic stroke, intracranial hemorrhage (ICH), or death between warfarin and aspirin, but found a significant reduction in the rate of ischemic stroke with warfarin compared to aspirin and an increased rate of major hemorrhage with warfarin. Other recommendations for the use of antiplatelet agents, including aspirin, for primary prophylaxis are as follows:

- Antiplatelet agents and aspirin are recommended for primary prophylaxis for people whose risk is sufficiently high (10-year risk >10%) when the benefits outweigh the risks of bleeding (CLASS IIA; Level of Evidence A).
- Aspirin might be considered for the prevention of a first stroke in people with chronic kidney disease (Class IIB; Level of Evidence C). This does not apply to severe kidney disease (stage 4 or 5; Glomerular Filtration Rate <30 mL/min).
- Cilostazol may be reasonable for primary prevention of stroke in people with PAD (Class IIb; Level of Evidence B).
- As a result of a lack of relevant clinical trials, antiplatelet regimens other than aspirin and cilostazol are not recommended for primary prevention (Class III; Level of evidence C).

Peripheral Artery Disease

Guidelines for PAD have not been recently updated. The 2011 AHA/ACCF guidelines recommend aspirin or clopidogrel daily for symptomatic PAD.[21] Combination aspirin and clopidogrel may be considered for patients with symptomatic lower extremity PAD at perceived high CV risk (Level B evidence).

Antiplatelet therapy in asymptomatic PAD is not supported in patients with ankle-brachial indexes 0.91-0.99 (Level A evidence) but may be beneficial in ankle-brachial indexes ≤ 0.90 (Level C evidence).

Randomized Controlled Trials: A recent DERP literature scan[1] tabulated the potentially relevant new RCTs by drug comparison and population. Overall, 2 new head-to-head trials, 5 post-hoc or secondary analyses of published trials (Appendix 2), and 2 placebo-controlled trials were considered potentially relevant. One head to head trial was not designed to evaluate a clinically important outcome. [34] The head to head trials are summarized in Table 1 below. Full abstracts are included in Appendix 2.

In addition, 3 relevant RCTs were identified; of these, the DAPT trial[1] and the ISAR-SAFE trial[33] were included in systematic reviews assessed above, exploring the optimal duration of DAPT following ACS and will not be evaluated further. The remaining study is summarized in Table 1 below. Full abstracts are included in Appendix 2.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results		Quality*
PEGASUS-TIMI 54[4] RCT, DB	Ticagrelor 90 mg BID vs. ticagrelor 60 mg BID vs. placebo (all with background aspirin therapy)	Patients with a MI 1-3 years previously (median time 1.7 years)(n=21,162)	Composite of CV death, MI, or stroke	Composite Endpoint: Ticagrelor 90: 7.85% Ticagrelor 60: 7.77% Placebo: 9.04% Tic90 vs. placebo: HR 0.85; 95% CI 0.75 to 0.96; p=0.008 Tic60 vs. placebo: HR 0.84; 95% CI 0.74 to 0.95; p=0.004	TIMI major bleeding: Ticagrelor 90: 2.6% Ticagrelor 60: 2.3% Placebo: 1.06% Tic90 vs. placebo: HR 02.69; 95% CI 1.96 to 3.70; p<0.001 Tic60 vs. placebo: HR 2.32; 95% CI 1.68 to 3.21; p<0.001	Good
Gasparovic[35]	Clopidogrel + ASA vs. ASA	Aspirin-resistant patients following CABG	Composite of all-cause death, nonfatal MI, stroke, or CV hospitalization at 6 months postoperatively	Composite Endpoint: DAPT: 6% ASA: 10% RR 0.61; 95% CI 0.25 to 1.51; p=0.33 DAPT did lower the incidence of the primary endpoint in obese patients and those < 65 y/o	Bleeding events DAPT: 25% ASA: 19% RR 1.34; 95% CI 0.8 to 2.23; p=0.33	Fair

Abbreviations: BID = twice daily; CV = cardiovascular; DB = double-blind; MI = myocardial infarction; RCT = randomized controlled trial; TIMI = Thrombolysis in Myocardial Infarction.
*Quality of each study is ranked as "Good", "Fair" or "Poor" based on DURM Standard Methods for Quality Assessment and Grading the Evidence.

New FDA Safety Alerts:
None identified.

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Appendix 1: Current Status on Preferred Drug List

Current Status of PDL Class:

- Preferred Agents: ASPIRIN, CLOPIDOGREL, DIPYRIDAMOLE, DIPYRIDAMOLE ER 200MG/ASPIRIN 25MG (D-ER/ASA)
- Non Preferred Agents: TICAGRELOR (BRILINTA), PRASUGREL (EFFIENT), TICLOPIDINE, VORAPAXAR (ZONTIVITY)

Appendix 2: RCTs identified by DERP Literature Scan[1]

Table 2. Secondary publications of trials listed above or included in report previously (N=32)*

Study	Subgroup or Secondary Outcome	Comparison
PLATO	**ACS**	Ticagrelor vs. Clopidogrel
Kotsia, 2014	Clinical events and safety in relation to extent of CAD	
Mahaffey, 2014	MI and impact of event adjudication	
Varenhorst, 2014	Factors associated with mortality	
TRITON-TIMI-38	**ACS**	Prasugrel vs Clopidogrel
Kohli, 2014	Discharge aspirin dose and clinical outcomes	
TRILOGY ACS	**ACS**	Prasugrel vs Clopidogrel
Cornel, 2014	Impact of smoking status on clinical outcomes in ACS patients without revascularization	

1. Dasbiswas A[1], Rao MS[2], Babu PR[3], Vijayvergiya R[4], Nayak R[5], Dani S[6], Tyagi S[7], Hiremath S[8], Patel T[9], Alexander T[10], Prakash VS[11], Singh DP[8], Yadav MK[4], Pathak K[12], Srivastava A[12]. A comparative evaluation of prasugrel and clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *J Assoc Physicians India.* 2013 Feb;61(2):114-6, 126.

OBJECTIVE: Primary objective of this study was to compare the efficacy of Prasugrel vs. Clopidogrel in the patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) by measuring inhibition of platelet aggregation after loading and maintenance dose of both the drugs. The patients were also assessed for safety of the drugs.

METHODS: This was a randomised, double-blind, double-dummy, comparative, multicentric clinical trial in patients with acute coronary syndrome (unstable angina, non-ST elevation MI and ST elevation MI) undergoing PCI. The patients were randomly assigned to receive prasugrel (loading dose of 60 mg followed by maintenance dose of 10-mg once daily) or clopidogrel (loading dose of 300 mg followed by maintenance dose of 75 mg once daily) for a period of 12 weeks. All the patients were co-prescribed aspirin 325 mg with both the drugs. The primary efficacy end point in this study was percentage inhibition of ADP induced platelet aggregation (IPA) at 4 +/- 1 hours after the loading dose and at 30 +/- 3 days during maintenance treatment. The platelet aggregation of both the drugs was measured by whole blood aggregometer using 10 mmol of ADP as an aggregant. Though this study was not powered to see the difference in clinical efficacy parameters, the patients were observed for the incidence of nonfatal MI, nonfatal stroke, re-hospitalization, death, or need for urgent revascularization due to a cardiac ischemic event at days 30 and 90 during the study. The safety of study drugs were evaluated by incidence of major bleeding, reported adverse drug reaction and alterations of any laboratory parameters.

RESULT: A total of 220 patients were enrolled at 11 centres across India. Ten patients were given the loading dose of prasugrel or clopidogrel but did not underwent PCI due to change in investigator's decision to go for PCI. Out of 210 eligible patients, 21 patients were discontinued during the study. 157 patients were evaluated for platelet inhibition after loading dose at 4 hours and 150 patients at day 30 during maintenance phase of antiplalelet therapy. The investigators could not perform this test in remaining patients due to urgency and criticality of the patients. 189 patients were observed for the incidence of nonfatal MI, nonfatal stroke, rehospitalisation, urgent revascularisation or death due to a cardiac ischemic event. All eligible patients who received at least a loading dose were evalauted for safety. In prasugrel group, 85 and 77 patients were evaluated for IPA at 4 hours and day 30 respectively whereas in clopdogrel group 72 and 73 patients were tested for IPA at 4 hours and at 30 days. Patients in prasugrel group have demonstrated significantly higher inhibition of platelets as compared to clopidogrel group (82.5% vs 71.1%) at 4 hours and at 30 days (84.1% vs 67.4%). The difference in inhibition of platelets between prasugrel and clopidogrel after loading dose and maintenenace dose was statistically significant ($p < or = 0.01$). The patients were also evaluated for drug hyporesponsiveness to antiplatelet therapy if IPA was < 20% at day 30 from the baseline. More patients on prasugrel have shown response to antiplatlet therapy than on clopidogrel (97.4% vs 87.6%). The difference between the two groups was statistically significant ($p < 0.05$). There was no difference observed during the study in the incidence of nonfatal MI, nonfatal stroke, death, rehospitalisation or need for urgent revascularisation due to a cardiac event between prasugrel and clopidogrel. Both the drugs were found to be to be well tolerated and have comparable safety profile.

CONCLUSION: This study suggests that prasugrel is more effective than clopidogrel as an anti platelet drug as evident by inhibition of platelet aggregation. More patients on clopidogrel are likely to have poor response to therapy as compared to prasugrel. Both the drugs were well tolerated and have comparable safety profile.

2. Gasparovic H[1], Petricevic M[2], Kopjar T[2], Djuric Z[2], Svetina L[2], Biocina B[2]. Impact of dual antiplatelet therapy on outcomes among aspirin-resistant patients following coronary artery bypass grafting. Am J Cardiol. 2014 May 15;113(10):1660-7. doi: 10.1016/j.amjcard.2014.02.024. Epub 2014 Mar 1.

Coronary artery bypass grafting is pivotal in the contemporary management of complex coronary artery disease. Interpatient variability to antiplatelet agents, however, harbors the potential to compromise the revascularization benefit by increasing the incidence of adverse events. This study was designed to define the impact of dual antiplatelet therapy (dAPT) on clinical outcomes among aspirin-resistant patients who underwent coronary artery surgery. We randomly assigned 219 aspirin-resistant patients according to multiple electrode aggregometry to receive clopidogrel (75 mg) plus aspirin (300 mg) or

aspirin-monotherapy (300 mg). The primary end point was a composite outcome of all-cause death, nonfatal myocardial infarction, stroke, or cardiovascular hospitalization assessed at 6 months postoperatively. The primary end point occurred in 6% of patients assigned to dAPT and 10% of patients randomized to aspirin-monotherapy (relative risk 0.61, 95% confidence interval 0.25 to 1.51, p = 0.33). No significant treatment effect was noted in the occurrence of the safety end point. The total incidence of bleeding events was 25% and 19% in the dAPT and aspirin-monotherapy groups, respectively (relative risk 1.34, 95% confidence interval 0.80 to 2.23, p = 0.33). In the subgroup analysis, dAPT led to lower rates of adverse events in patients with a body mass index >30 kg/m(2) (0% vs 18%, p <0.01) and those <65 years (0% vs 10%, p = 0.02). In conclusion, the addition of clopidogrel in patients found to be aspirin resistant after coronary artery bypass grafting did not reduce the incidence of adverse events, nor did it increase the number of recorded bleeding events. dAPT did, however, lower the incidence of the primary end point in obese patients and those <65 years.

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Policy Evaluation: Prior Authorization of non-preferred platelet inhibitor drugs

Research Questions:

- What is the general utilization trend of the platelet inhibitor class since implementation of the clinical prior authorization (PA) in April 2012?
- How many patients encountering a PA for a platelet inhibitor drug do not continue on any antiplatelet therapy?
- What is the extent and length of concurrent dual antiplatelet therapy (DAPT) and does it conform to treatment guidelines?

Conclusions:

- The preferred drugs, aspirin (70.3%) and clopidogrel (28.1%) were associated with the majority of patient index events. There were no discernable utilization trends temporal to the implementation of the clinical prior authorization criteria in April 2012.
- Very few patients encountered the clinical PA (n=19 patients, 1.5%) in the 21 months evaluated. Five patients (26% of those encountering the PA) did not get appropriate antiplatelet therapy within 30 days. Only 5 patients of the 19 had prior authorization requests (all approved). The remaining patients transitioned to coordinating care organizations (CCO) (n=5) or were switched to clopidogrel (n=4). Delayed care appears linked to hospitalization or transitioning to CCOs.
- There was a low overall rate (n=50, 4.0%) of DAPT utilization. This could be because there was cash payment for aspirin that is not captured in this evaluation. There was anecdotal evidence of the PA contributing to 1 patient not getting appropriate DAPT. Three patients were on inappropriate DAPT (Aggrenox™ with additional aspirin or clopidogrel). Just over half (56%) of DAPT patients had supporting diagnoses, leaving just under half that did not have supporting diagnoses. Most patients were on DAPT for 6 months or less.

1

Recommendations:

- Continue the PA policy with minor modifications (**Appendix 1**) that are consistent with updated treatment guidelines.
- Implement a retrospective safety net program to identify patients that do not start antiplatelet therapy within 14 days for additional transition assistance with a focus on insuring patients qualifying for DAPT are not discontinued prematurely.

Background:

The platelet inhibitor class ranks 35th by net cost ($74,850) during quarter 1 2015 for the Oregon Health Plan (OHP) fee-for-service (FFS) program.[1] The platelet inhibitor drug class was added to the OHP Preferred Drug List on January 1, 2010.[2] Non-preferred drugs required only a funded diagnosis for approval. Additional clinical criteria for prasugrel and ticagrelor were implemented April 9, 2012[3] and upon market entry for vorapaxar.[4] Aspirin, clopidogrel, dipyridamole and aspirin/dipyridamole have been the preferred drugs since adding the class and now comprise 99% of market share.[1]

Concern has been raised about prior authorization policies for platelet inhibitor drugs delaying access to drugs and subsequently contributing to increased cardiovascular events.[5] In the previous policy evaluations of combination inhalers for asthma[6] and anticoagulants[7] it was reported that only about a third of patients encountering a PA requirement subsequently had one requested for them by their clinician. Many patients were prescribed the desired alternative therapies but a significant subset of patients in both prior policy evaluations were appreciably delayed in getting needed medication or did not get it at all. In response to these findings, the anticoagulant PA policy was discontinued[8] and a retrospective safety net program was created for the combination inhalers.[9]

As noted in the accompanying antiplatelet class review,[10] the recommendations for dual platelet inhibitor therapy (DAPT) is evolving for drug eluting stents. DAPT is recommended for 1 year in most patients receiving a drug eluting stent. DAPT is considered up to 30 months for patients at high risk for cardiovascular events and less than 6 months for patients at high risk of bleeding. The current recommendations are summarized below:

Indication	Dual DAPT Length	Source
secondary ACS or PCI with stent	At least 12 months for ACS & drug eluting stent / 1-12 months bare metal stent	ACCF/AHA
secondary stroke prevention	Not generally recommended (90 days maximum)	AHA/ASA
PAD	Not recommended	ACCF/AHA
primary CVD prevention	Not recommended	ACC/AHA; ADA

The purpose of this policy evaluation is to document the general utilization trend of the platelet inhibitor class since implementation of the clinical PA in April 2012, quantify the number of patients encountering a PA that do not continue any drug therapy and describe current DAPT to inform drug policy proposals.

Methods:

Patients were included if they had a paid FFS drug claim for any drug in Table 1 or a denied fee-for-service (FFS) drug claim with Explanation of Benefit (EOB) code 1056 (i.e. "PA Required") and simultaneously no EOB of 2017 (i.e. "Patient enrolled in MCO") from April 2012 and through March 2014. Patients were excluded if they had Medicare Part D coverage as indicated by benefit packages of BMM or BMD. Patients were also excluded if they had aspirin monotherapy that consisted of claims of less than 28 "Days Supply" or daily unit consumption equivalent to 80 mg (0.75 units – 2.25 units) to 325 mg per day (0.5 units to 1.25 units). Daily unit consumption is equal to quantity dispensed / days supply. Using only FFS claims, the *first platelet inhibitor paid or denied claim* per patient during the study period was designated the *index event*. If patients had both a paid claim and a denied claim, they were counted in the paid claim category and

their denied claim was ignored. Patients were excluded if they had less than 75% days of combined FFS or coordinated care organization eligibility for the 12 months after the index event.

Table 1. Platelet inhibitor Drugs

PDL	HSN	GSN	Brand	Generic
N	006232	016375	TICLOPIDINE HCL	TICLOPIDINE HCL
Y	012474	040303	AGGRENOX	ASPIRIN/DIPYRIDAMOLE
Y	017539	038164	PLAVIX	CLOPIDOGREL BISULFATE
Y	017539	063544	PLAVIX	CLOPIDOGREL BISULFATE
N	036159	064901	EFFIENT	PRASUGREL HCL
N	036159	064902	EFFIENT	PRASUGREL HCL
N	037328	066950	BRILINTA	TICAGRELOR
N	041137	072336	ZONTIVITY	VORAPAXAR SULFATE
Y	001820	004376	ASPIRIN	ASPIRIN 325 mg
Y	001820	004380	CHILDREN'S ASPIRIN	ASPIRIN 81 mg
Y	001820	004381	ASPIRIN EC	ASPIRIN 325 mg
Y	001820	016995	LOW DOSE ASPIRIN EC	ASPIRIN 81 mg

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

Patients were categorized by whether the index event was a paid or denied claim. Patients were also categorized by the generic drug name of index event. 3

Patients with paid index events were categorized in the following groups:

1) New platelet inhibitor start - no paid FFS or encounter platelet inhibitor claims within 102 days prior to *index event.*

2) Continuation Therapy - Patients where the *index event* is for the same hierarchical ingredient code list sequence number (HSN) as a paid FFS or encounter platelet inhibitor claim within 102 days prior.

3) Other - *Index event* does not fit in prior categories.

Patients with denied index events were categorized in the following groups to describe drug therapy disruption:

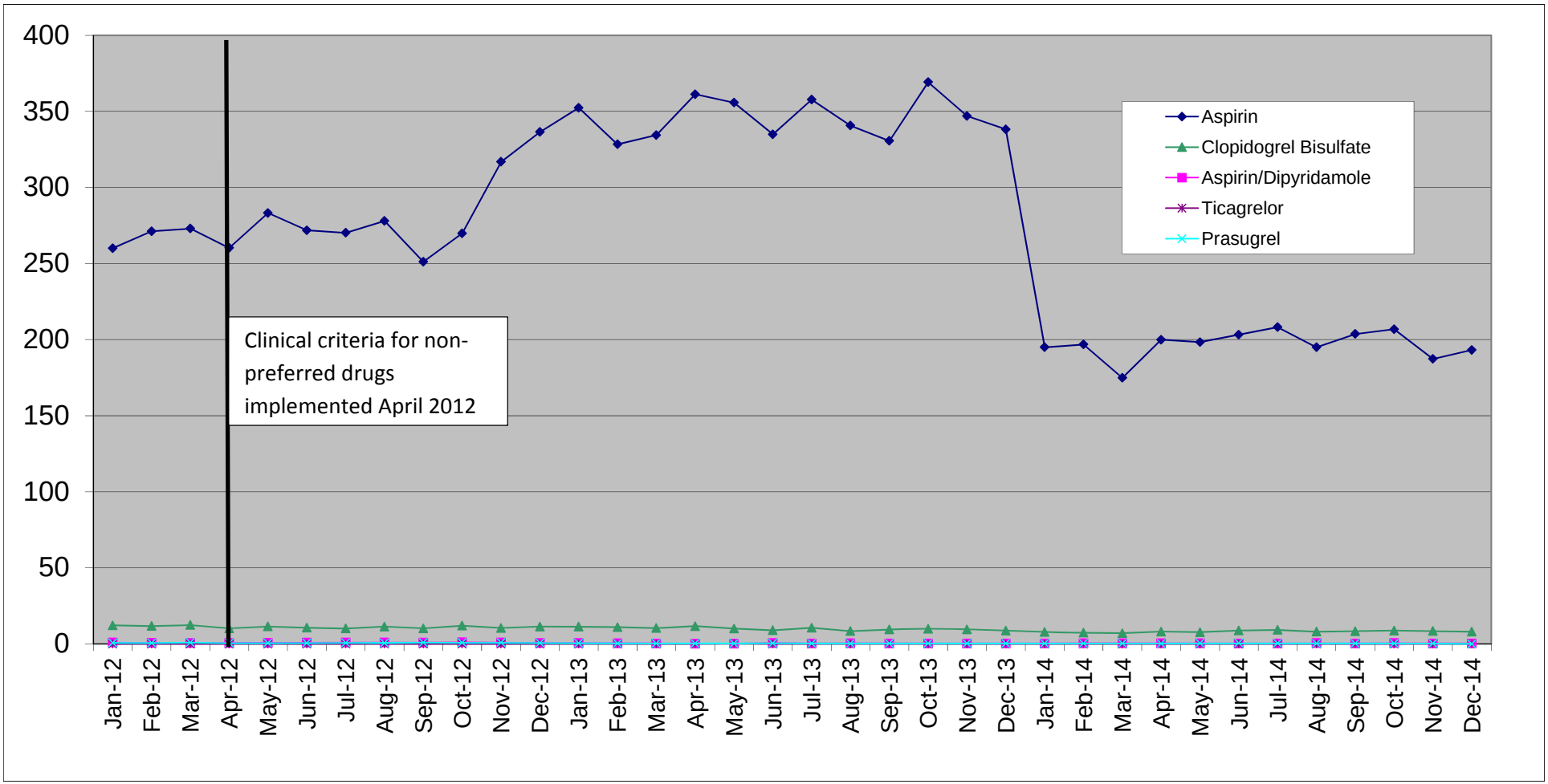
1) Platelet inhibitor drug ≤ 14 days
2) Platelet inhibitor drug > 14 and < 90 days
3) Platelet inhibitor drug > 90 days or no platelet inhibitor claims

Platelet inhibitor therapy length was determined for each HSN using the date of the first paid claim and last paid claim plus "Days Supply" entry with a minimum therapy gap in therapy of 7 days. Patients with a minimum of concurrent therapy of 60 days with overlapping therapy of 2 or more HSNs were included in the DAPT analysis. Length of concurrent therapy length was determined as the length in days from the date of last overlapping span minus the date of the first overlapping span. Patients were flagged if they had one of the selected diagnosis code (Table 6) on any paid FFS or encounter claim from 1 year prior to 1 month after the index event.

Results:

Figure 1 displays the number of patients per 10,000 members per month on each of the platelet inhibitor drugs. This chart does not distinguish daily aspirin use for antiplatelet effect from use for pain. Aspirin dominates the class and the gross number of patients is quite constant averaging 2677 (2560 – 2780) patients per month. The variation in trend is primarily due to enrollment fluctuations, notably the large influx of covered lives in January 2014. Clopidogrel averages 98 (66 – 121) patients per month and prasugrel averages 4 (0-8) patients per month. There was one unique patient on ticagrelor during the entire 2 years.

Figure 1 - Unique Utilizing Members per Fee-For-Service Members (x10000)



Authors: K. Ketchum

Table 2 displays the demographics of all patients with a FFS claim and where aspirin users were restricted to those on a daily dose of 80-325 mg per day. The study population also met the minimum eligibility requirements. The study population is very similar in demographics to those that do not meet the eligibility requirements. It is almost exclusively mid-aged adults, both genders are represented equally and about 33% are non-white.

Table 2 - Demographics

	All Patients with FFS Claim		Study Population	
N=	1,365	%	1,230	%
Mean age (range)	53.1	(0-89)	53.3	(0-89)
< 19	16	1.2%	16	1.3%
19-64	1,284	94.1%	1,153	93.7%
> 64	65	4.8%	61	5.0%
Female	671	49.2%	619	50.3%
White	917	67.2%	818	66.5%

Table 3 displays the type of index event. Only 1.8% of patients had denied index events indicating the preferred platelet inhibitors are prescribed predominately and relatively few patients encountered the prior authorization requirement.

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Table 3 - Platelet inhibitor Index Therapy Type

	All Patients with FFS Claim		Study Population	
N=	1,365	%	1,230	%
Denied	23	1.7%	22	1.8%
Paid New Start	747	54.7%	663	53.9%
Paid Continuation of Same Therapy	595	43.6%	545	44.3%

Table 4 displays the index events by drug. Preferred drugs account for 99.5% of paid index events. No patients were prescribed ticlopidine or vorapaxar. Six patients with paid index events had continued on prasugrel from the period prior to the clinical PA criteria being implemented.

There were 22 patients with denied index events. Three of 22 patients were prescribed preferred drugs (1 clopidogrel, 2 aspirin) and encountered a PA requirement because the dispensing pharmacy used a Dispense-As-Written (DAW) code of "1" which overrides the generic pricing. One aspirin patient (a

diabetic with no cardiac indications) subsequently got it paid for by a CCO the next day; the other aspirin patient had no apparent indication for antiplatelet therapy and did not ever have a subsequent claim for it; and the clopidogrel patient had no record of any paid drug claims and further investigation determined the patient had external drug coverage.

Nineteen of 22 patients were prescribed non-preferred drugs (18 prasugrel, 1 ticagrelor). Only 6 of the 19 patients had claims for any platelet inhibitor within 14 days (average of 7 days). Of these, 2 were switched to clopidogrel, 2 got prasugrel and the other ticagrelor. The last patient was already on aspirin when denied prasugrel and then eventually was switched to clopidogrel 150 days latter. This patient underwent a coronary bypass, was a diabetic, and also had atrial fibrillation and mitral valve disorder and qualified for DAPT. Nine of the remaining 13 patients with denied prasugrel index events had subsequent claims between 14 and 90 days (average 30 days). A manual review of these patients found 5 patients transitioned to CCOs where 4 had subsequent claims for prasugrel and 1 was switched to clopidogrel. Of the remaining 4 FFS patients, 3 got prasugrel and 1 clopidogrel. All 9 patients who had delayed antiplatelet therapy had indications of stent placement, bypass surgery or myocardial infarction. None were on dual antiplatelet therapy but all also had concurrent non-steroidal therapy, corticosteroid therapy or antiulcer therapy so may have been at higher risk of bleeding.

Six patients did not have a claim for platelet inhibitors within 90 days. Two mentioned above, encountered PA for DAW-1. Of the remaining 4, 1 had no apparent indication for antiplatelet therapy other than primary cardiovascular event prevention and was started on aspirin 3 months after the denied index and the remaining 3 patients had compelling cardiac indications. Two patients eventually started daily aspirin more than a year after the denied index event and one had no record of antiplatelet therapy.

In summary, 14 of 22 patients with denied index events got appropriate antiplatelet therapy within 30 days, 2 had no apparent indication for antiplatelet therapy, 1 had other insurance for drug coverage and 5 patients did not receive appropriate antiplatelet therapy within 30 days or ever.

Table 4 - Drug Distribution of Study Population

						Denied Index Events					
		Total Paid Index Events		Total Denied Index Events		*by subsequent paid platelet inhibitor claim*					
						<=14 Days		>14 & <90 Days		>=90 Days or Never	
	N=	1,208	%	22	%	7	31.8%	9	40.9%	6#	27.3%
006232	TICLOPIDINE HCL										
012474	ASPIRIN/DIPYRIDAMOLE	13	1.1%								
017539	CLOPIDOGREL BISULFATE	340	28.1%	1*	4.5%	2’	9.1%	2’	9.1%		
036159	PRASUGREL HCL	6	0.5%	18’	81.8%	2’	9.1%	7’	31.8%		
037328	TICAGRELOR			1^	4.5%	1^	4.5%				
041137	VORAPAXAR SULFATE										
001820	ASPIRIN	849	70.3%	2*	9.1%	1*+1’	9.1%			3’	13.6%

*****patients with Dispense-As-Written (DAW)-1 index;

‘ = patients with denied prasugrel index;

^ = patient with denied ticagrelor index;

#= 3 patients had no subsequent antiplatelet claims

Table 5 displays patients on a minimum of 60 days of concurrent platelet inhibitor. Only 50 of 1230 (4.0%) patients included in the study were on DAPT. The vast majority (n=46, 92%) were on aspirin and clopidogrel for an average of 188 days (about 6 months). There were 30 (60%) on DAPT for 6 months or less and 21 (42%) were on DAPT for more than 6 months. Patients could have more than one concurrent span. If one span was longer than 6 months, they were placed in > 6 months group and removed from the ≤ 6 months group. One patient was on aspirin and clopidogrel off and on for about 18 months and then aspirin and prasugrel for less than 6 months and is counted twice in Table 5. There are currently no recommendations for using the combination aspirin/dipyridamole with either aspirin (n=2) or clopidogrel (n=1).

Table 5 - Study Population Concurrent Therapy by Drug Combination

Concurrent therapy minimum of 60 days overlap in two years

		Concurrent Users		Length of Overlap		<= 6 months		> 6 months	
Drug 1	**Drug 2**	**50**	%	**Mean**	**Range**	30	60.0%	21*	42.0%
001820 Aspirin	017539 Clopidogrel Bisulfate	46	92.0%	188	60-761	26	52.0%	20*	40.0%
001820 Aspirin	036159 Prasugrel	2	4.0%	104	61-147	2*	4.0%		
001820 Aspirin	012474 Aspirin/Dipyridamole	2	4.0%	410	94-726	1	2.0%	1	2.0%
012474 Aspirin/Dipyridamole	017539 Clopidogrel Bisulfate	1	2.0%	155	155	1	2.0%		

* One patient was on aspirin and clopidogrel off and on for about 18 months and then aspirin and prasugrel for less than 6 months and is counted twice in Table 5.

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Table 7 displays the selected diagnoses of interest associated with the 50 patients on DAPT. The majority (56%) had documented diagnoses suggesting secondary prevention for acute coronary syndrome and likely appropriate.

Limitations:

It is difficult to distinguish patients using aspirin for pain versus for antiplatelet therapy. Patients on aspirin monotherapy were restricted to those on daily aspirin doses of 80 mg to 325 mg. This may have under-estimated the number of non-compliant patients on aspirin monotherapy. However, if a patient had any other antiplatelet drug plus any aspirin dose, the aspirin was included for purposes of identifying potential DAPT. Despite this liberal definition, the number of patients on DAPT appears low. There remains a possibility that patients are paying cash for over-the-counter aspirin and could not be identified as DAPT. There was no attempt to associate diagnoses to antiplatelet monotherapy. In retrospect, this may have helped to verify the apparent low rate of DAPT but also added complexity and was not the focus of this evaluation.

It has been reported that insurance coverage affects the type of stent used, with just 3.7% of those receiving drug-eluting stents having Medicaid insurance, which again would limit length of DAPT to 6 months.[11] Additionally, the patients in this evaluation are generally younger and may not warrant long-term therapy.

Anecdotally, the manual review of patients with delayed antiplatelet therapy identified one patient that was definitely appropriate for DAPT. The other manually reviewed patients had indicators of high risk of bleeding which may have precluded them from long-term DAPT, but they were still appropriate for short term DAPT.

Table 7: Diagnostic Distribution of All Patients with Dual Antiplatelet Therapy
Each group mutually-exclusive in priority of 1, 2, 3, 4, 5

		1 year Prior + Month After Index	
		n=50	%
1) Secondary acute coronary syndrome prevention		**28**	**56.0%**
1. AMI	410xx	15	30.0%
2. Other acute & sub-acute forms of ischemic heart disease	411xx	9	18.0%
3. Angina	413xx	8	16.0%
4. Chest Pain	7865x	27	54.0%
2) Secondary stroke prevention		**9**	**18.0%**
1. Occlusion and stenosis of precerebral arteries	433xx	4	8.0%
2. Occlusion of cerebral arteries	434xx	6	12.0%
3. Transient cerebral ischemia	435xx	3	6.0%
4. Acute, but ill-defined, cerebrovascular disease	436xx	7	14.0%
5. Hemiplegia and hemiparesis	342xx	2	4.0%
6. Other paralytic syndromes	344xx		0.0%
3) Diagnoses indicating primary prevention		**8**	**16.0%**
1. Other forms of chronic ischemic heart disease	414xx	7	14.0%
2. Atherosclerosis	440xx		0.0%
3. Other peripheral vascular disease	443xx	1	2.0%
4. Arterial embolism and thrombosis	444xx		0.0%
5. Personal history of diseases of circulatory system	V125xx		0.0%
4) Anticoagulant indications		**0**	**0.0%**
1. Cardiac dysrhythmias	427xx		0.0%
2. Other venous embolism and thrombosis	453xx		0.0%
3. Pulmonary embolism and infarction	4151x		0.0%
5) None of the above		**5**	**10.0%**

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Appendix 1: Platelet Inhibitor Prior Authorization Criteria

Platelet Inhibitors

Goal:

- Approve platelet inhibitors for covered diagnoses which are supported by medical literature.

Length of Authorization:

- Up to 12 months.

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis an OHP covered diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny, not funded by the OHP.
3. Will the prescriber consider a change to a preferred product?	**Yes:** Inform provider of covered alternatives in class.	**No:** Go to #4
4. Is this continuation of hospital treatment?	**Yes:** Approve for 30 days only and inform provider of preferred products.	**No:** Go to #5

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Approval Criteria		
~~5. Is the patient unable to take clopidogrel due to one of the following:~~ ~~• clopidogrel allergy~~ ~~• contraindications to clopidogrel therapy e.g. poor metabolizers of CYP2C19 (document)~~ ~~• drug-drug interactions e.g. omeprazole (document)~~ ~~• intolerable side effects~~	~~**Yes:** Go to #6~~	~~**No:** Pass to RPh. Deny (Medical Appropriateness)~~ ~~Recommend clopidogrel trial.~~
~~6.~~5. Is the request for either prasugrel or vorapaxar AND does the patient have a history of stroke, TIA or intracranial hemorrhage?	**Yes:** Deny for medical appropriateness	**No:** Approve for FDA-approved indications for up to 1 year. If vorapaxar is requested, it should be approved only when used in combination with aspirin and/or clopidogrel. There is limited experience with other platelet inhibitor drugs or as monotherapy.

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FDA Approved Indications (May 2014)

	2° Stroke	2° PAD	2° MI	ACS	
				No PCI	PCI
ASA/DP ER	x				
clopidogrel	x	x	x	x	x
prasugrel	CI				x
ticagrelor				x	x
vorapaxar	CI	x	x		

X = FDA indicated; CI=contraindication; ACS=Acute Coronary Syndrome;

PCI=Percutaneous Intervention

P&T / DUR Review: *7/15 (KK); 11/11*
Implementation: ***TBD**; 7/31/14; 4/9/12*

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Drug Use Evaluation: Tetracycline Antibiotics

Research Questions:

1. What are the most common durations of therapy, measured by both treatment duration and unique pharmacy claims, of tetracycline antibiotics?
2. What is the prevalence of members receiving short- (14 days or less), medium- (15-89 days) and long- (90 days or longer) term treatment with tetracyclines?
3. What is the prevalence and associated costs of members receiving tetracycline treatment of unfunded conditions?

Conclusions:

1. The majority of members (69.2%) received a single prescription with an average of a 13-day supply. A minority of members (17.8%) received more than two tetracycline prescriptions.
2. Most tetracycline claims were for short-term therapy (57%), followed by medium-term duration (28%) and long-term duration (15%).
3. Members with claims data indicating treatment of tetracyclines for only unfunded conditions comprised 27.9% of the total study population and represented 43.3% of the total prescription drug expenditures ($28,439).
4. When a funded condition for tetracyclines was identified, 86% of members received only short-term treatment.

Recommendations:

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

Background:

Tetracycline antibiotics are indicated for a variety of infections, including sexually transmitted diseases, respiratory tract infections, urinary tract infections, soft tissue infections, acne vulgaris, rosacea, as well as a variety of less common such as anthrax.[1–6] Therapy exceeding 21 days is rarely indicated for conditions other than acne and rosacea, with the most common durations for therapy limited to a 14 day course. Rosacea and most mild forms of acne fall below the current Oregon Health Plan (OHP) funded line on the Prioritized List of Health services.[7] The only funded form of acne is acne conglobata in the presence of recurrent abscesses or communicating sinuses.

Methods:

The study included patients with a paid (FFS) pharmacy claim for a qualifying tetracycline antibotic between January 1, 2014 and June 30, 2014. A complete list of qualifying appears in Table A1 of Appendix A. An Index Event (IE) was defined as the first paid FFS claim qualifying claims during the study period. All claims for tetracycline antibiotics for 6 months after the IE were included. Patients with dual Medicare and Medicaid coverage were excluded. Patients enrolled in a Coordinated Care Organization (CCO) within 6 months after the IE were excluded. Patients with more than a 25% gap in eligibility within 6 months after the IE were excluded.

ICD9 codes for the most likely indications for tetracyclines are included in table A2 of Appendix A. Diagnoses associated with medical claims ranging from 30 days before the IE to 7 days after the IE were used to identify likely indications for

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acute treatment. Diagnoses of chronic conditions (e.g. acne, rosacea) were included for all diagnoses from July 1, 2013 to December 31, 2014. This broad strategy was used in recognition that patients with stable, chronic conditions may not be seen more than once per year. Patients were categorized as having at least one funded condition (funded), at least one medical claim with a qualifying, unfunded diagnosis (unfunded), or no claims for qualifying diagnoses (no diagnosis available). Patients were also categorized based on the total number of days covered by a tetracycline antibiotic: short (14 days or less), medium (15-89) and long (90 days or longer).

Table 1 - Demographics

	#	%
Total	591	100.0%
Age		
0-11	3	0.5%
12-17	69	11.7%
18-30	218	36.9%
31-50	191	32.3%
51-64	108	18.3%
Over 65	2	0.3%
Gender		
F	380	64.3%
M	211	35.7%

Results:

Initial screening identified 927 members with qualifying tetracycline claims. Of these 10 were excluded due to dual Medicare/Medicaid coverage, 22 members were excluded due to gaps in eligibility, and 304 were excluded based on enrollment in a CCO. The basic demographics of the remaining 591 members appear in Table 1. A minority of members (n=236,40%) had a least one medical claim identified for a condition that would be an expected indication for a tetracycline antibiotic (Table 2). Of these, 165 had claims only for unfunded conditions. A small proportion (15%) of members received long term therapy (Table 3). A single member with claims for funded conditions received long term tetracycline therapy, while 86% of members with funded conditions received short term therapy (Table 3).

Table 2 – Prevalence of Diagnosis Information for Tetracycline Antibiotics

	Members		Amount Paid	
Diagnosis Funding Status	#	%	$	%
Funded	71	12.0%	$ 4,620	7.0%
No Diagnosis Available	355	60.1%	$ 32,636	49.7%
Unfunded	165	27.9%	$ 28,439	43.3%
Total	591	100.0%	$ 65,696	100.0%

Table 3 – Funded Status and Duration of Tetracycline Therapy

Duration of Therapy	Funded		Unfunded		No Diagnosis Available		Total Unique Members	
	#	%	#	%	#	%	#	%
Short	61	86%	62	38%	212	60%	335	57%
Medium	9	13%	65	39%	93	26%	167	28%
Long	1	1%	38	23%	50	14%	89	15%
Grand Total	71	100%	165	100%	355	100%	591	100%

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Members receiving three or fewer prescriptions had an average duration of therapy of 24 days or less (Table 4). With one exception, the average prescription length for members with more than 3 claims had an average prescription duration of 27 days or more.

Table 4 – Total Claims Per Member and Average Day Supply per Claim

Total Claims	Members		Average Days Supply
	#	%	
1	409	69.2%	13
2	77	13.0%	20
3	36	6.1%	24
4	13	2.2%	28
5	20	3.4%	27
6	20	3.4%	29
7	15	2.5%	28
8	1	0.2%	10

Limitations:

The intended indications for long term therapy are unclear from the available claims data. Only 45% of members on long term therapy had diagnosis data available. In all but one case, the conditions were unfunded. Members receiving between 4 and 7 prescriptions have durations of therapy consistent with chronic therapy (average 27-29 days). Based on the literature, the most common indications for chronic tetracycline use are unfunded dermatologic conditions (e.g. Acne, Rosacea, see Table A2). The precision and specificity of time periods used to identify potential diagnosis information have not been validated, raising the possibility of incorrect characterizations of the conditions being treated. Time related effects, such as seasonal variations in community acquired pneumonia and recent increases in the rates of sexually transmitted diseases were not considered.

References:

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7. Oregon Health Policy and Research Current Prioritized List of Health Services. http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx. Accessed June 1, 2015.

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Appendix A

Table A1 – Study Eligible Tetracyclines

GSN	Generic Name	Drug Form
009213	DEMECLOCYCLINE HCL	TABLET
009214	DEMECLOCYCLINE HCL	TABLET
009217	DOXYCYCLINE CALCIUM	SYRUP
009218	DOXYCYCLINE HYCLATE	CAPSULE
009219	DOXYCYCLINE HYCLATE	CAPSULE
043362	DOXYCYCLINE HYCLATE	CAPSULE
049446	DOXYCYCLINE HYCLATE	CAPSULE DR
009220	DOXYCYCLINE HYCLATE	CAPSULE DR
009223	DOXYCYCLINE HYCLATE	TABLET
048077	DOXYCYCLINE HYCLATE	TABLET
072633	DOXYCYCLINE HYCLATE	TABLET
072634	DOXYCYCLINE HYCLATE	TABLET
059573	DOXYCYCLINE HYCLATE	TABLET DR
059574	DOXYCYCLINE HYCLATE	TABLET DR
064119	DOXYCYCLINE HYCLATE	TABLET DR
070917	DOXYCYCLINE HYCLATE	TABLET DR
060942	DOXYCYCLINE MONOHYDRATE	CAP IR DR
062496	DOXYCYCLINE MONOHYDRATE	CAPSULE
063058	DOXYCYCLINE MONOHYDRATE	CAPSULE
015943	DOXYCYCLINE MONOHYDRATE	CAPSULE
016815	DOXYCYCLINE MONOHYDRATE	CAPSULE
009225	DOXYCYCLINE MONOHYDRATE	SUSP RECON
027050	DOXYCYCLINE MONOHYDRATE	TABLET
036747	DOXYCYCLINE MONOHYDRATE	TABLET
051756	DOXYCYCLINE MONOHYDRATE	TABLET
059845	DOXYCYCLINE MONOHYDRATE	TABLET
042778	MINOCYCLINE HCL	CAPSULE
009226	MINOCYCLINE HCL	CAPSULE
009227	MINOCYCLINE HCL	CAPSULE
009229	MINOCYCLINE HCL	ORAL SUSP
060730	MINOCYCLINE HCL	TAB ER 24H
060731	MINOCYCLINE HCL	TAB ER 24H
060732	MINOCYCLINE HCL	TAB ER 24H
065433	MINOCYCLINE HCL	TAB ER 24H
065434	MINOCYCLINE HCL	TAB ER 24H
066683	MINOCYCLINE HCL	TAB ER 24H
066684	MINOCYCLINE HCL	TAB ER 24H
066685	MINOCYCLINE HCL	TAB ER 24H
009230	MINOCYCLINE HCL	TABLET
009231	MINOCYCLINE HCL	TABLET
052057	MINOCYCLINE HCL	TABLET
009189	TETRACYCLINE HCL	CAPSULE
009190	TETRACYCLINE HCL	CAPSULE
009195	TETRACYCLINE HCL	ORAL SUSP
009196	TETRACYCLINE HCL	TABLET
009197	TETRACYCLINE HCL	TABLET

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Table A2 – Diagnosis Codes

ICD9	Description	Line	Chronic
020	Plague	N/A	0
0200	Bubonic plague	210	0
0201	Cellulocutaneous plague	210	0
0202	Septicemic plague	210	0
0203	Primary pneumonic plague	210	0
0204	Secondary pneumonic plague	210	0
0205	Pneumonic plague, unspecified	210	0
0208	Other specified types of plague	210	0
0209	Plague, unspecified	210	0
022	Anthrax	N/A	0
0220	Cutaneous anthrax	210	0
0221	Pulmonary anthrax	210	0
0222	Gastrointestinal anthrax	210	0
0223	Anthrax septicemia	210	0
0228	Other specified manifestations of anthrax	210	0
0229	Anthrax, unspecified	210	0
077	Oth diseases conjunctiva due viruses&chlamydiae	N/A	0
0779	Unspec dz conjunctiva due viruses&chlamydiae	N/A	0
07798	Unspecified diseases of conjunctiva due to chlamydiae	171	0
07799	Unspecified diseases of conjunctiva due to viruses	641	0
078	Other diseases due to viruses and chlamydiae	N/A	0
0788	Other specified diseases due viruses&chlamydiae	N/A	0
07888	Other specified diseases due to chlamydiae	623	0
08881	Lyme Disease	271	0
090	Congenital syphilis	N/A	0
0900	Early congenital syphilis, symptomatic	16	0
0901	Early congenital syphilis, latent	16	0
0902	Early congenital syphilis, unspecified	16	0
0903	Syphilitic interstitial keratitis	16	0
0904	Juvenile neurosyphilis	N/A	0
09041	Congenital syphilitic encephalitis	16	0
09042	Congenital syphilitic meningitis	16	0
09049	Other juvenile neurosyphilis	16	0
0905	Other late congenital syphilis, symptomatic	16	0
0906	Late congenital syphilis, latent	16	0
0907	Late congenital syphilis, unspecified	16	0
0909	Congenital syphilis, unspecified	16	0
091	Early syphilis, symptomatic	N/A	0
0910	Genital syphilis (primary)	42	0
0911	Primary anal syphilis	42	0
0912	Other primary syphilis	42	0
0913	Secondary syphilis of skin or mucous membranes	42	0
0914	Adenopathy due to secondary syphilis	42	0
0915	Early syphilis uveitis due to secondary syphilis	N/A	0
09150	Syphilitic uveitis, unspecified	42	0
09151	Syphilitic chorioretinitis (secondary)	42	0
09152	Syphilitic iridocyclitis (secondary)	42	0
0916	Early syphilis sec syphilis of viscera and bone	N/A	0
09161	Secondary syphilitic periostitis	42	0
09162	Secondary syphilitic hepatitis	42	0
09169	Secondary syphilis of other viscera	42	0
0917	Secondary syphilis, relapse	42	0
0918	Early syphilis other forms of secondary syphilis	N/A	0
09181	Acute syphilitic meningitis (secondary)	42	0
09182	Syphilitic alopecia	42	0
09189	Other forms of secondary syphilis	42	0
0919	Unspecified secondary syphilis	42	0
092	Early syphilis, latent	N/A	0
0920	Early syphilis, latent, serological relapse after treatment	42	0
0929	Early syphilis, latent, unspecified	42	0
093	Cardiovascular syphilis	N/A	0
0930	Aneurysm of aorta, specified as syphilitic	42	0
0931	Syphilitic aortitis	42	0
0932	Syphilitic endocarditis	N/A	0
0938	Other specified cardiovascular syphilis	N/A	0
09389	Other specified cardiovascular syphilis	42	0
0939	Cardiovascular syphilis, unspecified	42	0
094	Neurosyphilis	N/A	0
0943	Asymptomatic neurosyphilis	386	0
0948	Other specified neurosyphilis	N/A	0
095	Other forms of late syphilis with symptoms	N/A	0
0950	Syphilitic episcleritis	386	0
0951	Syphilis of lung	386	0
0952	Syphilitic peritonitis	386	0
0953	Syphilis of liver	386	0
0954	Syphilis of kidney	386	0
0955	Syphilis of bone	386	0
0956	Syphilis of muscle	386	0
0957	Syphilis of synovium, tendon, and bursa	386	0
0958	Other specified forms of late symptomatic syphilis	386	0
0959	Late symptomatic syphilis, unspecified	386	0
096	Late syphilis, latent	386	0
097	Other and unspecified syphilis	N/A	0
0970	Late syphilis, unspecified	386	0
0971	Latent syphilis, unspecified	386	0
0979	Syphilis, unspecified	386	0
098	Gonococcal infections	N/A	0
0980	Gonococcal infection (acute) of lower genitourinary tract	56	0
0981	Gonococcal infection upper genitourinary tract	N/A	0
09810	Gonococcal infection (acute) of upper genitourinary tract, site unspecified	56	0
09811	Gonococcal cystitis (acute)	56	0
09812	Gonococcal prostatitis (acute)	56	0
09813	Gonococcal epididymo-orchitis (acute)	56	0
09814	Gonococcal seminal vesiculitis (acute)	56	0
09815	Gonococcal cervicitis (acute)	56	0
09816	Gonococcal endometritis (acute)	56	0
09817	Gonococcal salpingitis, specified as acute	56	0
09819	Other gonococcal infection (acute) of upper genitourinary tract	56	0
0982	Gonococcal infection, chronic, of lower genitourinary tract	56	0
0983	Gonococcal infections chronic upper gu tract	N/A	0
09830	Chronic gonococcal infection of upper genitourinary tract, site unspecified	56	0
09831	Gonococcal cystitis, chronic	56	0
09832	Gonococcal prostatitis, chronic	56	0
09833	Gonococcal epididymo-orchitis, chronic	56	0
09834	Gonococcal seminal vesiculitis, chronic	56	0

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ICD9	Description	Line	Chronic
09835	Gonococcal cervicitis, chronic	56	0
09836	Gonococcal endometritis, chronic	56	0
09837	Gonococcal salpingitis (chronic)	56	0
09839	Other chronic gonococcal infection of upper genitourinary tract	56	0
0984	Gonococcal infection of eye	N/A	0
09840	Gonococcal conjunctivitis (neonatorum)	171	0
09841	Gonococcal iridocyclitis	171	0
09842	Gonococcal endophthalmia	171	0
09843	Gonococcal keratitis	171	0
09849	Other gonococcal infection of eye	171	0
0985	Gonococcal infection of joint	N/A	0
09850	Gonococcal arthritis	56	0
09851	Gonococcal synovitis and tenosynovitis	56	0
09852	Gonococcal bursitis	56	0
09853	Gonococcal spondylitis	56	0
09859	Other gonococcal infection of joint	56	0
0986	Gonococcal infection of pharynx	56	0
0987	Gonococcal infection of anus and rectum	56	0
0988	Gonococcal infection of other specified sites	N/A	0
09881	Gonococcal keratosis (blennorrhagica)	56	0
09882	Gonococcal meningitis	56	0
09883	Gonococcal pericarditis	56	0
09884	Gonococcal endocarditis	56	0
09885	Other gonococcal heart disease	56	0
09886	Gonococcal peritonitis	56	0
09889	Gonococcal infection of other specified sites	186	0
099	Other venereal diseases	N/A	0
0990	Chancroid	56	0
0991	Lymphogranuloma venereum	56	0
0992	Granuloma inguinale	56	0
0993	Reiter's disease	50	0
0994	Other nongonococcal urethritis	N/A	0
09940	Other nongonococcal urethritis, unspecified	56	0
09941	Other nongonococcal urethritis, chlamydia trachomatis	56	0
09949	Other nongonococcal urethritis, other specified organism	56	0
0995	Oth venereal diseases due chlamydia trachomatis	N/A	0
09950	Other venereal diseases due to chlamydia trachomatis, unspecified site	56	0
09951	Other venereal diseases due to chlamydia trachomatis, pharynx	56	0
09952	Other venereal diseases due to chlamydia trachomatis, anus and rectum	56	0
09953	Other venereal diseases due to chlamydia trachomatis, lower genitourinary sites	56	0
09954	Other venereal diseases due to chlamydia trachomatis, other genitourinary sites	56	0
09955	Other venereal diseases due to chlamydia trachomatis, unspecified genitourinary site	56	0
09956	Other venereal diseases due to chlamydia trachomatis, peritoneum	56	0
09959	Other venereal diseases due to chlamydia trachomatis, other specified site	56	0
0998	Other specified venereal diseases	56	0
0999	Venereal disease, unspecified	56	0
102	Yaws	N/A	0
1020	Initial lesions of yaws	276	0
1021	Multiple papillomata due to yaws and wet crab yaws	276	0
1022	Other early skin lesions of yaws	276	0
1023	Hyperkeratosis due to yaws	276	0
1024	Gummata and ulcers due to yaws	276	0
1025	Gangosa	276	0
1026	Bone and joint lesions due to yaws	276	0
1027	Other manifestations of yaws	276	0
1028	Latent yaws	276	0
1029	Yaws, unspecified	276	0
480	Viral pneumonia	N/A	0
4800	Pneumonia due to adenovirus	623	0
4801	Pneumonia due to respiratory syncytial virus	623	0
4802	Pneumonia due to parainfluenza virus	623	0
4803	Pneumonia due to SARS-associated coronavirus	623	0
4808	Pneumonia due to other virus not elsewhere classified	623	0
4809	Viral pneumonia, unspecified	623	0
481	Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]	208	0
482	Other bacterial pneumonia	N/A	0
4820	Pneumonia due to Klebsiella pneumoniae	208	0
4821	Pneumonia due to Pseudomonas	208	0
4822	Pneumonia due to Hemophilus influenzae [H. influenzae]	208	0
4823	Pneumonia due to streptococcus	N/A	0
48230	Pneumonia due to Streptococcus, unspecified	208	0
48231	Pneumonia due to Streptococcus, group A	208	0
48232	Pneumonia due to Streptococcus, group B	208	0
48239	Pneumonia due to other Streptococcus	208	0
4824	Pneumonia due to staphylococcus	N/A	0
48240	Pneumonia due to Staphylococcus, unspecified	208	0
48241	Methicillin susceptible pneumonia due to Staphylococcus aureus	208	0
48242	Methicillin resistant pneumonia due to Staphylococcus aureus	208	0
48249	Other Staphylococcus pneumonia	208	0
4828	Pneumonia due to other specified bacteria	N/A	0
48281	Pneumonia due to anaerobes	208	0
48282	Pneumonia due to escherichia coli [E. coli]	208	0
48283	Pneumonia due to other gram-negative bacteria	208	0
48284	Pneumonia due to Legionnaires disease	208	0
48289	Pneumonia due to other specified bacteria	208	0
4829	Bacterial pneumonia, unspecified	208	0
483	Pneumonia due to other specified organism	N/A	0
4830	Pneumonia due to mycoplasma pneumoniae	208	0
4831	Pneumonia due to chlamydia	208	0
4838	Pneumonia due to other specified organism	208	0
484	Pneumonia infectious diseases classified elsw	N/A	0
4841	Pneumonia in cytomegalic inclusion disease	208	0
4843	Pneumonia in whooping cough	208	0
4845	Pneumonia in anthrax	208	0
4846	Pneumonia in aspergillosis	208	0
4847	Pneumonia in other systemic mycoses	208	0
4848	Pneumonia in other infectious diseases classified elsewhere	208	0
485	Bronchopneumonia, organism unspecified	208	0

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ICD9	Description	Line	Chronic
486	Pneumonia, organism unspecified	208	0
487	Influenza	N/A	0
4870	Influenza with pneumonia	403	0
4871	Influenza with other respiratory manifestations	403	0
4878	Influenza with other manifestations	403	0
488	Influenza d/t certn identified influenza viruses	N/A	0
4880	Influenza due to identifid avian influenza virus	N/A	0
48801	Influenza due to identified avian influenza virus with pneumonia	403	0
48802	Influenza due to identified avian influenza virus with other respiratory manifestations	403	0
48809	Influenza due to identified avian influenza virus with other manifestations	403	0
4881	Influenza due to id novel h1n1 influenza virus	N/A	0
48811	Influenza due to identified 2009 H1N1 influenza virus with pneumonia	403	0
48812	Influenza due to identified 2009 H1N1 influenza virus with other respiratory manifestations	403	0
48819	Influenza due to identified 2009 H1N1 influenza virus with other manifestations	403	0
48881	Influenza due to identified novel influenza A virus with pneumonia	403	0
48882	Influenza due to identified novel influenza A virus with other respiratory manifestations	403	0
48889	Influenza due to identified novel influenza A virus with other manifestations	403	0
530	Diseases of esophagus	N/A	1
5300	Achalasia and cardiospasm	382	1
5301	Esophagitis	N/A	1
53010	Esophagitis, unspecified	519	1
53011	Reflux esophagitis	519	1
53012	Acute esophagitis	519	1
53013	Eosinophilic esophagitis	519	1
53019	Other esophagitis	519	1
5302	Ulcer of esophagus	N/A	1
53020	Ulcer of esophagus without bleeding	519	1
53021	Ulcer of esophagus with bleeding	519	1
5303	Stricture and stenosis of esophagus	382	1
5304	Perforation of esophagus	230	1
5305	Dyskinesia of esophagus	382	1
5306	Diverticulum of esophagus, acquired	519	1
5307	Gastroesophageal laceration-hemorrhage syndrome	60	1
5308	Other specified disorders of esophagus	N/A	1
53081	Esophageal reflux	519	1
53083	Esophageal leukoplakia	519	1
53084	Tracheoesophageal fistula	68	1
53085	Barrett's esophagus	519	1
53086	Infection of esophagostomy	427	1
53087	Mechanical complication of esophagostomy	427	1
53089	Other specified disorders of esophagus	519	1
5309	Unspecified disorder of esophagus	519	1
556	Ulcerative colitis	N/A	1
5560	Ulcerative (chronic) enterocolitis	32	1
5561	Ulcerative (chronic) ileocolitis	32	1
5562	Ulcerative (chronic) proctitis	32	1
5563	Ulcerative (chronic) proctosigmoiditis	32	1
5564	Pseudopolyposis of colon	32	1
5565	Left-sided ulcerative (chronic) colitis	32	1
5566	Universal ulcerative (chronic) colitis	32	1
5568	Other ulcerative colitis	32	1
5569	Ulcerative colitis, unspecified	32	1
590	Infections of kidney	N/A	0
5900	Chronic pyelonephritis	N/A	0
5901	Acute pyelonephritis	N/A	0
59010	Acute pyelonephritis without lesion of renal medullary necrosis	51	0
59011	Acute pyelonephritis with lesion of renal medullary necrosis	51	0
5902	Renal and perinephric abscess	51	0
5903	Pyeloureteritis cystica	51	0
5908	Oth pyelonephritis/pyonephrof not spec acut/chrn	N/A	0
59080	Pyelonephritis, unspecified	278	0
59081	Pyelitis or pyelonephritis in diseases classified elsewhere	N/A	0
5909	Infection of kidney, unspecified	278	0
591	Hydronephrosis	184	0
592	Calculus of kidney and ureter	N/A	0
5921	Calculus of ureter	355	0
5929	Urinary calculus, unspecified	355	0
593	Other disorders of kidney and ureter	N/A	0
5930	Nephroptosis	667	0
5931	Hypertrophy of kidney	667	0
5932	Cyst of kidney, acquired	561	0
5933	Stricture or kinking of ureter	184	0
5934	Other ureteric obstruction	184	0
5935	Hydroureter	184	0
5936	Postural proteinuria	667	0
5937	Vesicoureteral reflux	N/A	0
5938	Other specified disorders of kidney and ureter	N/A	0
59382	Ureteral fistula	234	0
5939	Unspecified disorder of kidney and ureter	343	0
594	Calculus of lower urinary tract	N/A	0
5940	Calculus in diverticulum of bladder	355	0
5941	Other calculus in bladder	355	0
5942	Calculus in urethra	355	0
5948	Other lower urinary tract calculus	355	0
5949	Calculus of lower urinary tract, unspecified	355	0
595	Cystitis	N/A	0
5950	Acute cystitis	278	0
5951	Chronic interstitial cystitis	331	0
5952	Other chronic cystitis	278	0
5953	Trigonitis	278	0
5954	Cystitis in diseases classified elsewhere	278	0
5958	Other specified types of cystitis	N/A	0
59581	Cystitis cystica	278	0
59582	Irradiation cystitis	278	0
59589	Other specified types of cystitis	278	0
5959	Cystitis, unspecified	278	0
596	Other disorders of bladder	N/A	0
5960	Bladder neck obstruction	331	0
5961	Intestinovesical fistula	234	0
5962	Vesical fistula, not elsewhere classified	234	0
5963	Diverticulum of bladder	331	0
5965	Other functional disorders of bladder	N/A	0
59652	Low bladder compliance	331	0
59655	Detrusor sphincter dyssynergia	331	0

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ICD9	Description	Line	Chronic
59659	Other functional disorder of bladder	331	0
5966	Rupture of bladder, nontraumatic	84	0
5967	Hemorrhage into bladder wall	331	0
5968	Other specified disorder of bladder	N/A	0
59681	Infection of cystostomy	331	0
59682	Mechanical complication of cystostomy	331	0
59683	Other complication of cystostomy	331	0
59689	Other specified disorders of bladder	331	0
5969	Unspecified disorder of bladder	331	0
597	Urethritis not sexually trnsmtted&urethral synd	N/A	0
5970	Urethral abscess	209	0
5978	Other urethritis	N/A	0
59780	Urethritis, unspecified	586	0
59781	Urethral syndrome NOS	586	0
59789	Other urethritis	586	0
598	Urethral stricture	N/A	0
5980	Urethral stricture due to infection	N/A	0
59800	Urethral stricture due to unspecified infection	331	0
59801	Urethral stricture due to infective diseases classified elsewhere	331	0
5981	Traumatic urethral stricture	331	0
5982	Postoperative urethral stricture	331	0
5988	Other specified causes of urethral stricture	331	0
5989	Urethral stricture, unspecified	331	0
599	Other disorders of urethra and urinary tract	N/A	0
5990	Urinary tract infection, site not specified	278	0
5991	Urethral fistula	434	0
5992	Urethral diverticulum	434	0
5993	Urethral caruncle	586	0
5993	Urethral caruncle	598	0
5994	Urethral false passage	586	0
5995	Prolapsed urethral mucosa	586	0
5995	Prolapsed urethral mucosa	598	0
5996	Urinary obstruction	N/A	0
59960	Urinary obstruction, unspecified	576	0
59969	Urinary obstruction, not elsewhere classified	576	0
5997	Hematuria	N/A	0
59971	Gross hematuria	N/A	0
59972	Microscopic hematuria	N/A	0
5998	Other specified disorder urethra&urinary tract	N/A	0
59981	Urethral hypermobility	459	0
59982	Intrinsic (urethral) sphincter deficiency [ISD]	331	0
59983	Urethral instability	331	0
59984	Other specified disorders of urethra	331	0
59989	Other specified disorders of urinary tract	331	0
5999	Unspecified disorder of urethra and urinary tract	586	0
614	Inflam dz of ovary-tube-pelvic tissue-peritoneum	N/A	0
6140	Acute salpingitis and oophoritis	55	0
6141	Chronic salpingitis and oophoritis	536	0
6142	Salpingitis and oophoritis not specified as acute, subacute, or chronic	536	0
6143	Acute parametritis and pelvic cellulitis	55	0
6144	Chronic or unspecified parametritis and pelvic cellulitis	536	0
6145	Acute or unspecified pelvic peritonitis, female	536	0
6146	Pelvic peritoneal adhesions, female	536	0

ICD9	Description	Line	Chronic
	(postoperative) (postinfection)		
6147	Other chronic pelvic peritonitis, female	536	0
6148	Other specified inflammatory disease of female pelvic organs and tissues	55	0
6149	Unspecified inflammatory disease of female pelvic organs and tissues	55	0
647	Infect-parasitic maternal cce-complicating pc/p	N/A	0
6470	Mtrn syphilis comp pg childbirth/the puerperium	N/A	0
64700	Syphilis of mother, complicating pregnancy, childbirth, or the puerperium, unspecified as to episode of care or not applicable	1	0
64701	Syphilis of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition	1	0
64702	Syphilis of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with mention of postpartum complication	1	0
64703	Syphilis of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication	1	0
64704	Syphilis of mother, complicating pregnancy, childbirth, or the puerperium, postpartum condition or complication	1	0
6471	Mtrn gonorrhea comp pg childbirth/the puerperium	N/A	0
64710	Gonorrhea of mother, complicating pregnancy, childbirth, or the puerperium, unspecified as to episode of care or not applicable	1	0
64711	Gonorrhea of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition	1	0
64712	Gonorrhea of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with mention of postpartum complication	1	0
64713	Gonorrhea of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication	1	0
64714	Gonorrhea of mother, complicating pregnancy, childbirth, or the puerperium, postpartum condition or complication	1	0
6472	Oth maternal venereal diseases-complicating pc/p	N/A	0
64720	Other venereal diseases of mother, complicating pregnancy, childbirth, or the puerperium, unspecified as to episode of care or not applicable	1	0
64721	Other venereal diseases of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition	1	0
64722	Other venereal diseases of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with mention of postpartum complication	1	0
64723	Other venereal diseases of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication	1	0
64724	Other venereal diseases of mother, complicating pregnancy, childbirth, or the puerperium,postpartum condition or	1	0

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ICD9	Description	Line	Chronic
	complication		
6473	Mtrn tb comp pg childbirth/the puerperium	N/A	0
64730	Tuberculosis of mother, complicating pregnancy, childbirth, or the puerperium, unspecified as to episode of care or not applicable	1	0
64731	Tuberculosis of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition	1	0
64732	Tuberculosis of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with mention of postpartum complication	1	0
64733	Tuberculosis of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication	1	0
64734	Tuberculosis of mother, complicating pregnancy, childbirth, or the puerperium,postpartum condition or complication	1	0
6474	Mtrn malaria comp pg childbirth/the puerperium	N/A	0
64740	Malaria in the mother, unspecified as to episode of care or not applicable	1	0
64741	Malaria in the mother, delivered, with or without mention of antepartum condition	1	0
64742	Malaria in the mother, delivered, with mention of postpartum complication	1	0
64743	Malaria in the mother, antepartum condition or complication	1	0
64744	Malaria in the mother, postpartum condition or complication	1	0
6475	Mtrn rubella comp pg childbirth/the puerperium	N/A	0
64750	Rubella in the mother, unspecified as to episode of care or not applicable	1	0
64751	Rubella in the mother, delivered, with or without mention of antepartum condition	1	0
64752	Rubella in the mother, delivered, with mention of postpartum complication	1	0
64753	Rubella in the mother, antepartum condition or complication	1	0
64754	Rubella in the mother, postpartum condition or complication	1	0
6476	Oth mtrn virl dz comp pg chldbrth/the puerperium	N/A	0
64760	Other viral diseases in the mother, unspecified as to episode of care or not applicable	1	0
64761	Other viral diseases in the mother, delivered, with or without mention of antepartum condition	1	0
64762	Other viral diseases in the mother, delivered, with mention of postpartum complication	1	0
64763	Other viral diseases in the mother, antepartum condition or complication	1	0
64764	Other viral diseases in the mother, postpartum condition or complication	1	0
6478	Oth maternal infectious-parasitic dz-compli pc/p	N/A	0
64780	Other specified infectious and parasitic diseases of mother, unspecified as to episode	1	0

ICD9	Description	Line	Chronic
	of care or not applicable		
64781	Other specified infectious and parasitic diseases of mother, delivered, with or without mention of antepartum condition	1	0
64782	Other specified infectious and parasitic diseases of mother, delivered, with mention of postpartum complication	1	0
64783	Other specified infectious and parasitic diseases of mother, antepartum condition or complication	1	0
64784	Other specified infectious and parasitic diseases of mother, postpartum condition or complication	1	0
6479	Uns maternal infection/infestation-compli pc/p	N/A	0
64790	Unspecified infection or infestation of mother, unspecified as to episode of care or not applicable	1	0
64791	Unspecified infection or infestation of mother, delivered, with or without mention of antepartum condition	1	0
64792	Unspecified infection or infestation of mother, delivered, with mention of postpartum complication	1	0
64793	Unspecified infection or infestation of mother, antepartum condition or complication	1	0
64794	Unspecified infection or infestation of mother, postpartum condition or complication	1	0
694	Bullous dermatoses	N/A	1
6940	Dermatitis herpetiformis	216	1
6941	Subcorneal pustular dermatosis	216	1
6942	Juvenile dermatitis herpetiformis	216	1
6943	Impetigo herpetiformis	216	1
6944	Pemphigus	216	1
6945	Pemphigoid	216	1
6946	Benign mucous membrane pemphigoid	N/A	1
69460	Benign mucous membrane pemphigoid without mention of ocular involvement	216	1
69461	Benign mucous membrane pemphigoid with ocular involvement	216	1
6948	Other specified bullous dermatoses	216	1
6949	Unspecified bullous dermatoses	216	1
6953	Rosacea	510	1
706	Diseases of sebaceous glands	N/A	1
7060	Acne varioliformis	528	1
7061	Other acne	528	1
7062	Sebaceous cyst	632	1
7063	Seborrhea	593	1
7068	Other specified diseases of sebaceous glands	665	1
7069	Unspecified disease of sebaceous glands	593	1
7090	Dyschromia	N/A	1
70900	Dyschromia, unspecified	665	1
70901	Vitiligo	665	1
70909	Other dyschromia	665	1
V027	Carrier or suspected carrier of gonorrhea	3	0
V6545	Counseling on other sexually transmitted diseases	3	0
V73	Special scr examination viral&chlamydial dz	N/A	0
V738	Screening oth specific viral&chlamydial diseases	N/A	0
V7388	Special screening examination for other specified chlamydial diseases	3	0

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ICD9	Description	Line	Chronic
V7389	Special screening examination for other specified viral diseases	3	0

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Policy Evaluation: Low Dose Quetiapine Safety Edit

Research Questions:

- What is the general utilization trend of quetiapine and other mental health drug since implementation of the clinical prior authorization (PA) in January 2011?
- What was the ultimate disposition of any encounter to the policy (i.e. not requested, requested and approved, or requested or denied)?
- How many patients experienced adverse outcomes as a result of the PA?

Conclusions:

- The low dose quetiapine safety edit policy appears successful at limiting off-label prescribing of low dose quetiapine.
- The policy was not associated with increased psychiatric-related harms. However, the high volume of requests and near 100% approval of these requests suggest that policy adjustments may be necessary.

Recommendations:

- Implement a step-edit to automatically approve low dose quetiapine prescriptions for:
    - Patients with a claim for a second generation antipsychotic in the past six months
    - Patients with prior medical claims evidence of schizophrenia or bipolar disorder
    - Prescriptions identified as being written by a mental health provider when the claims system has this capability

Background:

Quetiapine (Seroquel®) is a second generation antipsychotic that is FDA approved for the treatment of schizophrenia and bipolar disorder, and as adjunctive use in the treatment of major depressive disorder. Low-doses (<150 mg per day) of quetiapine are prescribed off-label to treat many conditions, including insomnia, anxiety, post-traumatic stress disorder, and dementia.[1] The evidence and safety of off-label use is not typically as strong relative to FDA-approved indications.[2] A recent systematic review update by the Agency for Healthcare Research and Quality found that there is increasing evidence of efficacy in some off-label uses such as dementia but the evidence for the majority of off-label uses is still of low quality or absent.[1]

There has been ongoing concern about the safety of low-dose quetiapine use. Quetiapine is associated with many adverse events such as an increase in cholesterol and triglycerides, glycemic abnormalities, and weight gain. [1,3] Other serious adverse events identified in trials of low dose quetiapine were fatal hepatotoxicity, restless leg syndrome, and akathisia.[4] However, despite these concerns, there has been an increase in off-label prescribing of many second-generation antipsychotics, including quetiapine. As a result the increase in off-label use, many Medicaid programs have restricted the use of low dose quetiapine.[5–10]

A drug use evaluation in 2010 showed 56% of OHP clients with claims for low-dose quetiapine for more than 60 days did not have an FDA approved diagnosis available suggesting the potential for considerable off-label use of quetiapine. Subsequently, the Oregon Medicaid program implemented a safety edit policy to identify patients who were using low-

dose quetiapine off-label. All mental health drugs are paid for by the OHP fee-for-service program regardless if patients are enrolled in managed care or not. The goals of this analysis are to evaluate the effects of this policy on quetiapine and other mental drug utilization; to assess for possible harms and identify options to improve the policy.

Methods:

The safety edit for low-dose quetiapine was implemented on January 1, 2011. Claims for prescriptions with a calculated daily dose of less than 150 mg of quetiapine were denied with a message to the pharmacy to notify the prescriber to request an authorization by phone, fax, or electronically. Approval required a diagnosis of an FDA approved indication for quetiapine and a medically appropriate reason for low-dose use. The claims processor adjudicated all requests within 24 hours of receipt allowing all approvals to be paid at the pharmacy. The policy did not "grandfather" (automatically approve payment) for any patients, nor were concurrent quetiapine prescriptions looked for in claims history. This analysis included patients enrolled in the Oregon Medicaid program between January 1, 2009 and December 31, 2013 and that had a minimum of two months continuous Medicaid enrollment before and after an index event. For the policy group, the index event was the earliest date the patient had a low-dose quetiapine claim denied with a message of "PA required" between January 1, 2011 and December 31, 2011

Total utilization was quantified using paid claims per member per month (PMPM) of low dose quetiapine and other potentially substitutable drugs (see Appendix 1). To assess the impact of the PA policy on dose of quetiapine used, we converted filled quetiapine doses to daily dose and categorized these prescriptions into <150 mg doses (low-dose quetiapine) and ≥150 mg doses (lowest therapeutic dose of quetiapine).

Patients were followed longitudinally to assess if an authorization was requested by their prescriber, and the ultimate disposition of any request. Patient demographics, disease severity, and subsequent drug therapy were then characterized by final request disposition (i.e. not requested, requested and approved or requested and denied).

To assess harms, a policy group of patients who had a denied claim for low dose quetiapine claim (the index event) between January 1, 2011 and December 31, 2011 was compared to a historical comparison group including patients who had a paid low-dose quetiapine claim (the index event) between January 1, 2009 and December 31, 2009, and therefore were not affected by the policy. To ensure the groups were independent, patients in the comparison group (2009) were excluded if they were also in the policy group (2011). Patients were excluded if their demographic data (e.g. age, sex or ethnicity) were not available, they were less than 18 or greater than 64 years old at the time of the index event, if they had dual Medicare eligibility, or if they did not have continuous enrollment for 2 months prior to and 2 months after the month of their index event.

The primary outcomes were: a composite of an emergency department or hospitalization due to psychiatric illness within 30 days of the index event; a composite of emergency department or hospital claims due to schizophrenia within 30 days of the index event; a composite of emergency department or hospital claims due to bipolar disorder within 30 days of the index event; and all cause hospitalization and emergency department visits within 30 days of the index event. The analyses were repeated using a 60 day post index event assessment window.

Results:

Figure 1 shows aggregated prescriptions filled per member per month (PMPM) by drug type (see appendix 1 for a list of drugs in each category). After the policy was implemented (January 1, 2011), there appears to be a decrease in all second generation antipsychotics, but no significant changes in other classes.

FIGURE 1. AGGREGATED PRESCRIPTIONS FILLED PMPM BY DRUG TYPE

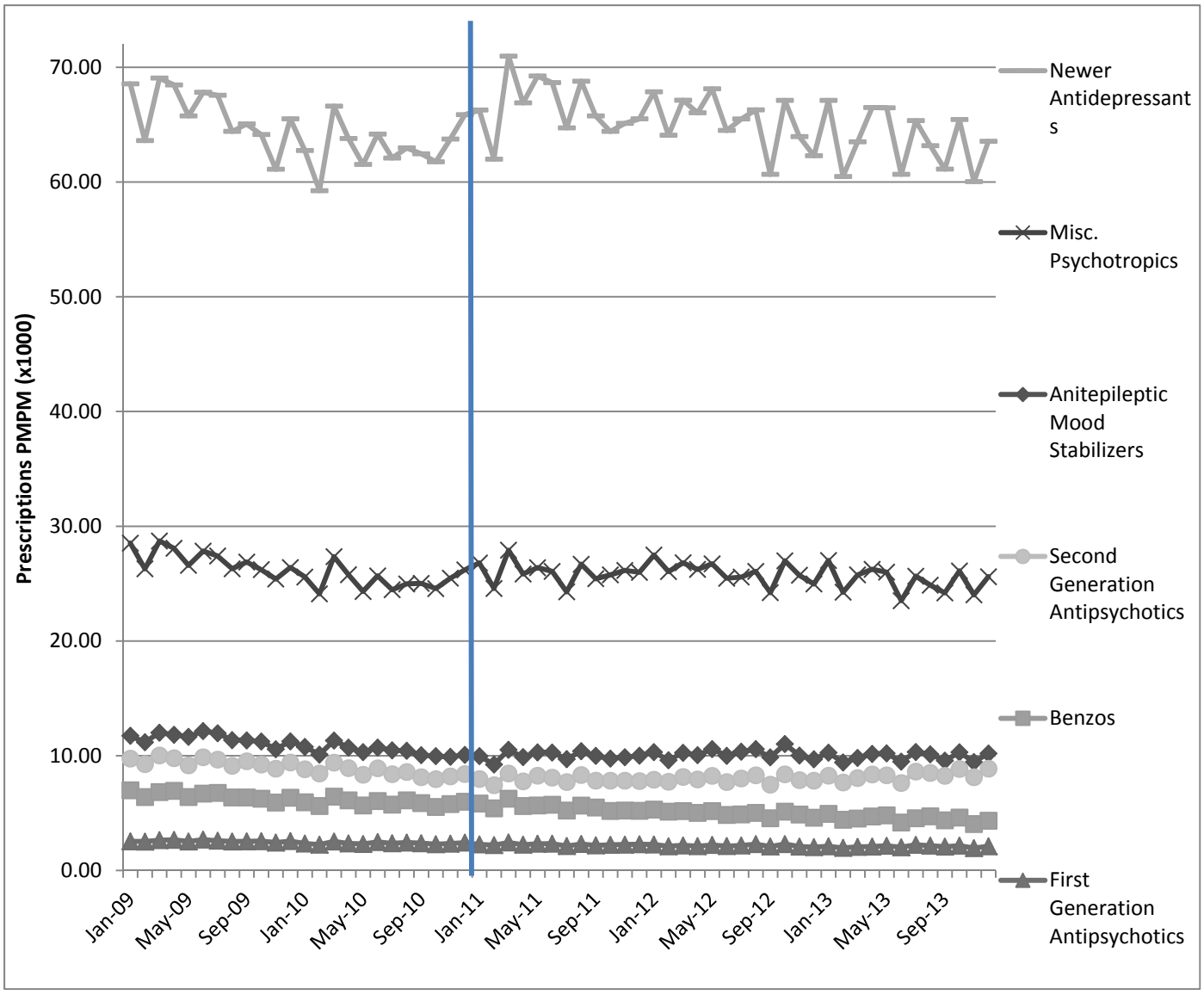
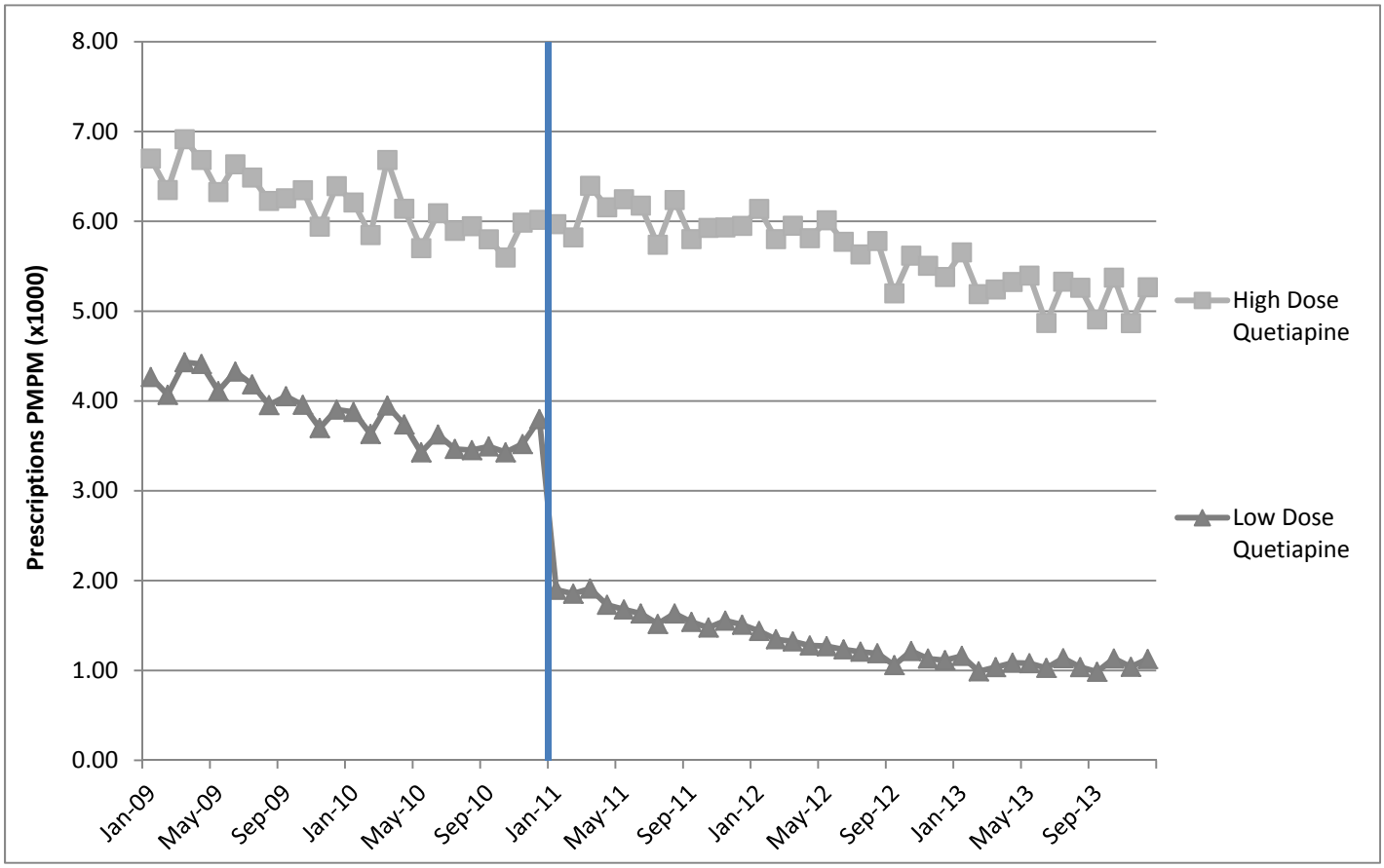


Figure 2 shows aggregated prescriptions filled PMPM for quetiapine, broken out by low dose prescriptions and non-low dose prescriptions. There is a sharp, sustained drop in the amount of low dose prescriptions filled after the policy was enacted. While there appears to be a small increase in the number of non-low dose prescriptions filled just after the policy was enacted, over time the number of prescriptions PMPM decreases.

FIGURE 2. AGGREGATED PRESCRIPTIONS OF NON-LOW DOSE (≥150 MG PER DAY) AND LOW DOSE (<150 MG PER DAY) QUETIAPINE FILLED PER ENROLLED MEMBER PER MONTH (PMPM).



We evaluated all OHP clients who had a denied claim for low dose quetiapine in the first three years of the policy. A total of 7,749 clients had a denied claim in 2011-2013. Of these, 2,867 authorizations requests were submitted (37%). Only 7 requests were denied, resulting in a 99.8% approval rate for submitted request. No request was submitted for 4,882 clients (63%). There were no differences in the average age, sex, or racial demographics between those who had an approved request and those who had no request submitted. However, clients who had a request approved were more likely to be in managed care than fee-for-service and were more likely to have been prescribed the drug by a mental health provider.

TABLE 1. BASELINE CHARACTERISTICS OF ALL PATIENTS WITH A DENIED CLAIM FOR QUETIAPINE (2011-2013)

	Total (N=7,749)	**Approval (N=2,860)**	**Denial (N=7)**	**No Request (N=4,882)**
Average Age (min-max)	39 (4-101)	36 (4-82)	31 (6-49)	41 (4-101)
Female	4,823 (62%)	1,777 (62%)	3 (43%)	3,043 (62%)
Non-White	1,200 (15%)	433 (15%)	1 (14%)	766 (16%)
Enrollment at Index				
Fee-For-Service	1,517 (20%)	485 (17%)	4 (57%)	1,028 (21%)
Managed Care	6,125 (79%)	2,341 (82%)	3 (43%)	3,781 (77%)
Unknown	107 (1%)	34 (1%)	0 (0%)	73 (1%)
Long Term Care	766 (10%)	260 (9%)	0 (0%)	506 (10%)
Prescriber				
Primary Care	4,918 (63%)	1,709 (60%)	4 (57%)	3,205 (66%)
Mental Health	2,308 (30%)	992 (35%)	3 (43%)	1,314 (27%)
Other	262 (3%)	77 (3%)	0 (0%)	185 (4%)
Unknown	261 (3%)	82(3%)	0 (0%)	178 (4%)
Pharmacy Type				
Chain	4,759 (61%)	1,741 (61%)	4 (57%)	3,014 (62%)
Independent	1,842 (24%)	709 (25%)	3 (43%)	1,130 (23%)
Long Term Care	1,118 (14%)	394 (14%)	0 (0%)	724 (15%)
Mail Order	30 (0%)	16(1%)	0 (0%)	14 (0%)

For the harms analysis, there were 3,290 patients with index events for the policy group (2011) and 3,885 patients identified with index events for the comparison group (2009). After excluding patients less than 18 and greater than 64 years old or without baseline demographics (study n=0, control n=697), those covered by Medicare (study n= 162, control n=169), those without continuous eligibility (study n=334, control n= 246), and those in the intervention group from the comparison group (833), the final policy group was 2,794 patients and the comparison group was 1,940 patients. Table 1 displays the baseline characteristics of the groups, prescriber demographics and baseline pharmacy utilization. Baseline percentages of schizophrenia were similar, but more people in the comparison group had bipolar disorder than those in the policy group. Those who had a request approved were more likely to have a diagnosis of schizophrenia or bipolar disorder in the prior two months than those who had no request submitted.

TABLE 2. BASELINE CHARACTERISTICS FOR HARMS ANALYSIS

	Comparison Group (N= 1,940)		Policy Group*					
			Total (N= 2,794)		Approval (N= 1,205)		No Request (N= 1,548)	
Demographics								
Average Age (min-max)	39.6	(18-64)	39.1	(18-60)	39.1	(18-60)	39.1	(18-60)
Female	1395	72%	1889	68%	808	67%	1079	68%
Non-White	309	16%	436	16%	170	14%	265	17%
Medications in Prior 2 months								
Antiepileptic Mood Stabilizers	238	12%	331	12%	168	14%	163	10%
Benzodiazepines	110	6%	117	4%	46	4%	71	4%
First Generation Antipsychotics	62	3%	72	3%	41	3%	31	2%
Misc. Psychotropics								
Non-Benzodiazepine Sedative	432	22%	574	21%	250	21%	324	20%
Hypnotics	4	0%	4	0%	2	0%	2	0%
Second Generation Antipsychotics	834	43%	1489	53%	757	63%	731	46%
Diagnosis in Prior 2 Months								
Bipolar	430	22%	482	17%	234	19%	248	16%
Schizophrenia	297	15%	416	15%	220	18%	196	12%
Major Depressive Disorder	703	36%	892	32%	360	30%	529	33%

*Denials not included in table

Table 3 displays the results of primary outcomes. There were 263 psych-related ED visits or hospitalizations during the 30 day follow-up period, 141 (5% of the population) in the policy group and 122 (6%) in the comparison group (OR 0.80, 95% confidence interval [CI] 0.62 to 1.03). There were 58 schizophrenia-related ED visits or hospitalizations during the 30 day follow-up period, 35 (1% of the population) in the policy group and 23 (1% of the population) in the comparison group (OR 1.06, 95% CI 0.61 to 1.86). There were 28 psych-related ED visits or hospitalizations during the 30 day follow-up period, 16 (1% of the population) in the policy group and 12 (1% of the population) in the comparison group (OR 0.93, 95% CI 0.41 to 2.09). There were 895 all cause ED visits or hospitalizations during the 30 day follow-up period, 488 (17% of the population) in the policy group and 407 (21% of the population) in the comparison group (OR 0.80, 95% CI 0.69 to 0.93). There were no significant differences in the primary endpoints at 60 days compared to 30 days.

TABLE 3. PRIMARY AND SECONDARY OUTCOMES 30 DAYS AFTER STUDY ENTRY

	Comparison Group (N= 1,940)		Policy Group*					
			Total (N= 2,794)		Approval (N= 1,205)		No Request (N= 1,548)	
ED/Hospitalizations at 30 Days								
Primary: Psych-related	122	6%	141	5%	54	4%	87	5%
Schizophrenia	23	1%	35	1%	16	1%	19	1%
Bipolar	12	1%	16	1%	7	1%	9	1%
All Cause	407	21%	488	17%	198	16%	289	18%
ED/Hospitalizations at 60 Days								
Primary: Psych-related	176	9%	218	8%	88	7%	130	8%
Schizophrenia	32	2%	47	2%	21	2%	26	2%
Bipolar	16	1%	24	1%	11	1%	13	1%
All Cause	596	31%	756	27%	311	26%	444	28%

*Denials not included in table

Discussion:

In this analysis, patients encountering the safety edit did not experience more ED visits or hospitalizations for psych-related events, including for schizophrenia or bipolar disorder compared to patients who had a claim for low dose quetiapine prior to this policy. They had less all cause ED visits or hospitalizations, the cause of which is unknown. There were no significant differences between the subgroup of clients who encountered the safety edit and had a request submitted (and subsequently approved) and those who did not have a request submitted.

Policy group patients whose prescribers made a request were more likely to have a diagnosis of schizophrenia or bipolar disorder and were more likely to have had pharmacy claims for a second generation antipsychotic in the two months prior to the index event, suggesting the safety edit was effective at restricting use consistent with the FDA recommendation. The policy did decrease the overall use of low dose quetiapine.

Similar to other OHP fee-for-service PA analyses, only 37% of patients encountering the safety edit subsequently had a request for approval. That is, for a majority of cases no attempt was made by the prescriber to submit a request. It is difficult to infer causality between no request and subsequent adverse outcomes because having a request submitted was associated with increasing disease severity. Despite this limitation, rates of the primary outcomes were not different in the group that did not have a request submitted compared to the group that did have a request submitted. The rates of ED visits and hospitalizations for psych-related events, schizophrenia and bipolar disorder were similar to the comparison group at 30 days, while the rates of all cause ED visits and hospitalizations were lower in both intervention groups at 30 days; it is unclear if this decrease is related to the safety edit policy. It is also unclear what factors made the all cause hospitalizations and ED visits statistically significantly lower in the policy group compared to the historical comparison group.

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Appendix 1. DRUG CLASSIFICATION TABLE.

Drug Class Code	Generic Drug Name
Second Generation Antipsychotic	Quetiapine
Second Generation Antipsychotic	Olanzapine
Second Generation Antipsychotic	Aripiprazole
Second Generation Antipsychotic	Ziprasidone
Second Generation Antipsychotic	Clozapine
Second Generation Antipsychotic	Risperidone
Second Generation Antipsychotic	Iloperidone
Second Generation Antipsychotic	Paliperidone
Second Generation Antipsychotic	Lurasidone
Second Generation Antipsychotic	Asenapine
Benzodiazepine	Oxazepam
Benzodiazepine	Alprazolam
Benzodiazepine	Lorazepam
Benzodiazepine	Diazepam
Benzodiazepine	Temazepam
Benzodiazepine	Clonazepam
Benzodiazepine	Clorazepate
Benzodiazepine	Chlordiazepoxide
Benzodiazepine	Diazepam
Benzodiazepine	Midazolam
Benzodiazepine	Triazolam
Benzodiazepine	Flurazpam
Antiepileptic Mood Stabilizer	Divalproex
Antiepileptic Mood Stabilizer	Lamotrigine
Antiepileptic Mood Stabilizer	Gabapentin
Antiepileptic Mood Stabilizer	Topiramate
Antiepileptic Mood Stabilizer	Carbamazepine
Antiepileptic Mood Stabilizer	Oxcarbazepine
Non-Benzodiazepine Sedative Hypnotic	Eszpiclone
Non-Benzodiazepine Sedative Hypnotic	Zaleplon
Non-Benzodiazepine Sedative Hypnotic	Ramelteon
Non-Benzodiazepine Sedative Hypnotic	Zolpidem
Miscellaneous Psychotropic	Mirtazapine
Miscellaneous Psychotropic	Amitriptyline
Miscellaneous Psychotropic	Doxepin
Miscellaneous Psychotropic	Nortriptyline
Miscellaneous Psychotropic	Trazodone
Miscellaneous Psychotropic	Hydroxyzine
Miscellaneous Psychotropic	Diphenhydramine
First Generation Antipsychotic	Chlorpromazine
First Generation Antipsychotic	Fluphenazine
First Generation Antipsychotic	Haloperidol

First Generation Antipsychotic	Loxapine
First Generation Antipsychotic	Perphenazine
First Generation Antipsychotic	Thioridazine
First Generation Antipsychotic	Thiothixene
First Generation Antipsychotic	Trifluoperazine

Appendix 2. PROPOSED LOW DOSE QUETIAPINE PRIOR AUTHORIZATION CRITERIA.

Low Dose Quetiapine

Goal(s):

- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia.

Initiative:

- Low dose quetiapine (Seroquel® and Seroquel XR®)

Length of Authorization:

- Up to 12 months (criteria-specific)

Requires PA:

- Quetiapine (HSN = 14015) doses <150 mg/day
- Auto PA approvals for :
    - Patients with a claim for a second generation antipsychotic in the last 6 months
    - Patients with prior claims evidence of schizophrenia or bipolar disorder
    - Prescriptions identified as being written by a mental health provider

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org
- Zolpidem and benzodiazepine sedatives are available for short-term use (15 doses/30 days) without PA.

Table 1. Adult (Age >18 years) FDA-approved indications for Quetiapine

Bipolar Disorder	296.0, 296.4, 296.6-296.8,296.89	
Major Depressive Disorder	296.2, 296.24, 296.3, 296.23, 296.33, 296.34, 296.5, 296.53, 296.54	For Seroquel XR® only, Adjunctive therapy with antidepressants for Major Depressive Disorder
Schizophrenia	295, 295.4, 295.44, 295.45, 295.6,295.62, 295.64, 295.85, 295.95, 295.80-295.82,295.40-295.42, 295.90-295.92	
Bipolar Mania	296.1, 296.3, 296.4, 296.43, 296.44	
Bipolar Depression	296.5	

Table 2. Pediatric FDA-approved indications

Schizophrenia	Adolescents (13-17 years)	
Bipolar Mania	Children and Adolescents (10 to 17 years)	Monotherapy

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-9 code. Do not proceed and deny if diagnosis is not listed in Table 1 or Table 2 above (medical appropriateness)	
2. Is the prescription for quetiapine less than 150 mg/day? (verify days' supply is accurate)	Yes: Go to #3	No: Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy longer than 90 days?	Yes: Go to #4	No: Approve for titration up to maintenance dose (60 days).
4. Is reason for dose <150 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance? • any diagnosis in table 1 or 2 above?	Yes: Approve for up to 1 year	No: Pass to RPh. Deny for medical appropriateness. • May approve up to 6 months to allow taper.

P&T/DUR Review: *7/15 (AM); 9/10; 5/10*
Implementation: *TBA; 1/1/11*

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Drug Use Evaluation: modafinil and armodafinil

Research Questions:

- What is the overall Oregon Health Plan (OHP) utilization trend of modafinil and armodafinil from 2014 to present?
- What was the impact on utilization of the dose and age limits implemented in September 2014?
- What diagnoses are most commonly associated with OHP patients with modafinil and armodafinil drug claims?
- What is the evidence for efficacy and safety of modafinil and armodafinil for the most prevalent diagnoses and are they funded by OHP?

Conclusions:

- The number of OHP patients with claims for either drug has increased 40% over the 15 months from January 2014 to March 2015 and 14% per 1000 members per month. The attention deficit hyperactivity disorder (ADHD) drug class ranked 3rd by net cost in quarter 1 of 2015 and modafinil ranked 26th.[1]
- The absolute number (31 vs. 6) and the rate (23.3% vs 4.4%) of patients newly started on modafinil or armodafinil and that exceeded recommended doses dramatically decreased after the prior authorization policy was implemented. The number of pediatric patients were very low initially (n=2) and increased slightly (n=4) after the age limit was implemented. The net cost of modafinil and armodafinil was $560,000 in quarter 3 of 2014[2] but dropped to $300,000 in quarter 1 of 2015.[1]
- The most common diagnoses were organic sleep apnea (35.8%), narcolepsy (19.0%), all depressions combined (19.0%), attention deficit hyperactivity disorder (7.1%) and multiple sclerosis (5.6%). The highest association by diagnostic group was to funded FDA diagnoses (45.9%). Funded off-label diagnoses were associated with 26.5% of patients. Only 4.1% had only a non-funded diagnosis of interest but, there was no diagnosis of interest associated with 23.5% of patients.
- There is moderate level evidence modafinil and armodafinil statistically improves sleep latency in patients with narcolepsy or with continuous positive airway pressure (CPAP) treated obstructive sleep apnea as measured by the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test. The clinical relevance of the seemingly modest mean differences is debatable.[3,4,5] No normal sleep latency has been established, there is a wide range of sleep latency among healthy people and the degree of change that is clinically significant has not been established.[6] Treatment guidelines indicate obstructive sleep apnea be first treated with CPAP or mandibular advancement devices.[5]
- There is insufficient evidence for armodafinil for any off-label use evaluated here.
- There is low level and inconsistent evidence of short-term benefit of modafinil for fatigue associated with multiple sclerosis,[7,8,9] cancer[9,10] and anti-psychotic use.[11] Despite the low level evidence, consensus based guidelines recommend its use for both multiple sclerosis- and cancer-related fatigue.[12] There is insufficient evidence of modafinil efficacy for fatigue associated with other conditions.
- There is low level evidence from small, heterogeneous and poorly controlled trials that modafinil used as augmentation treatment improves short-term depression scores.[13,14,15] There is low evidence of inconsistent benefit for residual fatigue in patients responsive to antidepressants or mood stabilizers.[16]
- There is insufficient and inconsistent evidence of modafinil for adult ADHD.[17,18] The data are more robust, but still low level for pediatrics.
- There are reports of potential use for cognition enhancement with little supporting evidence.[19,20,21]

Recommendations:

- Implement a prior authorization for patients initiated on modafinil or armodafinil (no claims evidence within 102 days) and without previous claims evidence of narcolepsy or obstructive sleep apnea (ICD9:347.00-347.01327.20-327.21, 327.23-327.29, 780.51, 780.53, 780.57) See Proposed PA criteria **Appendix 4**

Background:

Modafinil[22] and armodafinil[23] are both approved by the United States Food and Drug Administration (FDA) for treatment of excessive somnolence associated with narcolepsy, obstructive sleep apnea and shift work sleep disorder. They are also used extensively off-label with varying levels of evidence (**Appendix 1**). The OHP currently funds treatment of obstructive sleep apnea and narcolepsy but does not fund treatment of shift work disorder.[24] A prior authorization (PA) of excessive doses (>250 mg of armodafinil or > 200mg of modafinil) and use in patients younger than 18 was implemented in September of 2014.[25] The net cost of modafinil and armodafinil was $560,000 in quarter 3 of 2014[2] but dropped to $300,000 in quarter 1 of 2015.[1] The ADHD class ranked 3rd by net cost in quarter 1 of 2015 and modafinil ranked 26th.[1]

Modafinil and armodafinil (the R enantiomer of modafinil) produce alterations in mood, perception, thinking and feelings that are typical of central nervous system stimulants but differ from the sympathomimetic amines in pharmacological profile.[26,27] Modafinil and armodafinil stimulate discrete brain regions rather than broad brain activation.[26,27] They also do not bind to norepinephrine, serotonin, dopamine, gamma-aminobutyric acid, adenosine, histamine 3, melatonin, or benzodiazepine receptors, nor do they inhibit monoamine oxidase-B or phosphodiesterases II through V.[26,27] The mechanism of action is still unknown.[26,27] Modafinil and armodafinil appear to be well tolerated, with the main adverse effects being headache and nausea.[26,27]

Narcolepsy is characterized primarily by excessive daytime sleepiness with involuntary episodes of falling asleep and frequently includes episodes of cataplexy.[28] It can also include sleep paralysis, hallucinations at sleep initiation or awakening or disturbed nighttime sleep.[28] The prevalence is estimated to be 25 per 100,000 in white populations.[29] The majority of cases have no discernable secondary cause and are first diagnosed from age 15 to 35 years old.[28] It is a life-long illness that can affect all aspects of life quality.[29] Scheduled sleep periods (daytime napping plus regular bedtime) is recommended and may reduce symptom severity.[28] Modafinil is recommended first-line for daytime sleepiness[29] based upon a 9 week randomized trial (n=271) comparing modafinil 400 mg versus 200 mg versus placebo. Sleep latency was evaluated using the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test.[3] At baseline the mean Multiple Sleep Latency Test score in minutes was 2.7, 3.0 and 2.2 respectively, and at 9 weeks was 5.1 ($p < 0.001$), 4.9 ($p = 0.03$) and 3.5.[3] The Maintenance of Wakefulness Test was 5.9, 6.1 and 6 minutes at baseline and increased to 7.8 ($p < 0.001$), 8.2 ($p < 0.001$) and 5.5 minutes at 9 weeks.[3] Armodafinil was studied in 196 patients aged 18-65 years who were randomized to armodafinil 150 mg versus armodafinil 250 mg versus placebo once daily for 12 weeks. Change in mean Maintenance of Wakefulness Test at 12 weeks was +1.3 minutes, +2.6 minutes and -1.9 minutes ($p < 0.01$).[4] The clinical relevance of the statistical, but seemingly modest differences on objective sleep measures by modafinil and armodafinil is debatable. No normal sleep latency has been established, there is a wide range of sleep latency among healthy people and the degree of change that is clinically significant has not been established.[6] Methylphenidate has been recommended second line treatment for excessive daytime sleepiness based upon lower levels of evidence for efficacy.[29]

Obstructive sleep apnea is a sleep disorder where the upper airway is obstructed causing repeated complete or partial apnea and resulting in frequent awakenings and poor sleep.[30] One cohort study of 1149 adults from Cleveland, estimates the 5-year incidence to be 10% - 16%.[5] Risk factors include obesity and

older age.[5] Complications of untreated obstructive sleep apnea include cardiovascular disease and increased risk of motor vehicle accidents.[5] The Maintenance of Wakefulness Test does not reliably predict safer drivers.[5] Treatment recommendations include weight reduction for overweight patients, correction of positional apnea issues, CPAP and mandibular advancement devices to reduce the apneic episodes and improve sleep quality.[5] There is moderate level evidence that modafinil and armodafinil may reduce residual daytime sleepiness in CPAP treated patients.[5] The studies are limited by subjective measures and the unknown clinical relevance of statistical difference over placebo.

The goals of this drug use evaluation are to describe overall utilization trends, assess the effectiveness of the age and dose restrictions implemented in September 2014 and document the diagnoses associated with patients who use modafinil and armodafinil to inform drug policy.

Methods:

All patients with OHP fee-for-service (FFS) paid drug claims for modafinil (HSN = 010865) or armodafinil (HSN = 034868) from January 1, 2014 through March 30, 2015 were included in the trend analysis. Only patients newly initiated on either drug during quarter 1 of 2014 (Pre-Policy) and quarter 1 of 2015 (Post-Policy) were included in the diagnostic and dose analyses. Newly started patients were identified if they had no prior claim in the 100 days prior to the first drug claim and the first claim was labeled the index event. Patients not initiated during either quarter were excluded. Part D patients identified with drug benefit packages BMM or BMD were excluded. No eligibility length restrictions were applied.

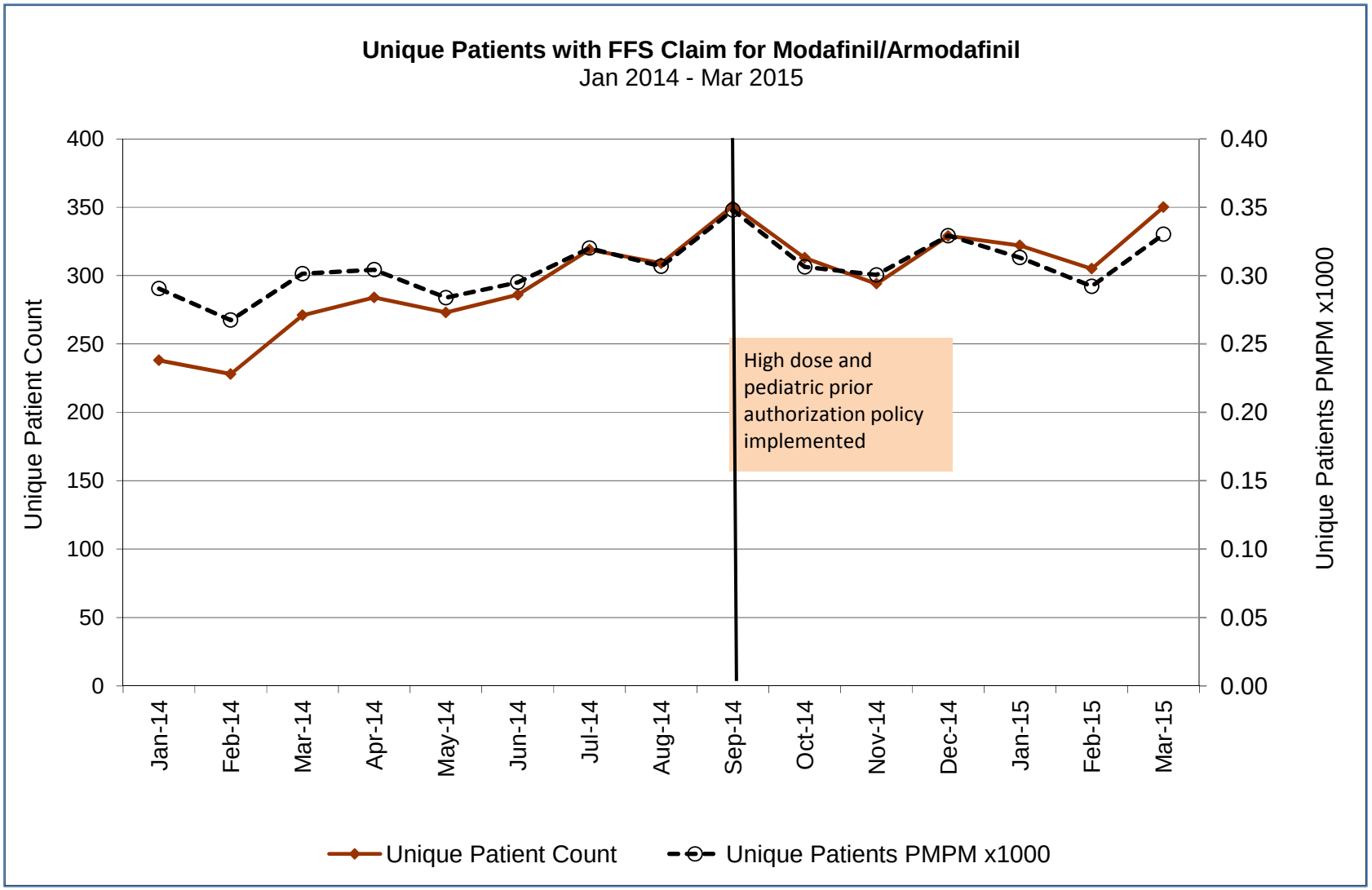
Off-label diagnoses (**Appendix 1**) were identified from Micromedex™ and American Hospital Formulary Service™ and included if there was mid-level evidence of benefit in either reference. Patients were categorized into the diagnostic groups in **Appendix 1** if a diagnosis code occurred on either FFS or encounter medical claim within 5 years prior to and including the date of index event. Patients that exceeded the recommended maximum dose (**Appendix 2**), as calculated using "Dispensed Quantity" divided by "Days Supply", for any claim during in quarter of 2014 and 2015 were identified.

A Medline™ literature search for systematic reviews or meta-analyses assessing modafinil or armodafinil efficacy or effectiveness for the most prevalent off-label diagnoses (depression, fatigue associated with multiple sclerosis or cancer and attention deficit hyperactivity disorder) was conducted. The Medline™ search strategies used for this review are available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed™, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool.

Results:

Figure 1 indicates the number of unique patients with claims for either drug has increased 40% over the 15 months from January 2014 to March 2015. When controlled for enrollment, the increase rate drops to 14% per 1000 members per month.

Figure 1 - Unique Patient Count with Drug Claim for Modafinil or Armodafinil



After exclusion of Medicare patients, a total of 811 unique patients were identified (348 in the Pre-PA Group and 463 in the Post-PA Group). After limiting to patients newly initiated, the Pre-PA group was 133 and the Post-PA Group was 135. There were 7 patients that met the criteria for both groups. Table 1 displays the demographics of patients initiated on either modafinil or armodafinil before and after the dose and pediatric limit policy was implemented September 2014. The absolute number and rate of pediatric patients actually increased slightly from 2 (1.5%) prior to the PA to 4 (3.0%) after the PA. However, the lowest age increased from 14 to 15 years. In general, the Post-PA group is somewhat younger and more patients are enrolled in coordinating care organizations.

Table 1: New Modafinil and Armodafinil Patient Demographics

	Pre-PA		Post-PA	
	133	%	**135**	%
Mean age (range)	43.3	(14-63)	41.4	(15-65)
<19	2	1.5%	4	3.0%
19-30	16	12.0%	28	20.7%
>30	115	86.5%	103	76.3%
Female	87	65.4%	88	65.2%
White	105	78.9%	113	83.7%
FFS (at index claim)	25	18.8%	12	8.9%

Table 2 displays the number of patients initiated on modafinil or armodafinil who exceeded the maximum recommended dose per day. The absolute number (31 vs. 6) and the rate (23.3% vs 4.4%) dramatically decreased after the prior authorization policy was implemented.

Table 2: Patients Exceeding Maximum Dose Per Day

	Pre-Policy		Post-Policy	
	133	%	**135**	%
Modafinil 200mg daily	27	20.3%	5	3.7%
Armodafinil 250mg daily	4	3.0%	1	0.7%
Total	31	23.3%	6	4.4%

Table 3 displays the selected diagnoses associated with patients on modafinil and armodafinil and puts them in mutually exclusive groups in priority order. The most common diagnoses were organic sleep apnea (35.8%), narcolepsy (19.0%), all depressions combined (19.0%), attention deficit hyperactivity disorder (7.1%) and multiple sclerosis (5.6%). The highest association by diagnostic group was to funded FDA diagnoses (45.9%). Funded off-label diagnoses were associated with 26.5% of patients. Only 4.1% had a non-funded diagnosis of interest but there was no diagnosis of interest associated with 23.5% of patients.

Table 3: Associated Diagnoses of All New Patients Combined
Mutually-exclusive groups in priority of 1, 2, 3, 4

	n=	268	
FDA Funded Indications (Group 1)		**123**	**45.9%**
Narcolepsy		51	19.0%
Organic sleep apnea (except high altitude)		96	35.8%
Funded Off-Label Indications (Group 2)		**71**	**26.5%**
Attention deficit hyperactivity disorder		19	7.1%
Depression (unipolar or bipolar)		51	19.0%
Steinert myotonic dystrophy syndrome		0	0.0%
Cancer		2	0.7%
Multiple sclerosis		15	5.6%
Non-Funded Indications (Group 3)		**11**	**4.1%**
Narcolepsy in conditions classified elsewhere		0	0.0%
Organic sleep disorders except organic sleep apneas		1	0.4%
Shift work sleep disorder		6	2.2%
Hypersomnia, unspecified		8	3.0%
No Diagnosis of Interest (Group 4)		**63**	**23.5%**

A summary of the Medline literature search results, including abstracts is in **Appendix 3**. There were 10 reviews including modafinil or armodafinil for fatigue (2 excluded as not systematic reviews,[31,32] 2 were unavailable[33,34] 1 excluded for irrelevant intervention[35]), 5 reviews for depression (1 excluded for irrelevant outcomes assessed[36] and 1 excluded for irrelevant intervention[37]), 4 reviews for ADHD (2 excluded for intervention irrelevance[38,39]). There were 4 reviews for cognition enhancement[19,20,21,40] and 2 general reviews documenting off-label uses.[41,42] The remaining reviews and those identified from the gray literature sources are discussed below.

FATIGUE

Cancer (0.7%) and multiple sclerosis (5.6%) was associated new modafinil and armodafinil users. The evidence of efficacy for fatigue related to these conditions and to drug-related sedation is limited and inconsistent.

Multiple Sclerosis Fatigue

The most recent systematic review included studies that evaluated modafinil treatment versus placebo for fatigue and excessive daytime sleepiness associated with neurological disorders.[7] Eight randomized controlled trials (RCTs) were included: 3 for multiple sclerosis, 2 for Parkinson's Disease, 2 for traumatic brain injury and 1 for post-polio syndrome.[7] The meta-analyses of the 3 multiple sclerosis studies (n=800, 5-8 weeks duration) used the Fatigue Severity Scale and the Modified Fatigue Impact Scale and failed to prove a beneficial effect.[7] The efficacy of modafinil on excessive daytime sleepiness in patients with multiple sclerosis was investigated in two of the studies (n=600, 5-8 weeks duration) and was not confirmed in the pooled studies.[7] The authors conclude that the majority of studies are small and the evidence is insufficient to recommend modafinil for routine treatment for fatigue or excessive daytime sleepiness associated with multiple sclerosis and the other diagnoses that were reviewed.[7]

Six trials (3 open-label, n= 100; 1 single-blind, n=72; and 2 double-blind RCTs n=136) were included in another systematic review of modafinil for treatment of multiple sclerosis-related fatigue.[8] Six different, self-reported symptom scales were used to measure outcomes.[8] Lower doses had positive results in the open-label trials and higher doses did not.[8] Only one of the RCTs found a reduction on the Fatigue Severity Scale at 8 weeks, the other did not.[8] The evidence was conflicting.

Cancer Fatigue

The Cochrane Collaborative produced a review of pharmacological treatment for fatigue associated with palliative care.[9] There were 45 studies included (n=4696) involving 18 different drugs.[9] There was a very high degree of statistical and clinical heterogeneity in the trials.[9] Studies of modafinil for multiple sclerosis-related fatigue were also included.[9] There was weak and inconclusive evidence for the efficacy of modafinil in multiple sclerosis.[9] Modafinil was evaluated for cancer-related fatigue in 2 studies (n=704) with mixed results.[9] The first found an interaction with baseline fatigue; those with severe fatigue benefited and those with mild or moderate fatigue did not.[9] The second study found that both modafinil and placebo produced a clinically significant improvement and there was no difference between them.[9] The meta-analysis showed an estimated superior effect for methylphenidate in cancer-related fatigue as measured by the Brief Fatigue Inventory instrument (standardized mean difference 0.49, 95% confidence interval (CI) 0.15 to 0.83).[9]

Four trials (2 open-label, 1 RCT with open-label extension, 1 RCT published in abstract only) were included in another systematic review of modafinil for the treatment of cancer-related fatigue.[10] The open-label trials involved 133 breast cancer patients treated for 1 month.[10] The open-label extension trial was in patients with cerebral tumors and the RCT involved 888 patients with unknown cancers.[10] The studies all used different self-reported scales or lacked detail.[10] Published results were statistically significant but of unknown clinical relevance.[10]

Drug-related Fatigue

A systematic review of modafinil for adjunctive treatment of antipsychotic-related sedation evaluated the evidence from 6 trials (2 RCTs, 3 randomized cross-over trials and 1 open-label).[11] The results were inconsistent with only 1 study finding a significant beneficial effect of treating antipsychotic-induced fatigue. The authors concluded the available trials were too limited by small samples, contradictory results and differences in cognitive testing to draw conclusions.

DEPRESSION

Depression (either unipolar or bipolar) was associated with 19.0% of new modafinil or armodafinil users. Stimulants are used for adjunctive treatment for patients non-responsive to antidepressants or mood stabilizers and also to treat lingering fatigue symptoms in responsive patients. There is low level evidence of short-term improvement of depression scores when added to antidepressants or mood stabilizers. There is insufficient evidence of benefit for residual fatigue symptoms.

Acute Bipolar Depression

A recent systematic review of all treatments for acute bipolar depression limited study designs to randomized, double-blind and placebo controlled trials with clearly defined outcomes identified 2 studies; 1 of modafinil (n=87, 6 weeks) and 1 of armodafinil (n=257, 8 weeks).[13] Both studies were reported to significantly reduce the Inventory of Depressive Symptomatology score when added to a mood stabilizer. Over half of the participants were also on an antidepressant. Few study details were presented and no author conclusions were drawn from this information.

Unipolar or Bipolar Depression Augmentation

Another systematic review,[14] criticized by Database of Abstracts of Reviews of Effects[43] as potentially unreliable due to the small, heterogeneous and unclear quality of the evidence base, identified 6 RCTs (n=910) evaluating modafinil: 4 for major depressive disorder (n=568) and 2 for bipolar depression (n=342).[14] Study durations ranged from 6-8 weeks and outcomes were measured using a variety of depression scales.[14] Selective serotonin reuptake inhibitors were the primary treatment in the major depression studies. Lithium was the primary treatment one bipolar study and mood stabilizer with or without antidepressant was used in the other. The results were pooled using the percentage reduction in the various depression scores. The point estimate for the pooled studies was -0.3543 95% CI -0.6071 to -0.1016 p=0.006, I^2 = 67.39%.[14] The authors concluded modafinil is an effective augmentation strategy for acute depressive episodes.[14]

Cochrane published a review of stimulants for depression that was last updated in 2008.[15] It included 5 drugs (dexamphetamine, methylphenidate, methyl-amphetamine, pemoline and modafinil). Most trials were short-term, up to 6 weeks. Modafinil was evaluated separately due to its unique pharmacology and 3 trials (n=642) were included. The results obtained using fixed effects models suggest that for people with depression, treatment with oral stimulants in comparison with a placebo in the short term (up to 4 weeks) statistically reduces symptoms. The effect was not replicated in the meta-analysis of trials that used modafinil. The authors could draw few clinically relevant conclusions due to the small sample sizes and heterogeneity.

Residual fatigue after depression treatment

A systematic review included studies where modafinil was used to treat patients with residual fatigue from depression and the effects were measured with validated fatigue subscales.[16] One retrospective, 5 open-label and 2 RCTs were included. Modafinil improved residual fatigue scores in the open-label trials but the results were not confirmed in the RCTs. The open-label trials were limited by small numbers or lack of control. Outcome measures were also inconsistent.

ADHD

ADHD was associated with 7.1% of new of new modafinil or armodafinil users. There are inconsistent results and little evidence to support this use in adults and low level evidence in children.

Adult ADHD comorbid with mood disorders

The Canadian Network for Mood and Anxiety Treatments task force published a systematic review[44] and treatment recommendations for adult patients with comorbid mood disorders (depression or bipolar disease) with ADHD. This review is comprehensive in nature and includes epidemiology, clinical presentation, neurobiology, and treatment recommendations. Mean comorbidity rates for ADHD and bipolar disease were reported at 12.8%; for ADHD and major depression was reported as 7.8%. These are 3 and 2 times more prevalent than in the general population for adults (i.e. 3%-4%). Modafinil was not assessed in comorbid individuals but there were 2 placebo-controlled studies conducted in adult ADHD patients that demonstrated short-term efficacy. The 2 studies were not described but, they are the same as described in the following review below. Modafinil is recommended second-line after bupropion for adult ADHD comorbid with bipolar disease. This recommendation is made with the caution that there is a potential to destabilize mood during the long-term as there is no data beyond 6 weeks. Modafinil was not recommended for ADHD comorbid with major depression.

Adult ADHD

An earlier systematic review of modafinil for ADHD included 4 RCTs.[17] Two were placebo controlled and conducted in children (n= 272) for 6-9 weeks, 1 was a single dose placebo-controlled crossover trial in 20 adults and the last was a phase 3 crossover trial comparing modafinil to dextro-amphetamine in 22 adults for 6 weeks. All used different outcome scales and all showed significant improvements. The populations met ADHD diagnostic criteria but were not required to fail other therapies. Patients were excluded if they had comorbid developmental or psychiatric diagnoses. The authors conclude that modafinil may be viable for some patients for whom the standard ADHD treatment are ineffective or not tolerated but that additional long-term studies are needed.

The Canadian Agency for Drugs and Technologies in Health reviewed non-stimulant therapies (including modafinil) for treatment of adult ADHD.[18] Two studies were included, one of which is the 6 week placebo crossover trial described above. The other was a 9-week, placebo RCT. The authors conclude that the efficacy of modafinil in reducing ADHD symptoms is not statistically significantly different than dextro-amphetamine and superiority over placebo was not consistent across the trials.

COGNITION ENHANCEMENT

There were 3 systematic reviews[19,20,21] exploring the evidence of modafinil for enhanced cognition. All focused on healthy adults. Each found the evidence gaps to be large and generally conclude that expectations likely exceed the actual drug effect.

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Appendix 1 – Diagnoses of Interest[27,26,45,12]

Diagnoses	OHP Funded codes
Funded*[24] *FDA Indications (Group 1)	
Narcolepsy	347.00-347.01
Organic sleep apnea (except high altitude)	327.20-327.21, 327.23-327.29, 780.51, 780.53, 780.57
Funded*[24] *Off-Label Indications (Group 2)	
Attention deficit hyperactivity disorder: *AHFS Level C* *MM Level B (Adult), A (Pediatric)*	314.00-314.9
Depression, Unipolar or bipolar; Adjunct: *MM Level B (Adult)*	296.20-296.22, 296.25-296.26, 296.90-296.99, 298.0, 311, 625.4
Steinert myotonic dystrophy syndrome: *MM Level B (Adult)*	359.21
Fatigue in adult cancer survivors: *AHFS Level G*	140.xx - 209.xx
Multiple sclerosis-related fatigue: *AHFS Levels B & G* *MM Level B*	340.xx
Non-Funded*[24] *Indications (Group 3)	
Narcolepsy in conditions classified elsewhere	347.10 -347.11
Organic sleep disorders except organic sleep apneas	327.00, 327.01, 327.02, 327.09-327.13, 327.14, 327.15, 327.19, 327.22
Shift work sleep disorder	327.30-327.8
Hypersomnia, unspecified *Adverse reaction to drug - Somnolence: MM Level B* *Sleep deprivation: MM Level B (Adult)*	780.54
No Diagnosis of Interest (Group 4)	

Micromedex (MM) Evidence Levels:
Category A evidence is based on data derived from: Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.
Category B evidence is based on data derived from: Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies).
Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series.

AHFS Evidence Levels:
A - Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form (e.g., results of the introduction of penicillin treatment) to support the off-label use. Further research is unlikely to change confidence in the estimate of benefit.
B - Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.
C - Evidence from observational studies (eg, retrospective case series/reports providing significant impact on patient care), unsystematic clinical experience, or from potentially flawed randomized, controlled trials
G - Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.

Appendix 2 – Maximum daily dose for drugs of interest

HSN	GSN	Brand	Generic	Strength	Maximum Units per Day
010865	025848	PROVIGIL	MODAFINIL	100 mg	2
010865	041478	PROVIGIL	MODAFINIL	200 mg	1
034868	062819	NUVIGIL	ARMODAFINIL	150 mg	1
034868	062820	NUVIGIL	ARMODAFINIL	50 mg	5
034868	062821	NUVIGIL	ARMODAFINIL	250 mg	1
034868	072017	NUVIGIL	ARMODAFINIL	200 mg	1

Appendix 3 – Medline literature search details

Ovid Technologies, Inc. Email Service----------Search for: limit 10 to (meta analysis or systematic reviews)Results: 27

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to June Week 2 2015> Search Strategy:
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1 modafinil.mp. (1256)
2 armodafinil.mp. (99)
3 1 or 2 (1281)
4 exp Depression/ (82108)
5 exp Fatigue/ (21739)
6 exp Cognition/ (116136)
7 exp Attention Deficit Disorder with Hyperactivity/ (21441)
8 4 or 5 or 6 or 7 (234593)
9 3 and 8 (317)
10 limit 9 to (english language and humans) (284)
11 limit 10 to (meta analysis or systematic reviews) (25)

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1. Moulton CD, Hopkins CW, Bevan-Jones WR. Systematic review of pharmacological treatments for depressive symptoms in Huntington's disease. Mov Disord. 2014;29(12):1556-61. doi:10.1002/mds.25980
AB BACKGROUND: Depressive symptoms are common in Huntington's disease (HD), profoundly affect quality of life, and predict suicidal ideation. However, no recent review of antidepressant treatment in HD has been published. METHODS: We performed a PRISMA systematic review of HD studies, which used a recognized antidepressant and measured change in depressive symptoms using a validated psychiatric scale. Controlled trials, uncontrolled trials, observational studies, and case series were included. RESULTS: Eleven studies were included, totalling 190 patients. One study examined venlafaxine, one fluoxetine, one citalopram, one atomoxetine, one modafinil, one lithium, and five antipsychotics. No studies were of adequate duration, size, or outcome, and no controlled trial in a depressed population produced a positive result. CONCLUSIONS: Inadequate evidence exists to guide antidepressant treatment in HD. Further research is needed to assess antidepressant efficacy and to examine whether treatment of depression represents a modifiable target for the high suicide rate in HD.

EXCLUDED; INTERVENTION

2. Bagot KS, Kaminer Y. Efficacy of stimulants for cognitive enhancement in non-attention deficit hyperactivity disorder youth: a systematic review. Addiction. 2014;109(4):547-57. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=24749160. Accessed June 23, 2015.

AB BACKGROUND AND AIMS: Increasing prescription stimulant abuse among youth without diagnoses of attention deficit hyperactivity disorder (ADHD) is of concern. The most frequently cited motive for abuse is improved academic achievement via neurocognitive enhancement. Our aim in reviewing the literature was to identify neurocognitive effects of prescription stimulants in non-ADHD youth. METHODS: A systematic review

was conducted for youth aged 12-25 years using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Fourteen papers were included. RESULTS: Modafinil appears to improve reaction time (P < 0.04), logical reasoning (P < 0.05) and problem-solving. Methylphenidate appears to improve performance in novel tasks and attention-based tasks (P < 0.05), and reduces planning latency in more complex tasks (P < 0.05). Amphetamine has been shown to improve consolidation of information (0.02 > P < 0.05), leading to improved recall. Across all three types of prescription stimulants, research shows improved attention with lack of consensus on whether these improvements are limited to simple versus complex tasks in varying youth populations. CONCLUSIONS: The heterogeneity of the non-attention deficit hyperactivity disorder youth population, the variation in cognitive task characteristics and lack of replication of studies makes assessing the potential global neurocognitive benefits of stimulants among non-attention deficit hyperactivity disorder youth difficult; however, some youth may derive benefit in specific cognitive domains.

EXCLUDED: DIAGNOSIS NOT OF INTEREST

3. Wood S, Sage JR, Shuman T, Anagnostaras SG. Psychostimulants and cognition: a continuum of behavioral and cognitive activation. Pharmacol Rev. 2014;66(1):193-221. doi:10.1124/pr.112.007054

AB Psychostimulants such as cocaine have been used as performance enhancers throughout recorded history. Although psychostimulants are commonly prescribed to improve attention and cognition, a great deal of literature has described their ability to induce cognitive deficits, as well as addiction. How can a single drug class be known to produce both cognitive enhancement and impairment? Properties of the particular stimulant drug itself and individual differences between users have both been suggested to dictate the outcome of stimulant use. A more parsimonious alternative, which we endorse, is that dose is the critical determining factor in cognitive effects of stimulant drugs. Herein, we review several popular stimulants (cocaine, amphetamine, methylphenidate, modafinil, and caffeine), outlining their history of use, mechanism of action, and use and abuse today. One common graphic depiction of the cognitive effects of psychostimulants is an inverted U-shaped dose-effect curve. Moderate arousal is beneficial to cognition, whereas too much activation leads to cognitive impairment. In parallel to this schematic, we propose a continuum of psychostimulant activation that covers the transition from one drug effect to another as stimulant intake is increased. Low doses of stimulants effect increased arousal, attention, and cognitive enhancement; moderate doses can lead to feelings of euphoria and power, as well as addiction and cognitive impairment; and very high doses lead to psychosis and circulatory collapse. This continuum helps account for the seemingly disparate effects of stimulant drugs, with the same drug being associated with cognitive enhancement and impairment.

EXCLUDED: DIAGNOSIS NOT OF INTEREST; NARRATIVE REVIEW

4. Sheng P, Hou L, Wang X, et al. Efficacy of modafinil on fatigue and excessive daytime sleepiness associated with neurological disorders: a systematic review and meta-analysis. PLoS ONE. 2013;8(12):e81802. doi:10.1371/journal.pone.0081802

AB BACKGROUND: Modafinil is a novel wake-promoting agent approved by the FDA ameliorating excessive daytime sleepiness (EDS) in three disorders: narcolepsy, shift work sleep disorder and obstructive sleep apnea. Existing trials of modafinil for fatigue and EDS associated with neurological disorders provided inconsistent results. This meta-analysis was aimed to assess drug safety and effects of modafinil on fatigue and EDS associated with neurological disorders. METHODS: A comprehensive literature review was conducted in order to identify published studies assessing the effects of modafinil on fatigue and EDS associated with neurological disorders. Primary outcomes included fatigue and EDS. Secondary outcomes included depression and adverse effects. FINDINGS: Ten randomized controlled trials were identified including 4 studies of Parkinson's disease (PD), 3 of multiple sclerosis (MS), 2 of traumatic brain injury (TBI) and 1 of post-polio syndrome (PPS). A total of 535 patients were enrolled. Our results suggested a therapeutic effect of modafinil on fatigue in TBI (MD -0.82 95% CI -1.54 - -0.11 p=0.02, I(2)=0%), while a beneficial effect of modafinil on fatigue was not confirmed in the pooled studies of PD or MS. Treatment results demonstrated a clear beneficial effect of modafinil on EDS in patients with PD (MD -2.45 95% CI -4.00 - -0.91 p=0.002 I(2)=14%), but not with MS and TBI. No difference was seen between modafinil and placebo treatments in patients with PPS. Modafinil seemed to have no therapeutic effect on depression. Adverse events were similar between modafinil and placebo groups except that more patients were found with insomnia and nausea in modafinil group. CONCLUSIONS: Existing trials of modafinil for fatigue and EDS associated with PD, MS, TBI and PPS provided inconsistent results. The majority of the studies had small sample sizes. Modafinil is not yet sufficient to be recommended for these medical conditions until solid data are available.

INCLUDED

5. Barsevick AM, Irwin MR, Hinds P, et al. Recommendations for high-priority research on cancer-related fatigue in children and adults. J Natl Cancer Inst. 2013;105(19):1432-40. doi:10.1093/jnci/djt242

AB Over the past decades, some scientific progress has been made in understanding and treating cancer-related fatigue (CRF). However, three major problems have limited further progress: lack of agreement about measurement, inadequate understanding of the underlying biology, and problems in the conduct of clinical trials for CRF. This commentary reports the recommendations of a National Cancer Institute Clinical Trials Planning Meeting and an ongoing National Cancer Institute working group to address these problems so that high-priority research and clinical trials can be conducted to advance the science of CRF and its treatment. Recommendations to address measurement issues included revising the current case definition to reflect more rigorous criteria, adopting the Patient Reported Outcomes Measurement Information System fatigue scales as standard measures of CRF, and linking legacy measures to the scales. With regard to the biology of CRF, the group identified the need for longitudinal research to examine biobehavioral mechanisms underlying CRF and testing mechanistic hypotheses within the context of intervention research. To address clinical trial issues, recommendations included using only placebo-controlled trial designs. setting eligibility to minimize sample heterogeneity or enable subgroup analysis, establishing a CRF severity threshold for participation in clinical trials, conducting dissemination trials of efficacious interventions (such as exercise), and combining

nonpharmacologic and pharmacologic interventions to exploit the potential synergy between these approaches. Accomplishing these goals has the potential to advance the science of CRF and improve the clinical management of this troubling symptom.

EXCLUDED: DESIGN (COMMENTARY)

6. Cerullo MA, Strakowski SM. A systematic review of the evidence for the treatment of acute depression in bipolar I disorder. CNS Spectr. 2013;18(4):199-208. doi:10.1017/S1092852913000102

AB In this article, we examined evidence for the acute treatment of depression in bipolar I disorder, focusing on double-blind, placebo-controlled studies with a definite primary outcome measure and published in peer review journals. Quetiapine and olanzapine/fluoxetine are currently approved by the FDA for the treatment of bipolar depression, and a number of additional agents (including other atypical antipsychotics, mood stabilizers, antidepressants, and novel compounds) have been studied with varying degrees of efficacy. The medication with the most evidence for efficacy in bipolar depression is quetiapine, with five studies showing positive efficacy compared to placebo. In contrast, five studies of lamotrigine were negative, although meta-analyses of the pooled have found some treatment effects. Two studies of olanzapine and olanzapine/fluoxetine and three small studies of divalproex showed significant efficacy in treating bipolar depression. Two studies of aripiprazole found no differences compared to placebo. Early research on lithium in bipolar depression had significant methodological flaws, and only one study of lithium met our primary search criteria. To better understand the role of antidepressants, we also examined studies of antidepressants as adjunctive treatment of bipolar depression in participants taking mood stabilizers or atypical antipsychotics. These studies reported mixed results for a variety of antidepressants, but the majority found no differences compared to placebo. Other studies of adjunctive treatment were also discussed. There has been one positive adjunctive study each of lamotrigine, omega-3 fatty acids, modafinil, and armodafinil, while there was one negative trial each of omega-3 fatty acids, ziprasidone, and levetiracetam.

INCLUDED

7. Scoriels L, Jones PB, Sahakian BJ. Modafinil effects on cognition and emotion in schizophrenia and its neurochemical modulation in the brain. Neuropharmacology. 2013;64:168-84. doi:10.1016/j.neuropharm.2012.07.011

AB Modafinil is a central nervous system wake promoting agent used for the treatment of excessive daytime sleeping. Its vigilance promoting properties and low abuse potential has intrigued the scientific community and has led to use it as a cognitive enhancer, before its neural functions were understood. Here, we review the effects of modafinil in human cognition and emotion and its specific actions on symptoms in patients with schizophrenia and whether these are consistently effective throughout the literature. We also performed a systematic review on the effects of modafinil on neurotransmitter signalling in different areas of the brain in order to better understand the neuromechanisms of its cognitive and emotional enhancing properties. A review of its effects in schizophrenia suggests that modafinil facilitates cognitive functions, with pro-mnemonic effects and problem solving improvements. Emotional processing also appears to be enhanced by the drug, although to date there are only a limited number of studies. The systematic review on the neurochemical modulation of the modafinil suggests that its mnemonic enhancing properties might be the result of glutamatergic and dopaminergic increased neuronal activation in the hippocampus and in the prefrontal cortex respectively. Other neurotransmitters were also activated by modafinil in various limbic brain areas, suggesting that the drug acts on these brain regions to influence emotional responses. These reviews seek to delineate the neuronal mechanisms by which modafinil affects cognitive and emotional function. This article is part of a Special Issue entitled 'Cognitive Enhancers'.

EXCLUDED – OUTCOMES NOT OF INTEREST

8. Kelley AM, Webb CM, Athy JR, Ley S, Gaydos S. Cognition enhancement by modafinil: a meta-analysis. Aviat Space Environ Med. 2012;83(7):685-90. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22779312. Accessed June 23, 2015.

AB INTRODUCTION: Currently, there are a number of pharmaceuticals available that have potential to enhance cognitive functioning, some of which may ultimately be considered for such use in military operations. Some drugs with potential for cognition enhancement have already been studied for use in military operations specific to their primary effect in sleep regulation (i.e., dextroamphetamine, modafinil, caffeine). There is considerable information available on many of these drugs. However, considerations for military appropriateness must be based on proficient research (e.g., randomly controlled trial design). METHODS: A meta-analysis was conducted to summarize the current state of knowledge of these potentially cognition-enhancing drugs. The analysis only included studies which met inclusion criteria relevant to military research. RESULTS: The results of the literature review reveal a gap in research of the enhancement properties of the drugs of interest. The results yielded three studies (all of which studied modafinil) that met the criteria. The meta-analysis of these three studies revealed a relatively weak pooled effect of modafinil on some aspects of cognitive performance in normal, rested adults. DISCUSSION: While the results of this study support the efficacy of modafinil, the main finding is the large literature gap evaluating the short- and long-term effects of these drugs in healthy adults.

EXCLUDED: DIAGNOSIS NOT OF INTEREST

9. Bond DJ, Hadjipavlou G, Lam RW, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid attention-deficit/hyperactivity disorder. Ann Clin Psychiatry. 2012;24(1):23-37. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22303520. Accessed June 23, 2015.

AB BACKGROUND: Patients with bipolar disorder (BD) and major depressive disorder (MDD) experience adult attention-deficit/hyperactivity disorder (ADHD) at rates substantially greater than the general population. Nonetheless, ADHD frequently goes untreated in this population. METHODS: We reviewed the literature regarding the management of adult ADHD in patients with mood disorders. Because a limited number of studies have been conducted in adults, our treatment recommendations also are partly informed by research in children and adolescents with BD+ADHD or MDD+ADHD, adults with ADHD, and our clinical experience. RESULTS: In individuals with mood disorders, ADHD is best diagnosed when typical symptoms persist during periods of sustained euthymia. Individuals with BD+ADHD, particularly those with bipolar I disorder (BD I), are at risk for mood destabilization with many ADHD treatments, and should be prescribed mood-stabilizing medications before initiating ADHD therapies. Bupropion is a reasonable first-line treatment for BD+ADHD, while mixed amphetamine salts and methylphenidate also may be considered in patients determined to be at low risk for manic switch. Modafinil and cognitive-behavioral therapy (CBT) are second-line choices. In patients with MDD+ADHD and moderate to severe depression, MDD should be the treatment priority, whereas in mildly depressed or euthymic patients the order may be reversed. First-line treatments for MDD+ADHD include bupropion, an antidepressant plus a long-acting stimulant, or an antidepressant plus CBT. Desipramine, nortriptyline, and venlafaxine are second-line options. CONCLUSIONS: Clinicians should be vigilant in screening for comorbid ADHD in mood disorder patients. ADHD symptoms can respond to appropriately chosen treatments.

INCLUDED

10. Kirshbaum M. Pharmacologic treatments for fatigue associated with palliative care. Clin J Oncol Nurs. 2011;15(4):438-9. doi:10.1188/11.CJON.438-439

EXCLUDED: UNAVAILABLE AT OHSU

11. Castells X, Ramos-Quiroga JA, Bosch R, Nogueira M, Casas M. Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults. Cochrane Database Syst Rev. 2011;(6):CD007813. doi:10.1002/14651858.CD007813.pub2

AB BACKGROUND: Attention Deficit Hyperactivity Disorder (ADHD) is a childhood onset disorder that can persist into adulthood. Amphetamines are used to treat adult ADHD, but uncertainties persist about their efficacy and safety. OBJECTIVES: To examine the efficacy and safety of amphetamines for adults with ADHD, as well as the influence of dose, drug type and release formulation type. SEARCH STRATEGY: We searched CENTRAL, PubMed, EMBASE, CINAHL, PsycINFO, clinicaltrials.gov, UK Clinical Trials Gateway and references obtained from articles and experts in the field. We conducted the electronic searches on 25 February 2010. SELECTION CRITERIA: Randomized controlled trials comparing the efficacy of amphetamine derivatives against placebo or an active intervention. DATA COLLECTION AND ANALYSIS: Two authors extracted data from each included study. We used the standardized mean difference (SMD) and the risk ratio (RR) to assess continuous and dichotomous outcomes, respectively. We conducted a stratified analysis to determine the influence of moderating variables. We assessed the trials for risk of bias and drew a funnel plot to investigate the possibility of publication bias. MAIN RESULTS: We included seven studies, which enrolled 1091 participants. All studies were placebo-controlled and three included an active comparator: guanfacine, modafinil and paroxetine. Most studies had short-term follow-up, with a mean study length of 8.1 weeks. Amphetamines improved ADHD symptom severity (SMD = -0.72; 95% CI -0.87 to -0.57) but did not improve retention in treatment overall and were associated with increased dropout due to adverse events (RR 3.03; 95% CI 1.52 to 6.05). The three amphetamine derivatives investigated (dextroamphetamine, lisdexamphetamine and mixed amphetamine salts (MAS)) were all efficacious for reducing ADHD symptoms, but MAS also increased retention in treatment. Different doses did not appear associated with differences in efficacy. We investigated immediate and sustained drug release formulations but found no difference between them on any outcome. When amphetamines were compared to other drug interventions, no differences were found. We did not find any study to be at low risk of bias overall, mainly because amphetamines have powerful subjective effects that may reveal the assigned treatment. AUTHORS' CONCLUSIONS: Amphetamines improved short-term ADHD symptom severity. MAS also increased retention in treatment. Amphetamines were associated with higher attrition due to adverse events. The short study length and the restrictive inclusion criteria limit the external validity of these findings. Furthermore, the possibility that the results of the included studies were biased was high, which could have led to an overestimation of amphetamine efficacy.

EXCLUDED: INTERVENTION

12. Chamberlain SR, Robbins TW, Winder-Rhodes S, et al. Translational approaches to frontostriatal dysfunction in attention-deficit/hyperactivity disorder using a computerized neuropsychological battery. Biol Psychiatry. 2011;69(12):1192-203. doi:10.1016/j.biopsych.2010.08.019

AB Attention-deficit/hyperactivity disorder (ADHD) is a prevalent condition associated with cognitive dysfunction. The Cambridge Neuropsychological Test Automated Battery is a computerized set of tests that has been widely used in ADHD and in translation/back-translation. Following a survey of translational research relevant to ADHD in experimental animals, a comprehensive literature review was conducted of studies that had used core Cambridge Neuropsychological Test Automated Battery tests 1) to evaluate cognitive dysfunction in ADHD and 2) to evaluate effects of salient drugs in patients and in volunteers. Meta-analysis was conducted where four or more independent datasets were available. Meta-analysis revealed medium-large decrements in ADHD for response inhibition ($d = .790$, $p < .001$), working memory ($d = .883$, $p < .001$), executive planning ($d = .491$, $p < .001$), and a small decrement in attentional set shifting ($d = .160$, $p = .040$). Qualitative review of the literature showed some consistent patterns. In ADHD, methylphenidate improved working memory, modafinil

improved planning, and methylphenidate, modafinil, and atomoxetine improved inhibition. Meta-analysis of modafinil healthy volunteer studies showed no effects on sustained attention or set shifting. Results were paralleled by findings in experimental animals on comparable tests, enabling further analysis of drug mechanisms. Substantial cognitive deficits are present in ADHD, which can be remediated somewhat with current medications and which can readily be modeled in experimental animals using back-translational methodology. The findings suggest overlapping but also distinct early cognitive effects of ADHD medications and have important implications for understanding the pathophysiology of ADHD and for future trials.

EXCLUDED: OUTCOMES NOT OF INTEREST

13. Frost J, Okun S, Vaughan T, Heywood J, Wicks P. Patient-reported outcomes as a source of evidence in off-label prescribing: analysis of data from PatientsLikeMe. J Med Internet Res. 2011;13(1):e6. doi:10.2196/jmir.1643

AB BACKGROUND: Evaluating a new use for an existing drug can be expensive and time consuming. Providers and patients must all too often rely upon their own individual-level experience to inform clinical practice, which generates only anecdotal and unstructured data. While academic-led clinical trials are occasionally conducted to test off-label uses of drugs with expired patents, this is relatively rare. In this work, we explored how a patient-centered online research platform could supplement traditional trials to create a richer understanding of medical products postmarket by efficiently aggregating structured patient-reported data. PatientsLikeMe is a tool for patients, researchers, and caregivers (currently 82,000 members across 11 condition-based communities) that helps users make treatment decisions, manage symptoms, and improve outcomes. Members enter demographic information, longitudinal treatment, symptoms, outcome data, and treatment evaluations. These are reflected back as longitudinal health profiles and aggregated reports. Over the last 3 years, patients have entered treatment histories and evaluations on thousands of medical products. These data may aid in evaluating the effectiveness and safety of some treatments more efficiently and over a longer period of time course than is feasible through traditional trials. OBJECTIVE: The objective of our study was to examine the illustrative cases of amitriptyline and modafinil - drugs commonly used off-label. METHODS: We analyzed patient-reported treatment histories and drug evaluations for each drug, examining prevalence, treatment purpose, and evaluations of effectiveness, side effects, and burden. RESULTS: There were 1948 treatment histories for modafinil and 1394 treatment reports for amitriptyline reported across five PatientsLikeMe communities (multiple sclerosis, Parkinson's disease, mood conditions, fibromyalgia/chronic fatigue syndrome, and amyotrophic lateral sclerosis). In these reports, the majority of members reported taking the drug for off-label uses. Only 34 of the 1755 (1%) reporting purpose used modafinil for an approved purpose (narcolepsy or sleep apnea). Only 104 out of 1197 members (9%) reported taking amitriptyline for its approved indication, depression. Members taking amitriptyline for off-label purposes rated the drug as more effective than those who were taking it for its approved indication. While dry mouth is a commonly reported side effect of amitriptyline for most patients, 88 of 220 (40%) of people with amyotrophic lateral sclerosis on the drug reported taking advantage of this side effect to treat their symptom of excess saliva. CONCLUSIONS: Patient-reported outcomes, like those entered within PatientsLikeMe, offer a unique real-time approach to understand utilization and performance of treatments across many conditions. These patient-reported data can provide a new source of evidence about secondary uses and potentially identify targets for treatments to be studied systematically in traditional efficacy trials.

17

EXCLUDED: NOT RELEVANT

14. Peuckmann V, Elsner F, Krumm N, Trottenberg P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. Cochrane Database Syst Rev. 2010;(11):CD006788. doi:10.1002/14651858.CD006788.pub2

AB BACKGROUND: In healthy individuals, fatigue is a protective response to physical or mental stress, often relieved by rest. By contrast, in palliative care patients fatigue can be severely debilitating, thereby impacting daily activity and quality of life, often with rest not counteracting fatigue. Fatigue frequently occurs in patients with advanced disease and modalities treating cancer often contribute or cause fatigue. Further complicating issues are its multidimensionality, subjective nature, and lack of a consensus definition of fatigue. Pathophysiology is not fully understood and evidence-based treatment approaches are needed. OBJECTIVES: The objective was to determine efficacy of pharmacological treatments on non-specific fatigue in palliative care. The focus was on patients at an advanced stage of disease, including cancer and other chronic diseases associated with fatigue, aiming to relieve fatigue. Studies aiming at curative treatment (e.g. surgical intervention for early breast cancer) were not included. SEARCH STRATEGY: We searched EMBASE; Psych Lit, CENTRAL and MEDLINE to June 2009. SELECTION CRITERIA: We considered randomised controlled trials (RCTs) concerning adult palliative care with focus on pharmacological treatment of fatigue. The primary outcome had to be non-specific fatigue (or related terms such as asthenia). DATA COLLECTION AND ANALYSIS: Results were screened and included if they met the selection criteria. If two or more studies were identified that investigated a specific drug in a population with the same disease, meta-analysis was conducted. In addition, comparison of type of drug investigated in a specific population as well as comparison of frequent adverse effects of fatigue treatment was done by creating overview tables. MAIN RESULTS: More than 2000 publications were screened, and 22 met inclusion criteria. In total, data from 11 drugs and 1632 participants were analysed. Studies investigating amantadine, pemoline, and modafinil in participants with Multiple Sclerosis (MS)-associated fatigue and methylphenidate in patients suffering from advanced cancer and fatigue could be used for meta-analysis. Amantadine in MS and methylphenidate in cancer patients showed a superior effect. Most studies had low participant numbers and were heterogenous. AUTHORS' CONCLUSIONS: Based on limited evidence, we cannot recommend a specific drug for treatment of fatigue in palliative care patients. Surprisingly, corticosteroids have not been a research focus for fatigue treatment, although these drugs are frequently used. Recent fatigue research seems to focus on modafinil, which may be beneficial although there is no evidence currently. Amantadine and methylphenidate should be further examined. Consensus regarding fatigue assessment in advanced disease is needed.

INCLUDED

15. Repantis D, Schlattmann P, Laisney O, Heuser I. Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review. Pharmacol Res. 2010;62(3):187-206. doi:10.1016/j.phrs.2010.04.002

AB The term neuroenhancement refers to improvement in the cognitive, emotional and motivational functions of healthy individuals through, inter alia, the use of drugs. Of known interventions, psychopharmacology provides readily available options, such as methylphenidate and modafinil. Both drugs are presumed to be in widespread use as cognitive enhancers for non-medical reasons. Based on a systematic review and meta-analysis we show that expectations regarding the effectiveness of these drugs exceed their actual effects, as has been demonstrated in single- or double-blind randomised controlled trials. Only studies with sufficient extractable data were included in the statistical analyses. For methylphenidate an improvement of memory was found, but no consistent evidence for other enhancing effects was uncovered. Modafinil on the other hand, was found to improve attention for well-rested individuals, while maintaining wakefulness, memory and executive functions to a significantly higher degree in sleep deprived individuals than did a placebo. However, repeated doses of modafinil were unable to prevent deterioration of cognitive performance over a longer period of sleep deprivation though maintaining wakefulness and possibly even inducing overconfidence in a person's own cognitive performance.

EXCLUDED: HEALTHY INDIVIDUALS

16. Jong E, Oudhoff LA, Epskamp C, et al. Predictors and treatment strategies of HIV-related fatigue in the combined antiretroviral therapy era. AIDS. 2010;24(10):1387-405. doi:10.1097/QAD.0b013e328339d004

AB OBJECTIVE: To assess predictors and reported treatment strategies of HIV-related fatigue in the combined antiretroviral (cART) era. METHOD: Five databases were searched and reference lists of pertinent articles were checked. Studies published since 1996 on predictors or therapy of HIV-related fatigue measured by a validated instrument were selected. RESULTS: A total of 42 studies met the inclusion criteria. The reported HIV-related fatigue prevalence in the selected studies varied from 33 to 88%. The strongest predictors for sociodemographic variables were unemployment and inadequate income. Concerning HIV-associated factors, the use of cART was the strongest predictor. Comorbidity and sleeping difficulties were important factors when assessing physiological influences. Laboratory parameters were not predictive of fatigue. The strongest and most uniform associations were observed between fatigue and psychological factors such as depression and anxiety. Reported therapeutic interventions for HIV-related fatigue include testosterone, psycho-stimulants (dextroamphetamine, methylphenidate hydrochloride, pemoline, modafinil), dehydroepiandrosterone, fluoxetine and cognitive behavioural or relaxation therapy. CONCLUSION: HIV-related fatigue has a high prevalence and is strongly associated with psychological factors such as depression and anxiety. A validated instrument should be used to measure intensity and consequences of fatigue in HIV-infected individuals. In the case of fatigue, clinicians should not only search for physical mechanisms, but should question depression and anxiety in detail. There is a need for intervention studies comparing the effect of medication (antidepressants, anxiolytics) and behavioural interventions (cognitive-behavioural therapy, relaxation therapy, graded exercise therapy) to direct the best treatment strategy. Treatment of HIV-related fatigue is important in the care for HIV-infected patients and requires a multidisciplinary approach.

EXCLUDED: INTERVENTION

17. Brown JN, Howard CA, Kemp DW. Modafinil for the treatment of multiple sclerosis-related fatigue. Ann Pharmacother. 2010;44(6):1098-103. doi:10.1345/aph.1M705

AB OBJECTIVE: To review the efficacy and safety of off-label use of modafinil in the treatment of multiple sclerosis (MS)-related fatigue. DATA SOURCES: Literature was accessed via MEDLINE (1966-January 2010) and International Pharmaceutical Abstracts (1960-2010), using the medical subject heading terms modafinil, multiple sclerosis, and fatigue. STUDY SELECTION AND DATA EXTRACTION: All English-language, peer reviewed publications were analyzed for relevance. Studies appropriate to the objective were evaluated, including 3 open-label trials, 1 single-blind trial, and 2 randomized placebo-controlled trials. DATA SYNTHESIS: Fatigue symptoms, assessed by a variety of self-reported symptom scales, improved in each of the uncontrolled studies reviewed when participants with MS received modafinil 200 mg or less daily for up to 12 weeks. These benefits were not maintained, however, in one uncontrolled study when modafinil was increased to 400 mg daily. Of the 2 randomized, controlled trials, 1 study found that modafinil 200 mg once daily resulted in a reduction in fatigue symptoms measured by the Fatigue Severity Scale at 8 weeks. The other study found no difference in the reduction of fatigue symptoms, measured by the Modified Fatigue Impact Scale at 5 weeks, between the placebo group and patients who received modafinil 100-200 mg twice daily. The most common adverse reactions associated with modafinil use in all studies included gastrointestinal and central nervous system effects. CONCLUSIONS: Based on the available data, use of modafinil for the treatment of MS-related fatigue has demonstrated benefit in all uncontrolled studies but has conflicting results from 2 controlled studies. Modafinil is a reasonable therapeutic option in this patient population, although larger, long-term, randomized controlled studies are necessary to further elucidate the appropriate dose of modafinil, its effects on MS-related fatigue, and adverse effects associated with its use. [References: 26]

INCLUDED

18. Cooper MR, Bird HM, Steinberg M. Efficacy and safety of modafinil in the treatment of cancer-related fatigue. Ann Pharmacother. 2009;43(4):721-5. doi:10.1345/aph.1L532

AB OBJECTIVE: To review the efficacy and safety of modafinil in the treatment of cancer-related fatigue (CRF). DATA SOUCES: Literature was accessed via MEDLINE (1950-week 3, November 2008), International Pharmaceutical Abstracts, and Google Scholar using the terms modafinil, cancer, and fatigue. Reference citations from articles identified were reviewed. STUDY SELECTION AND DATA EXTRACTION: All English-language publications identified were analyzed for significance. Studies relevant to the objective were used, including 2 prospective open-label studies, one randomized double-blind, dose-controlled trial with an open-label extension, and one Phase 3 randomized, placebo-controlled, double-blind trial. DATA SYNTHESIS: Fatigue is a nearly universal adverse effect of cancer and its treatment that is unrelated to physical exertion, is not relieved by sleep or rest, and negatively affects quality of life. Modafinil is a central nervous system stimulant with minimal toxicity and a low propensity for abuse. Clinical data demonstrate that modafinil significantly reduces fatigue in patients who have received cancer treatment or are currently undergoing chemotherapy. Additional benefits include improvement in cognitive function, mood, general activity, walking ability, normal work ability, relations with other people, and enjoyment of life. Limitations of the available data include open-label design in 3 of the 4 studies; the absence of numerical results of fatigue assessments in the abstract of 1 trial, preventing the determination of clinical significance; and the full inclusion/exclusion criteria, which were not included in the published abstracts. These limitations leave readers without a clear picture of the study populations. Finally, different patient populations at different points in treatment with varying durations of therapy were used, which makes extrapolation of data to the general population challenging. CONCLUSIONS: Further randomized placebo-controlled trials are necessary to amass evidence for the effective and safe use of modafinil for CRF; however, if traditional therapies have failed or are intolerable, modafinil can be considered a treatment option. [References: 19]

INCLUDED

19. Saavedra-Velez C, Yusim A, Anbarasan D, Lindenmayer JP. Modafinil as an adjunctive treatment of sedation, negative symptoms, and cognition in schizophrenia: a critical review. J Clin Psychiatry. 2009;70(1):104-12. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=19026265. Accessed June 23, 2015.

AB OBJECTIVE: Given recent reports about the off-label use of modafinil as an adjuvant for the treatment of antipsychotic-associated sedation in schizophrenia patients and the recent interest in its putative cognitive-enhancing effects in this population, we present a systematic review of available data on trials of modafinil as an adjuvant in the treatment of cognitive deficits, negative symptoms, and antipsychotic-induced fatigue, and its tolerability. DATA SOURCES: PubMed was searched for trials published in English up to January 2008 evaluating modafinil's effects on fatigue, negative symptoms, and cognition in schizophrenia with combinations of the following terms: schizophrenia, modafinil, cognition, negative symptoms, and fatigue. STUDY SELECTION: Six trials were identified: 2 randomized, prospective, double-blind placebo-controlled trials; 3 randomized, prospective, double-blind placebo-controlled crossover trials; and 1 open-label pilot study. Case series and case reports were excluded in the data analysis, except to identify potential adverse reactions to modafinil. DATA EXTRACTION: Studies were examined for number of subjects, trial duration, design, dosing, and outcomes with respect to sedation, negative symptoms, cognitive function, and tolerability. RESULTS: One of 4 reviewed studies found a significant effect of modafinil as an alerting agent for antipsychotic-induced fatigue and sedation. Neither of 2 reviewed studies found modafinil to improve negative symptoms of schizophrenia. Three of 6 reviewed studies showed that modafinil may improve short-term memory, attention, and the ability to shift mental sets. Two neuroimaging studies identified functional correlates in areas associated with working memory functions. The main adverse effect was found to be a small risk of psychosis exacerbation, which was seen in 5 of 83 patients (6.0%) in the active treatment groups as compared to 2 of 70 patients (2.9%) in the placebo groups. CONCLUSIONS: While the available data suggest that modafinil is generally well tolerated and may have some efficacy in the treatment of antipsychotic-induced sedation and cognitive domains, the small sample sizes, contradictory results, and methodological differences between trials, especially with respect to cognitive testing, make it difficult to draw firm conclusions about the overall effectiveness of modafinil as an adjunct in the treatment of schizophrenia. Well-powered, prospective, randomized placebo-controlled trials using the MATRICS battery concomitantly with functional outcome measures are necessary to elucidate modafinil's efficacy and effectiveness as an adjunctive treatment for sedation, negative symptoms, and cognitive deficits in schizophrenia. Hence, before prescribing modafinil to a schizophrenia patient, the possible risks and benefits of each particular case should be evaluated. [References: 56]

INCLUDED.

20. Harris JD. Fatigue in chronically ill patients. Curr. opin. support. palliat. care. 2008;2(3):180-6. doi:10.1097/SPC.0b013e32830baed0

AB PURPOSE OF REVIEW: Fatigue is the most common symptom among palliative patients, often considered more distressing than pain, nausea or vomiting. This article reviews the current literature and puts forward up to date treatment recommendations. RECENT FINDINGS: Methylphenidate showed a small but significant improvement versus placebo in a recently published systematic review. Donepezil did not show a significant benefit versus placebo in a double blind, placebo-controlled study. Hypogonadism is a frequent condition that can cause fatigue in patients with advanced cancer and other chronic illnesses and androgen replacement therapy warrants further investigation. Among antidepressants, bupropion has shown encouraging results. The role of hematopoietic agents for advanced cancer patients receiving palliative care is minimal as anemia is less of a contributing factor in this setting. Cytokine receptor antagonists play an important theoretical role but further studies are needed before they could be recommended. L-Carnitine has shown encouraging results. SUMMARY: Methylphenidate is still considered the first choice of treatment among pharmacological therapies. Modafinil shows promise, but insufficient studies have been conducted in this setting. Bupropion may have benefits in treating depression and fatigue. Among complementary therapies, L-carnitine has the most potential. Further studies are needed before cytokine receptor antagonists and androgen replacement therapy can be recommended. [References: 63]

EXCLUDED: UNAVAILABLE AT OHSU

21. Candy M, Jones L, Williams R, Tookman A, King M. Psychostimulants for depression. Cochrane Database Syst Rev. 2008;(2):CD006722. doi:10.1002/14651858.CD006722.pub2

AB BACKGROUND: Depression is common, disabling, costly and under-treated. There are problems in the current first-line drug treatment, antidepressants, for moderate or severe depression. There is a body of research that has evaluated the effect of psychostimulants (PS) in the treatment of depression. This has not been reviewed systematically. OBJECTIVES: To determine the effectiveness of PS in the treatment of depression and to assess adverse events associated with PS. SEARCH STRATEGY: Databases CCDANCTR-Studies and CCDANCTR-References were searched on 21/6/2006. Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, PsycInfo, AMED, CINAHL, Dissertation Abstracts and the National Health Service Research Register were searched. SELECTION CRITERIA: Randomised controlled trials (RCTs) assessing the effectiveness of PS were included. The trial population comprised adults of either sex with a diagnosis of depression. DATA COLLECTION AND ANALYSIS: Two review authors extracted the data independently and assessed trial quality. Meta-analysis was considered for trials with comparable key characteristics. The primary outcome was depression symptoms, based on a continuous outcome, using the standardised mean difference (SMD), or a dichotomous measure of clinical response, using odds ratios (OR), with 95% confidence intervals (CI). MAIN RESULTS: Twenty-four RCTs were identified. The overall quality of the trials was low. Five drugs were evaluated; dexamphetamine, methylphenidate, methylamphetamine, pemoline and modafinil. Modafinil was evaluated separately as its pharmacology is different to that of the other PS. PS were administered as a monotherapy, adjunct therapy, in oral or intravenous preparation and in comparison with a placebo or an active therapy. Most effects were measured in the short term (up to four weeks). Thirteen trials had some usable data for meta-analyses. Three trials (62 participants) demonstrated that oral PS, as a monotherapy, significantly reduced short term depressive symptoms in comparison with placebo (SMD -0.87, 95% CI -1.40, -0.33, with non-significant heterogeneity. A similar effect was found for fatigue. In the short term PS were acceptable and well tolerated. Tolerance and dependence were under evaluated. No statistically significant difference in depression symptoms was found between modafinil and placebo. AUTHORS' CONCLUSIONS: There is some evidence that in the short-term, PS reduce symptoms of depression. Whilst this reduction is statistically significant, the clinical significance is less clear. Larger high quality trials with longer follow-up and evaluation of tolerance and dependence are needed to test the robustness of these findings and, furthermore, to explore which PS may be more beneficial and in which clinical situations they are optimal. [References: 126]

INCLUDED

22. Carroll JK, Kohli S, Mustian KM, Roscoe JA, Morrow GR. Pharmacologic treatment of cancer-related fatigue. Oncologist. 2007;12 Suppl 1:43-51. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=17573455. Accessed June 23, 2015.

AB Fatigue is the most commonly reported symptom in patients with cancer, with a prevalence of over 60% reported in the majority of studies. This paper systematically reviews pharmacologic agents in the treatment of cancer-related fatigue (CRF). We conducted a literature review of clinical trials that assessed pharmacologic agents for the treatment of CRF. These agents include hematopoietics (for anemia), corticosteroids, and psychostimulants. Other therapeutic agents that are less well studied for CRF but are currently the focus of clinical trials include l-carnitine, modafinil, bupropion, and selective serotonin reuptake inhibitors such as paroxetine. Disclosure of potential conflicts of interest is found at the end of this article. [References: 75]

EXCLUDED: UNAVAILABLE AT OHSU

23. Lam JY, Freeman MK, Cates ME. Modafinil augmentation for residual symptoms of fatigue in patients with a partial response to antidepressants. Ann Pharmacother. 2007;41(6):1005-12. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=17519297. Accessed June 23, 2015.

AB OBJECTIVE: To evaluate the literature discussing the use of modafinil in the treatment of residual symptoms of fatigue in patients with depression. DATA SOURCES: PubMed (1966-March 2007) and International Pharmaceutical Abstracts (1970-March 2007) were searched using the key words modafinil and depression. A manual search of the reference section of the articles retrieved was conducted to identify articles not indexed in either of these sources. STUDY SELECTION AND DATA EXTRACTION: All articles published in English were evaluated. Studies were included if modafinil was used to treat patients with residual fatigue from depression and the effects were measured with validated fatigue subscales. DATA SYNTHESIS: One retrospective study, 5 open-label trials, and 2 randomized controlled clinical trials met the inclusion criteria for assessment of residual symptoms of fatigue as assessed by commonly used fatigue subscales after modafinil administration. Although improvement with fatigue has occurred with modafinil therapy, literature regarding the topic is limited by the lack of well-controlled clinical trials. Modafinil does appear to improve residual fatigue with depression as evidenced by open-label trials; however, the efficacy of this agent has not been duplicated in randomized controlled trials. The open-label trials that have been conducted often had no comparator and a small number of patients. In addition, outcome measures used in the studies were not consistent between trials. Modafinil appears to be well tolerated, with the main adverse effects being headache and nausea. CONCLUSIONS: Open-label trials indicate that modafinil may be effective in ameliorating fatigue associated with depression; however, this effect has not been reproduced in randomized, double-blind, placebo-controlled clinical trials. Therefore, the use of modafinil for the treatment of residual fatigue is not recommended due to the lack of reproducible data of its efficacy. Long-term, adequately powered clinical trials should be conducted to determine its place in therapy. [References: 24]

INCLUDED

24. Lindsay SE, Gudelsky GA, Heaton PC. Use of modafinil for the treatment of attention deficit/hyperactivity disorder. Ann Pharmacother. 2006;40(10):1829-33. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=16954326. Accessed June 23, 2015.

AB OBJECTIVE: To review the evidence for the use of modafinil in the treatment of attention deficit/hyperactivity disorder (ADHD). DATA SOURCES: A MEDLINE search (January 1990-May 2006) was conducted using MeSH terms ADHD and modafinil. The search was limited to English-language articles on clinical trials in humans. The Cochrane Database was also searched. STUDY SELECTION AND DATA EXTRACTION: The literature search yielded 4 randomized clinical trials. DATA SYNTHESIS: The use of modafinil in the treatment of ADHD is associated with significant improvements in primary outcome measures used to assess the status of patients diagnosed with ADHD. Several aspects of cognitive function in ADHD patients also appear to improve following modafinil treatment. Modafinil shows a favorable adverse effect profile. Insomnia and headache were the most common adverse effects, seen in approximately 20% of treated individuals. However, it has not been demonstrated that the beneficial effects of modafinil are maintained with chronic administration. CONCLUSIONS: Modafinil may be a viable option for some patients in the treatment of ADHD, perhaps those for whom standard ADHD therapies have not been successful or tolerated. There remains a need for additional large, long-term studies using flexible titration methods to optimize the dose of modafinil to establish safety and efficacy, as well as head-to-head comparisons between modafinil and both long- and short-acting stimulants to determine the role of modafinil in the treatment of ADHD. [References: 13]

INCLUDED

25. Ballon JS, Feifel D. A systematic review of modafinil: Potential clinical uses and mechanisms of action. J Clin Psychiatry. 2006;67(4):554-66. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=16669720. Accessed June 23, 2015.

AB BACKGROUND: Modafinil is a novel wake-promoting agent that has U.S. Food and Drug Administration approval for narcolepsy and shift work sleep disorder and as adjunctive treatment of obstructive sleep apnea/hypopnea syndrome. Modafinil has a novel mechanism and is theorized to work in a localized manner, utilizing hypocretin, histamine, epinephrine, gamma-aminobutyric acid, and glutamate. It is a well-tolerated medication with low propensity for abuse and is frequently used for off-label indications. The objective of this study was to systematically review the available evidence supporting the clinical use of modafinil. DATA SOURCES: The search term modafinil OR Provigil was searched on PubMed. Selected articles were mined for further potential sources of data. Abstracts from major scientific conferences were reviewed. Lastly, the manufacturer of modafinil in the United States was asked to provide all publications, abstracts, and unpublished data regarding studies of modafinil. DATA SYNTHESIS: There have been 33 double-blind, placebo-controlled trials of modafinil. Additionally, numerous smaller studies have been performed, and case reports of modafinil's use abound in the literature. CONCLUSIONS: Modafinil is a promising drug with a large potential for many uses in psychiatry and general medicine. Treating daytime sleepiness is complex, and determining the precise nature of the sleep disorder is vital. Modafinil may be an effective agent in many sleep conditions. To date, the strongest evidence among off-label uses exists for the use of modafinil in attention-deficit disorder, postanesthetic sedation, and cocaine dependence and withdrawal and as an adjunct to antidepressants for depression. [References: 146]

EXCLUDED: OUTCOMES

Modafinil/Armodafinl

Goal(s):

- Limit use to diagnoses where there is sufficient evidence of benefit and that are funded by OHP. Excessive daytime sleepiness related to shift-work is not funded by OHP.
- Limit to safe doses

Length of Authorization:

Initial approval of 90 days if criteria met; approval of up to 12 months with documented benefit OR doses above those in Table 2.

Requires PA:

- Payment for drug claims for modafinil or armodafinil without previous claims evidence of narcolepsy or obstructive sleep apnea (ICD9:347.00-347.01327.20-327.21, 327.23-327.29, 780.51, 780.53, 780.57)

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Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Table 1. Funded Indications

Indication	Modafinil (Provigil™)	Armodafinil (Nuvigil™)
Excessive daytime sleepiness in narcolepsy	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older
Residual excessive daytime sleepiness in obstructive sleep apnea patients treated with CPAP.	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older
Depression augmentation (unipolar or bipolar)	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence
CA-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence
MS-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence

Drug-related fatigue	**Not FDA approved; insufficient evidence**	**Not FDA approved;**
Excessive daytime sleepiness or fatigue related to other neurological disorders (e.g. Parkinson's Disease, traumatic brain injury, post-polio syndrome)	**Not FDA approved; insufficient evidence**	**Not FDA approved; insufficient evidence**
ADHD	**Not FDA approved; Insufficient evidence**	**Not FDA approved; insufficient evidence**
Cognition enhancement for any condition	**Not FDA approved; insufficient evidence**	**Not FDA approved; insufficient evidence**

Table 2. Maximum Recommended Dose (consistent evidence of benefit with lower doses)

Generic Name	Minimum Age	Maximum Daily Dose
armodafinil	**18**	**250mg**
modafinil	**18**	**200mg**

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is diagnosis funded? Not funded diagnoses: - Shift work disorder ICD9: 327.30-327.8 - Unspecified hypersomnia ICD9: 780.54	Yes: Go to #3.	No: Pass to R.Ph; Deny (Not funded by OHP)
3. Will prescriber consider a preferred alternative?	Yes: Inform prescriber of options (e.g. preferred methylphenidate or other CNS stimulants)	No: Go to #4.

Approval Criteria		
4. Is the request for continuation?	Yes: Pass to RPh, Go to #11	No: Go to #5.
5. Is dose above those recommended in Table 2?	Yes: Pass to RPh; Deny for Medical Appropriateness.	No: Go to #6
6. Is diagnosis narcolepsy or obstructive sleep apnea (ICD9:347.00-347.01327.20-327.21, 327.23-327.29, 780.51, 780.53, 780.57) AND Is the prescribing done by or in consultation with a sleep specialist or neurologist?	Yes: Approve for up to 12 months.	No: Go to #7
7. Is the request for armodafinil?	Yes: Pass to RPh; Deny for Medical Appropriateness. There is insufficient evidence for any off-label use.	No: Go to #8
8. Is the diagnosis unipolar or bipolar depression?	Yes: Approve for 90 days and inform prescriber further approval will require chart documented evidence of benefit.	No: Go to #9
9. Is the diagnosis CA-related or MS-related fatigue? - Amantadine is recommended first-line for MS - Methylphenidate is recommended first-line for CA	Yes: Inform prescriber of first-line options available without PA. May approve for 90 days and inform prescriber further approval will require chart documented evidence of benefit.	No: Go to #10

Approval Criteria		
10. Is the diagnosis ADHD?	Yes: Pass to RPh; Deny for Medical Appropriateness. There is insufficient evidence for benefit for ADHD. See available options at www.orpdl.org.	Go to #11
11. All other diagnoses must be evaluated as to funding level on OHP and evidence for benefit. Evidence supporting treatment for excessive daytime sleepiness or fatigue as a result of other conditions is currently insufficient and should be denied for Medical Appropriateness. Evidence to support cognition enhancement is insufficient and should be denied for Medical Appropriateness. If new evidence is provided by prescriber please forward request to Oregon MAP for provider reconsideration and potential changed to PA criteria.		
12. Continuation beyond initial 90-days requires submission of chart documentation (faxed copy or equivalent) of tolerability and demonstrated efficacy. The same clinical measure (e.g. Epworth score, Brief Fatigue Inventory or other validated measure) used to diagnose the fatigue or depression is recommended. Approve up to 12 months with chart documentation of positive response. Deny for "medical appropriateness" in absence of chart documentation.		

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P&T / DUR Review: *07/15 (kk)*
Implementation: *TBD*

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

Prior Authorization Review: Tesamorelin for injection

Background:
Human immunodeficiency virus (HIV)-infected persons who receive long-term anti-retroviral therapy (ART) often experience weight gain and abdominal body fat.[1] Tesamorelin is a growth hormone releasing factor (GRF) analog approved by the U.S. Food and Drug Administration (FDA) in 2010 to reduce excess abdominal fat in HIV-infected patients with lipodystrophy.[2] The Pharmacy and Therapeutics (P&T) Committee reviewed tesamorelin and approved Prior Authorization (PA) criteria in 2012 (see **Appendix 1**). A formal review was initiated to determine the clinical appropriateness of the implemented criteria.

When compared to placebo, tesamorelin decreases visceral adipose tissue (WMD -22.65 cm^2; 95% CI, -32.67 to -12.64 cm^2; $p<0.001$) but has no significant effect on subcutaneous adipose tissue mass (WMD 1.02 cm^2; 95% CI, -8.21 to +6.16 cm^2; $p=0.78$).[3] Use of tesamorelin leads to a weight-neutral effect and is not indicated for weight loss management.[2] Long-term cardiovascular benefit and safety of tesamorelin have not been studied, and there are no data to support improved compliance with anti-retroviral therapies (ART) in HIV-positive patients taking tesamorelin.[2]

No new indications, pertinent trials assessing clinically relevant outcomes (i.e., morbidity outcomes) or safety alerts were identified since the P&T Committee last reviewed this drug.

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

References:
1. Shlay JC, Bartsch G, Peng G, et al. Long-term body composition and metabolic changes in antiretroviral naive persons randomized to protease inhibitor-, nonnucleoside reverse transcriptase inhibitor-, or protease inhibitor plus nonnucleoside reverse transcriptase inhibitor-based strategy. *J Acquir Immune Defic Syndr*. 2007;44:506-517.
2. Egrifta® (tesamorelin for injection) [prescribing information]. Montreal, Quebec, Canada; Theratechnologies Inc., June 2015.
3. Sivakumar T, Mechanic OJ, Fehmie DA and Paul BT. Growth hormone axis treatments for HIV-associated lipodystrophy: a systematic review of placebo-controlled trials. *HIV Medicine*. 2011;12:453-462.

Tesamorelin (Egrifta®)

Goal(s):

- Cover for OHP-funded conditions
- Restrict to indications supported by medical literature

Requires PA:

- Tesamorelin (Egrifta®)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis a OHP-funded diagnosis?	Yes: Go to #3	No: Pass to RPh. Deny; not funded by the OHP.
3. Is the indicated treatment for reduction of excess abdominal fat in HIV-infected patients with lipodystrophy?	Yes: Pass to RPh. Deny; not funded by the OHP.	No: Pass to RPh. Deny; medical appropriateness

Drug Use Research & Management Program
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Prior Authorization Review: becaplermin topical gel

Background:
Human platelet-derived growth factor (PDGF) is a substance naturally produced in the body to help in wound healing. It promotes cellular proliferation and angiogenesis, helping to repair and replace dead skin and other tissues by attracting cells that repair wounds.[1] Becaplermin topical gel (Regranex®) is a genetically engineered product that mimics PDGF. It was approved by the U.S. Food and Drug Administration (FDA) in 1997 for the treatment of lower extremity diabetic neuropathic ulcers that have adequate blood supply and extend into the subcutaneous tissue and beyond.[2] The Pharmacy & Therapeutics Committee reviewed this drug previously and approved Prior Authorization (PA) for its use (see **Appendix 1**). The efficacy of becaplermin for lower extremity diabetic neuropathic ulcers has been established in clinical trials and confirmed in post-marketing experience.[3] No other indications have been approved by the FDA.

The efficacy of topical becaplermin has not been established for the treatment of pressure ulcers, venous stasis ulcers, or on exposed joints, tendons, ligaments and bone.[4] Off-label uses include management of necrotic mucosal flap after bone grafting;[5] necrobiosis lipoidica, a necrotizing skin condition is most frequently observed on the shins of both legs of patients with diabetes;[6] and hypertensive leg ulcers;[7] with insufficient or inconclusive evidence.

The FDA issued its strongest warning (Boxed Warning) in 2008 after increased rate of mortality secondary to malignancy distant from the site of application was observed in patients treated with 3 or more tubes of becaplermin gel in clinical studies and post-marketing use.[2] Though this risk has been disputed,[8] the FDA Boxed Warning and associated precautions are still in place.[4]

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

References:
1. Greer N, Foman N, Dorrian J, et al. Advanced wound care therapies for non-healing diabetic, venous and arterial ulcers: a systematic review. VA Evidence-based Synthesis Program Report, Washington (DC): Department of Veterans Affairs; November 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0054957/pdf/TOC.pdf . Accessed 10 June 2015.
2. Drugs@FDA. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo. Accessed 10 June 2015.
3. Diabetic Foot Problems, NICE Clinical Guideline 119. National Institute for Health and Clinical Excellence (NICE); March 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0041804/pdf/TOC.pdf . Accessed 10 June 2015.
4. Regranex® (becaplermin) [prescribing information]. Fort Worth, TX; Smith & Nephew Inc., August 2014.
5. Calhoun CC, Cardenes O, Ducksworth J and Le AD. Off-label use of becaplermin gel (recombinant platelet-derived growth factor-BB) for treatment of mucosal defects after corticocancellous bone graft: report of 2 cases with review of the literature. *Journal of Oral and Maxillofacial Surgery*. 2009;67:2516-20.
6. Tauveron V, Rosen A, Khashoggi M, et al. Long-term successful healing of ulcerated necrobiosis lipoidica after topical therapy with becaplermin. *Clinical and Experimental Dermatology*. 2013;38:745-47.
7. Senet P, Vicaut E, Beneton N, et al. Topical treatment of hypertensive leg ulcers with platelet-derived growth factor-BB: a randomized controlled trial. *Archives of Dermatology*. 2011;147:926-30.
8. Ziyadeh N, Fife D, Walker AM, et al. A matched cohort study of the risk of cancer in users of becaplermin. *Advances in Skin and Wound Care*. 2011;24:31-39.

Becaplermin (Regranex®)

Goal(s):

- To restrict use of drugs to conditions funded by the OHP that have demonstrated efficacy.

Length of Authorization:

Up to 6 months

Requires PA:

- Becaplermin topical gel

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis stated as diabetic neuropathic ulcer(s)?	Yes: Go to #3.	No: Pass to RPh. Deny; medical appropriateness.
3. Does the patient take medications for diabetes OR have documentation of diabetes mellitus?	Yes: Approve ONLY 15 grams for 6-month supply.	No: Pass to RPh. Deny; medical appropriateness.

2

P&T/DUR Review: *7/15; _/_*
Implementation: *_/_*

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

New Drug Evaluation: secukinumab for subcutaneous injection

Month/Year of Review: May 2015
Generic Name: secukinumab
PDL Class: Targeted immune modulators

End Date of Literature Search: March 2015
Brand Name (Manufacturer): Cosentyx™
Dossier Received: Yes

Research Questions:

- How does the efficacy of secukinumab compare with other systemic or biologic therapies for the treatment of moderate to severe plaque psoriasis?
- Does secukinumab improve the quality of life of patients with moderate to severe plaque psoriasis?
- Is secukinumab safe for the treatment of moderate to severe plaque psoriasis?

Conclusions:

- Two phase 3 randomized, controlled clinical trials provide high-quality evidence secukinumab 300 mg and 150 mg are superior to placebo for two co-primary efficacy endpoints assessing treatment of moderate-to-severe plaque psoriasis: the percentage of subjects achieving a 75% reduction in Psoriasis Areas and Severity Index (PASI 75) (number needed-to-treat (NNT) of 2 for both doses) and the percentage of subjects achieving a 0 or 1 on the modified Investigators Global Assessment (mIGA) (NNT 2 for both doses) at week 12. Data supporting the efficacy and effectiveness of secukinumab beyond 12 weeks are limited. Although one phase 3 study demonstrated secukinumab's superiority to a European Union-sourced formulation of etanercept (EU-etanercept) not currently approved in the United States (US). Therefore, the data should be viewed cautiously and no comparison has been made to a systemic product available in the US.
- High-quality evidence demonstrates secukinumab improves quality of life based on the Dermatological Life Quality Index (DQLI) compared with placebo at week 12 (NNT 2 and 3 for the 300 mg and 150 mg doses, respectively).
- Potential risks associated with immunomodulating monoclonal antibodies include infection, neutropenia, cardiovascular and cerebrovascular events, malignancies, autoimmune disorders, and administration and immune reactions. Week 52 safety data indicate that, compared with placebo, subjects treated with secukinumab experienced higher incidence rates of exacerbation of Crohn's disease (0.1 vs. 0 per 100 patient-years), hypersensitivity (11.3 vs. 4.5 per 100 patient-years), and neutropenia (1.4 vs. 0 per 100 patient-years). Although the incidence rates for infection were similar among study arms, the risk of infection was higher for secukinumab versus placebo over 12 weeks (NNH 10). Therefore, caution and monitoring are advised when prescribing the drug to patients with chronic or history of recurrent infection; pre-treatment screening for TB is required and live vaccinations should not be administered to patients taking the drug. Also, caution and monitoring are advised in prescribing the drug to patients with active Crohn's disease. Labeling provides no precautions or warnings with regard to neutropenia. Because the clinical trials are of short duration compared with the chronic nature of psoriasis, the full extent of adverse effects remains undetermined.

Recommendations:

- Approve modifications to the Oregon Health Plan (OHP) Prior Authorization (PA) criteria for systemic Biologicals and topical drugs for psoriasis. For ease of administration, PA criteria for topical therapies were removed from the systemic biologicals PA criteria and incorporated into the topical drugs for psoriasis PA criteria (see Appendix 2).
- Incorporate secukinumab into the OHP PA criteria for Biologicals and limit its use to patients with moderate to severe psoriasis, as diagnosed by a dermatologist and defined by the OHA, who have failed first-line therapies as defined by the OHA.
- Evaluate relative costs in executive session for PDL decision-making.

Background:

Secukinumab, a biologic agent, is the first interleukin-17A (IL-17A) inhibitor for the treatment of plaque psoriasis. Other approved biologic treatments include the tumor necrosis factor (TNF) blockers adalimumab, etanercept, infliximab; the IL-12 and IL-23 inhibitor ustekinumab. Approved conventional systemic agents include acitretin, methotrexate, cyclosporine, and apremilast. Non-systemic therapies include topical treatments and phototherapy (PUVA or UVB).[1, 2]

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

Treatment for moderate to severe psoriasis may include a combination of topical and phototherapy or a combination of topical and conventional or biologic systemic therapy.[5] Although United States, Canadian, German, and United Kingdom (UK) guidelines have not been updated since the introduction of secukinumab, these guidelines address the use of biologic agents as a class. Based on two randomized controlled trials of adalimumab vs methotrexate vs placebo and infliximab vs methotrexate, the American Academy of Dermatology (AAD) Position Statement on the Treatment of Psoriatic Patients states patients with moderate to severe psoriasis are candidates for conventional or biologic systemic therapy or phototherapy, without the need for stepwise-therapy. Treatment decisions should be based on the efficacy and safety profile of the therapy, previous therapies used by the patient, the patient's preference, the duration and severity of the disease, comorbidities and medical risk factors, and quality of life.[6, 7, 8]

Canadian (2012), UK (2012), and German (2012) guidelines are generally consistent with US guidelines.[5, 3, 9] Although UK guidelines list biologic therapies as third-line, they state to offer second-line (phototherapy or conventional systemic) or third-line therapy in moderate or severe psoriasis when topical therapy is likely to be insufficient; for example, >10% BSA involvement, at least "moderate" on the Physicians Global Assessment, and when topical therapy is ineffective.[9, 10] German guidelines qualify its recommendation for use of biologics with the statement (or a statement equivalent to): "especially if other forms of therapy have failed to achieve sufficient treatment success or are contraindicated or not tolerated." [3] The Oregon Health Authority (OHA) 1-1-2015 Prioritization List of Health covers biologics for moderate and severe plaque psoriasis after documented failure of first-line agents (i.e., topical agents, oral retinoids, phototherapy, and methotrexate) and second-line.[11]

Although in practice, severity is broadly defined and rather subjective, clinicians may use the following to assess the severity of disease: (1) Physicians Global Assessment (PGA), for which both the physician and patient both provide his or her perspective on the severity using the descriptors such as clear, nearly clear,

mild, moderate, and severe; (2) BSA affected, with moderate 5 to 10% and severe more than 10%; (3) plaque thickness; (4) disease location, including the presence of psoriasis in high impact or vulnerable areas; (5) the presence of systemic upset (e.g., fever, malaise); (6) the impact on functional, social, and psychological well-being.[2, 9, 12] However, the OHA defines severe inflammatory skin disease as functional impairment (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) AND either ≥10% body surface area involvement; hand, foot or mucous membrane involvement; or both.[11]

In clinical trials, moderate or severe psoriasis is commonly distinguished from mild based on scores from one or more clinical metrics, such as the Psoriasis Areas and Severity Index (PASI); the PGA, also referred to as the investigators global assessment (IGA); percentage BSA affected; and the Dermatological Life Quality Index (DLQI).[5] PASI, which is considered the gold standard for assessing severity of disease, measures overall severity and coverage by assessing BSA, erythema, induration, and scaling. Researchers primarily use a 75% reduction in PASI to document effectiveness of experimental therapies in patients with extensive disease. Some consider PASI a more sensitive instrument in patients with a BSA involvement of at least 10%.[2, 13]

The PGA (or IGA) is the second most commonly used tool; however, a variety of PGA instruments exist, with no consensus on the number of points on the scale, scale descriptors, and definitions. The modified IGA (mIGA), first used in the secukinumab clinical trials, is a five-point rating scale for overall psoriatic disease (mIGA), where 0, 1, 2, 3, and 4 indicates clear, almost clear, mild disease, moderate disease, and severe disease, respectively. This is a static scale that evaluates the subject's disease state at the time of the assessment, without comparison to baseline or any other previous disease states.[2]

The Oregon Health Authority (OHA) Prioritized List of Health Services covers biologics for moderate and severe plaque psoriasis after documented failure of first-line agents (i.e., topical agents, oral retinoids, and methotrexate). The OHA defines severe inflammatory skin disease as functional impairment (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) AND either ≥10% body surface area involvement; hand, foot or mucous membrane involvement; or both.

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

Clinical Efficacy:
The FDA approved secukinumab based on two good-quality pivotal, multicenter, randomized, double-blind, placebo-controlled, phase 3 trials (ERASURE [trial 2302] and FIXTURE [trial 2303]). In addition to the two pivotal trials, the researchers performed two small phase 3 trials using the prefilled syringe (PFS) and autoinjector (AI) dosage forms of secukinumab. Although the FDA determined it could not draw any conclusions from these trials because of the trials' small population size, the FDA reported the trials support the efficacy and safety of secukinumab in these dosage forms.[1]

Both ERASURE and FIXTURE assessed the superiority of secukinumab over placebo following a 12-week induction period, as well as the maintenance of response among subjects taking secukinumab following a subsequent 40-week maintenance period. At week 12, patients on placebo who did not meet PASI 75 were re-randomized to secukinumab 300 mg or 150 mg, so no comparison to placebo could be evaluated after this time point.

The two trials included two co-primary efficacy endpoints measuring disease severity: the percentages of patients achieving PASI 75 and the proportion achieving a response of 0 or 1 on the mIGA at week 12. Among the key secondary efficacy endpoints were the percentages of subjects achieving a reduction of

≥90% in the PASI score (PASI 90) at week 12, a score of 0 or 1 on the DLQI at week 12, the maintenance of PASI 75 at week 52, and the maintenance of a 0 or 1 on the DLQI at week 52. FIXTURE also included an assessment of the superiority of secukinumab over European Union-sourced (EU-) etanercept and the noninferiority of secukinumab to EU-etanercept for PASI 75 at week 12 as key secondary endpoints. The researchers evaluated each secukinumab dose independently and set the significance level at 0.025. The two trials enrolled similar populations: adults with moderate to severe plaque psoriasis who were candidates for systemic therapy (i.e., poorly controlled with topical, photo, previous systemic, or a combination of therapies), had a PASI score ≥12, an IGA score ≥3, and BSA involvement ≥10% at baseline. The mean PASI score and BSA involvement of subjects were 23 and 33%, respectively. The baseline and demographic characteristics exhibited no significant between-group differences.

The ERASURE trial randomized 738 subjects 1:1:1 to receive subcutaneous secukinumab 300 mg, secukinumab 150 mg, or placebo weekly for 5 weeks and then every 4 weeks until week 48. At week 12, higher percentages of patients in the secukinumab 300 mg and 150 mg groups achieved PASI 75, mIGA 0 or 1, and PASI 90 scores than those in the placebo group, respectively:

- PASI 75: 81.6% and 71.6% vs 4.5% ($p<0.001$ for both; NNT 2 for both)
- mIGA 0 or 1: 65.3% and 51.2% vs 2.4% ($p<0.001$ for both; NNT 2 for both)
- PASI 90: 59.2% and 39.1% vs 1.2% ($p<0.001$ for both; NNT 2 and 3, respectively)

A significantly higher percentage of subjects in the secukinumab 300 mg and 150 mg groups reported DLQI scores of 0 or 1 than those in the placebo group: 58.8% and 46.1% vs 10.3%, respectively ($p<0.001$ for both). At week 52, 80.5% and 72.4% of subjects in the secukinumab 300 mg and 150 mg groups continued to maintain PASI 75, and 66.3% and 48.6% of the groups' subjects, respectively, continued to have DLQI scores of 0 or 1.

The FIXTURE trial randomized 980 subjects 1:1:1:1 to receive subcutaneous secukinumab 300 mg, secukinumab 150 mg, EU-etanercept, or placebo. In a double-dummy design, patients received secukinumab and placebo per the same schedule as in ERASURE, while those randomized to etanercept received 50 mg twice weekly until week 12, then once weekly through week 51 according to the standard dosing regimen. At week 12, higher percentages of patients in the secukinumab 300 mg and secukinumab 150 mg groups achieved PASI 75, mIGA 0 or 1, and PASI 90 scores than those in the EU-etanercept and placebo groups, respectively:

- PASI 75: 77.1% and 67% vs 44% and 4.9% ($p<0.001$ for all comparisons; NNT 2, 2, 3, and 4 for secukinumab 300 mg and 150 mg vs placebo and vs EU-etanercept, respectively)
- mIGA 0 or 1: 62.5% and 51.1% vs 27.2% and 2.8% ($p<0.001$ for all comparisons; NNT 2, 2, 3, and 4 for secukinumab 300 mg and 150 mg vs placebo and vs EU-etanercept, respectively)
- PASI 90: 54.2% and 41.9% vs 20.7% and 1.5% ($p<0.001$ for all comparisons)

A significantly higher percentage of subjects in the secukinumab 300 mg and 150mg groups reported DLQI scores of 0 or 1 than those in the EU-etanercept and placebo groups: 56.2% and 50.6% vs 34.5% and 6.6%, respectively ($p<0.001$ for all comparisons). At week 52, 84.3% and 82.2% of subjects in the secukinumab 300 mg and 150 mg groups vs 72.5% of subjects in the EU-etanercept group ($p<0.001$ for both comparisons) continued to maintain PASI 75, and 69.7% and 56.2% of the groups' subjects, respectively, vs 46.9% of subjects in the EU-etanercept group continued to have DLQI scores of 0 or 1.

The limitations of these clinical trials included the following:

- The use of the mIGA, a previously unvalidated tool.
- The short duration of the comparative efficacy portion of the trial, as well as the maintenance phase. Response to secukinumab could decline with longer-term use.

- The large number of study centers created a small number of patients per center, making it difficult to assess drug effectiveness in any particular setting.
- The week 12 to 52 data were not placebo-controlled. Furthermore, by week 52 of ERASURE, PASI 75 data were available for 82% of subjects originally randomized to secukinumab 300 mg and 71% randomized to secukinumab 150 mg subjects. By week 52 of FIXTURE, PASI 75 data were available for 76% of subjects randomized to secukinumab 300 mg, 67% randomized to secukinumab 150 mg, and 44% randomized to EU-etanercept. Therefore, data supporting the effectiveness of secukinumab beyond 12 weeks must be viewed cautiously.[16]
- EU-etanercept is considered an investigational drug in the US. Therefore, data generated from the use of etanercept as a comparator should be viewed cautiously.

Clinical Safety:

Potential risks associated with immunomodulating monoclonal antibodies include infection, neutropenia, cardiovascular and cerebrovascular events, malignancies, autoimmune disorders, and administration and immune reactions (e.g., hypersensitivity reactions, injection site and infusion reactions, and immunogenicity).[1] For the entire treatment period of up to 52 weeks, patients taking secukinumab, placebo, or EU-etanercept experienced similar or lower incidence rates of major adverse cardiovascular events, cardio-cerebrovascular events, infections and infestations, and malignant and unspecified tumors. Secukinumab subjects exhibited higher incidence rates of hypersensitivity than placebo, as well as higher rates of exacerbation of Crohn's disease and neutropenia, but the rates were low. The incidence rates for these adverse events for secukinumab 300 mg (n=1410), secukinumab 150 mg (n=1395), placebo (n=793), and EU-etanercept (323) groups, respectively, were as follows:[14]

- 1.4, 1.3, 0, and 1.7 per 100 patient-years for neutropenia
- 0, 0.2, 0, and 0 per 100 patient-years for Crohn's disease
- 12, 10.7, 4.5, and 9.7 per 100 patient-years for hypersensitivity

For the 12-week pooled analysis of four phase 3 trials, adverse events reported by ≥1% of subjects receiving secukinumab 300 mg (n=691), secukinumab 150 mg (n=692), and placebo included nasopharyngitis, diarrhea, upper respiratory tract infection, rhinitis, oral herpes, pharyngitis, urticaria, and rhinorrhea (see Appendix 1 for percentages). Infections were reported in 28.7% of 1382 subjects receiving secukinumab versus 18.9% of 694 subjects receiving placebo, with 0.14% and 0.3% of subjects having serious infections, respectively. Over the entire treatment period of up to 52 weeks, infections were reported in 47.5% of the 3430 subjects receiving any dose of secukinumab, with serious infections reported in 1.2% of subjects. Therefore, caution and monitoring are advised when prescribing the drug to patients with chronic or history of recurrent infection; pre-treatment screening for TB is required; and live vaccinations should not be given to patients taking the drug. Three of the 3430 subjects experienced exacerbation of Crohn's disease. Therefore, caution and monitoring are advised in prescribing the drug to patients with active Crohn's disease. Although neutropenia occurred at a greater rate in subjects receiving secukinumab, the labeling provides no precautions or warnings with regard to neutropenia, because the neutropenia was transient and reversible and those few neutropenic incidents associated with infections were not serious infections.[15, 14]

For the 12-week and 52-week pooled safety sets, adverse events causing discontinuation were about 1% and 3%, respectively, for the secukinumab groups combined (n=1382); about 1% and 1%, respectively, for the placebo group; and about 2% and 4%, respectively, for the EU-etanercept group (n=323).[14]

Unanswered safety questions include the following:

- What are the potential interactions between secukinumab and other drugs? These have not been explored, though significant drug interactions between mAbs and low molecular weight drugs are considered unlikely.

- What are the long-term risks of secukinumab use, particularly for infection, autoimmune disease, malignancy, and cardiovascular and cerebrovascular diseases? Psoriasis is a chronic disease for which secukinumab would be used to control symptoms but not cure the disease.

Look-alike / Sound-alike Error Risk Potential: None

Pharmacology and Pharmacokinetic Properties:[15]

Parameter	
Mechanism of Action	Secukinumab, a human IgG1 monoclonal antibody, inhibits the release of pro-inflammatory cytokines and chemokines by selectively binding to IL-17A, thereby inhibiting IL-17A's interaction with the IL-17 receptor. Psoriatic plaques contain elevated levels of IL-17A, which is a naturally occurring cytokine involved in normal inflammatory and immune responses.
Bioavailability	55% to 77% following a single 150 mg dose or 300 mg dose
Distribution and Protein Binding	Volume of distribution following single intravenous dose: 7.10 to 8.60 L; protein binding not reported
Elimination	Not characterized
Half-Life	22 to 31 days
Metabolism	Not characterized

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Percent who achieve PASI 75
2) Percent who achieve a validated Investigators Global Assessment of clear or almost clear
3) Percent who achieve DLQI 0 or 1

Co-primary Study Endpoints:
1) Percent who achieve PASI 75
2) Percent who achieve mIGA 0 or 1

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR (%)/ NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. ERASURE[16, 14] June 2011 to April 2013 88 sites MC, Randomized, DB, PC, phase 3	Drug regimen 1. SEC SC 300 mg 2. SEC SC 150 mg 3. PLA Duration Induction period: 12 weeks	Demographics: 1, 2, 3, respectively • Age (yr): 45, 45, 45 • Male (%): 69, 69, 69 • Race (%) White: 70, 70, 71 Asian: 21, 22, 19 • Time since diagnosis (yr): 17, 18, 17 • PASI score: 23, 22, 21 • BSA involved: 33, 33, 30 • mIGA score (%): 3: 63, 66, 61 4: 37, 34, 39 Key Inclusion Criteria: • ≥18 years old • Moderate to severe plaque psoriasis diagnosed ≥6 months before randomization and poorly controlled with topical treatment, phototherapy, systemic therapy • PASI score ≥12 • mIGA score 3 or 4 • BSA involved ≥10% Key Exclusion Criteria: • Other forms of	ITT induction 1. 245 2. 245 3. 248 Attrition induction 1. 7 2. 15 3. 16	Co-primary endpoints: % PASI 75 at week 12: 1. SEC 300 mg: 81.6 2. SEC 150 mg: 71.6 3. PLA: 4.5 (p<0.001 for both) % mIGA 0 or 1 at week 12: 1. SEC 300 mg: 65.3 2. SEC 150 mg: 51.2 3. PLA: 2.4 (p<0.001 for both) Key secondary endpoints: % PASI 90 at week 12: 1. SEC 300 mg: 59.2 2. SEC 150 mg: 39.1 3. PLA: 1.2 (p<0.001 for both) % DLQI 0 or 1 at week 12: 1. SEC 300 mg: 58.8 2. SEC 150 mg: 46.1 3. PLA: 10.3 (p<0.001 for both)	77/2 67/2 63/2 49/2 58/2 38/3 49/2 36/3	% SAE at week 12: 1. SEC 300 mg: 2.4 2. SEC 150 mg: 1.6 3. PLA: 1.6 % Infections and infestations at week 12: 1. SEC 300 mg: 29.4 2. SEC 150 mg: 26.9 3. PLA: 16.2 % Discontinuation due to AE at 12 weeks: 1. SEC 300 mg: 1.2 2. SEC 150 mg: 2 3. PLA: 1.6	1/125 NA 13/8 11/9 NA 0.4/3	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: Nothing notable Performance: Nothing notable Detection: Nothing notable Attrition: Week 0 to 12 attrition: 3% SEC 300 mg, 6% SEC 150 mg, and 6% PLA. **Applicability**: Patient: The patients are similar to what will be seen in practice. Intervention: The duration of the study was short. The efficacy, effectiveness, or both could decline with longer-term use. Comparator: Nothing notable Outcomes: mIGA is not a validated tool Setting: The number of patients per center was small, making it difficult to assess drug effectiveness in any particular setting. **Analysis**: ERASURE provides good quality evidence for the efficacy of SEC over PLA for the co-primary endpoints and for the PASI 90 and DLQI secondary endpoints for the 12-week induction phase.

		psoriasis • Use of drugs that may confound efficacy (topical, photo-, biologic, systemic therapies; live virus vaccinations) • Active systemic infection or malignancy or history of malignancy in previous 5 years • Active TB • History of HIV, HVB, or HCV • Underlying immunocompro-mising conditions • Pregnancy, nursing, childbearing women without contraception • SCr>2 mg/dL, WBC>2500/µL, platelets >100K/µL, neutrophils <1500/µL						

2. FIXTURE[16, 14] June 2011 to June 2013 231 sites MC, Randomized, DB, PC, phase 3	Drug regimen 1. SEC SC 300 mg 2. SEC SC 150 mg 3. PLA 4. EUE Duration Induction period: 12 weeks	Demographics: 1, 2, 3, 4, respectively • Age (yr): 45, 45, 44, 44 • Male (%): 69, 72, 71, 73 • Race (%) White: 69, 67, 67, 67 Asian: 22, 22, 23, 22 • Time since diagnosis (yr): 16, 17, 16, 17 • PASI score: 24, 24, 23, 24 • BSA involved: 34, 35, 34, 35 • mIGA score (%): 3: 62, 63, 60, 62 4: 38, 37, 40, 38 • No response to prior TNF inhibitor use (%): 3, 3, 3, 1 Key Inclusion Criteria: Same as ERASURE Key Exclusion Criteria: Same as ERASURE and no prior use of etanercept	ITT induction 1. 327 2. 327 3. 326 4. 326 Attrition induction 1. 15 2. 12 3. 21 4. 25	Co-primary endpoints: %PASI 75 at week 12: 1. SEC 300 mg: 77.1 2. SEC 150 mg: 67 3. EUE: 44 4. PLA: 4.9 (p<0.001 for SEC vs PLA and SEC vs EUE) % mIGA 0 or 1 at week 12: 1. SEC 300 mg: 62.5 2. SEC 150 mg: 51.1 3. EUE: 27.2 4. PLA: 2.8 (p<0.001 for SEC vs PLA and SEC vs EUE) Key secondary endpoints: % PASI 90 at week 12: 1. SEC 300 mg: 54.2 2. SEC 150 mg: 41.9 3. EUE: 20.7 4. PLA: 1.5 (p<0.001 for SEC vs PLA and SEC vs EUE) % DLQI at week 12: 1. SEC 300 mg: 56.7 2. SEC 150 mg: 50.6 3. EUE: 34.5 4. PLA: 6.6 (p<0.001 for SEC vs PLA and SEC vs EUE)	72/2 PLA 33/3 EUE 62/2 PLA 23/4 EUE 60/2 PLA 35/3 EUE 48/2 PLA 24/4 EUE 53/2 PLA 34/3 EUE 40/3 PLA 21/5 EUE 50/2 PLA 22/5 EUE 44/2 PLA 16/6 EUE	% SAE at week 12: 1. SEC 300 mg: 1.2 2. SEC 150 mg: 2.1 3. EUE: 0.9 4. PLA: 1.8% % Infections and infestations at week 12: 1. SEC 300 mg: 26.7 2. SEC 150 mg: 30.9 3. EUE: 24.5 4. PLA: 19.3 % Discontinuation due to AE at week 12: 1. SEC 300 mg: 1.2 2. SEC 150 mg: 0.6 3. EUE: 1.8 4. PLA: 0.6	NA PLA NA EUE NA PLA NA EUE 7/14 2/45 12/9 6/16 1/167 NA NA NA	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: Nothing notable Performance: Nothing notable Detection: Nothing notable Attrition: Week 0 to 12 attrition: 5% SEC 300 mg, 4% SEC 150 mg, 6% EUC, 8% PLA. **Applicability**: Patient: The patients are similar to what will be seen in practice. Intervention: The duration of the study was short. The efficacy, effectiveness, or both could decline with longer-term use. Comparator: Etanercept is EU sourced, so may not reflect SEC efficacy versus US-sourced etanercept Outcomes: mIGA is not a validated tool Setting: The number of patients per center was small, making it difficult to assess drug effectiveness in any particular setting. **Analysis**: FIXTURE provides good quality evidence for the efficacy of SEC over PLA for the co-primary endpoints and for the PASI 90 and DLQI secondary endpoints for the 12-week induction phase. Data related to EUE must be viewed cautiously, because this product is investigational in the US.

Abbreviations [alphabetical order]: AE = adverse events; ARR = absolute risk reduction; BSA = body surface area; CI = confidence interval; EUE = European Union-sourced etanercept; HR = hazard ratio; ITT = intention to treat; MACE = major adverse cardiovascular event; mIGA = modified investigator's global assessment with 0=clear, 1=almost clear, 2=mild disease, 3=moderate disease, 4=severe disease; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PASI = psoriasis area and severity index on a scale of 0 to 72 with higher scores indicating more severe disease; PASI 75 = a reduction of ≥75% in baseline PASI score; PP = per protocol; PLA = placebo; SC = subcutaneous; SAE = serious adverse events; SEC = secukinumab; TNF = tumor necrosis factors; US =United States

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Appendix 1: Highlights of Prescribing Information and Adverse Reactions [15]

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

COSENTYX™ (secukinumab) injection, for subcutaneous use
COSENTYX™ (secukinumab) for injection, for subcutaneous use
Initial U.S. Approval: 2015

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

COSENTYX is a human interleukin-IL-17A antagonist indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. (1)

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

- Recommended dose is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4 followed by 300 mg every 4 weeks. For some patients, a dose of 150 mg may be acceptable. (2.1)
- See Full Prescribing Information for preparation of the Sensoready® pen and prefilled syringe. (2.3)
- Reconstitute COSENTYX lyophilized powder in a vial with Sterile Water for Injection. Reconstitution should be performed by a healthcare provider. (2.4)

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

- Injection: 150 mg/mL solution in a single-use Sensoready® pen (3)
- Injection: 150 mg/mL solution in a single-use prefilled syringe (3)
- For Injection: 150 mg, lyophilized powder in a single-use vial for reconstitution for healthcare professional use only (3)

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

Serious hypersensitivity reaction to secukinumab or to any of the excipients. (4)

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

- Infections: Serious infections have occurred. Caution should be exercised when considering the use of COSENTYX in patients with a chronic infection or a history of recurrent infection. If a serious infection develops, discontinue COSENTYX until the infection resolves. (5.1)
- Tuberculosis (TB): Prior to initiating treatment with COSENTYX, evaluate for TB. (5.2)
- Crohn's Disease: Exacerbations observed in clinical trials. Caution should be exercised when prescribing COSENTYX to patients with active Crohn's disease. (5.3)
- Hypersensitivity Reactions: If an anaphylactic reaction or other serious allergic reaction occurs, discontinue COSENTYX immediately and initiate appropriate therapy. (5.4)

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

Most common adverse reactions (> 1%) are nasopharyngitis, diarrhea, and upper respiratory tract infection. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Live Vaccines: Live vaccines should not be given with COSENTYX. (5.6, 7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2015

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Table 1 Adverse Reactions Reported by Greater Than 1% of Subjects with Plaque Psoriasis Through Week 12 in Trials 1, 2, 3 and 4

Adverse Reactions	COSENTYX		Placebo (N=694) n (%)
	300 mg (N=691) n (%)	150 mg (N=692) n (%)	
Nasopharyngitis	79 (11.4)	85 (12.3)	60 (8.6)
Diarrhea	28 (4.1)	18 (2.6)	10 (1.4)
Upper respiratory tract infection	17 (2.5)	22 (3.2)	5 (0.7)
Rhinitis	10 (1.4)	10 (1.4)	5 (0.7)
Oral herpes	9 (1.3)	1 (0.1)	2 (0.3)
Pharyngitis	8 (1.2)	7 (1.0)	0 (0)
Urticaria	4 (0.6)	8 (1.2)	1 (0.1)
Rhinorrhea	8 (1.2)	2 (0.3)	1 (0.1)

Biologicals for RA, Psoriasis, or Crohn's Disease

Goal(s):

- Cover biologicals according to OHP list guidelines.
- Promote use that is consistent with National Guidelines and medical evidence.
- Promote use of high value products.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Generic Name	Trade Name	Indication
Abatacept	Orencia	RA, juvenile RA, juvenile idiopathic arthritis
Adalimumab	Humira	RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, Crohn's disease, plaque psoriasis, ulcerative colitis
Anakinra	Kineret	RA
Apremilast	Otezla	Psoriatic arthritis, plaque psoriasis
Certolizumab	Cimzia	RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis
Etanercept	Enbrel	RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, plaque psoriasis
Golimumab	Simponi	RA, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis
Infliximab*	Remicade	RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, plaque psoriasis
Natalizumab*	Tysabri	Crohn's disease, multiple sclerosis
Rituximab*	Rituxan	RA, CLL, Wegnener granulomatosis, Microscopic polyangiitis, non-Hodgkin lymphoma
Secukinumab	Cosentyx	Plaque psoriasis
Tocilizumab*	Actemra	RA, juvenile idiopathic arthritis
Tofacitinib	Xeljanz	RA
Ustekinumab	Stelara	Plaque psoriasis, psoriatic arthritis
Vedolizumab	Entyvio	Ulcerative colitis, Crohn's disease

Abbreviations: CLL: chronic lymphocytic leukemia; RA: rheumatoid arthritis

* Must be billed via HCPC J-code and payment requires trial of preferred self-administered drug first.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis covered by OHP?	**Yes:** Go to #3	**No:** Pass to RPH; Deny for medical appropriateness.

Approval Criteria		
3. Will the provider change to a preferred product?	**Yes:** Inform provider of covered alternatives in class.	**No:** Go to #4.
4. Is the diagnosis chronic plaque psoriasis (ICD-9: 696.1-696.2, 696.8) and the product requested FDA approved for psoriasis (see table above)? * Moderate/Severe psoriasis treatments are covered by the OHP	**Yes:** ~~Refer to anti-psoriatic PA Criteria~~ Go to #5	No: Go to #7. Note: Seborrheic dermatitis (690.XX), keroderma (701.1-701.3) or other hypertrophic and atrophic conditions of skin (701.8, 701.9) are not covered by OHP?
5. Is the Psoriasis Moderate/Severe? Defined as functional impairment and one or more of the following: • At least 10% body surface area involved or with functional impairment? • Hand, foot or mucous membrane involvement	**Yes:** Go to #6.	**No:** Pass to RPh; deny, not covered by the OHP.
6. Has the patient tried and not had an adequate response to standard systemic therapies or has a contraindication to ALL of the following: • High-potency topical corticosteroids (betamethasone dipropionate, clobetasol, fluocinonide) • At least one other topical agent (calcipotriene, tazarotene, anthralin) • At least one other systemic therapy: cyclosporine, methotrexate or acitretin	**Yes**: Approve for length of treatment; maximum 1 year.	**No:** Pass to RPh; deny for medical appropriateness.
~~5.~~7. Is the diagnosis ankylosing spondylitis (ICD-9 720) and the product requested is FDA approved for ankylosing spondylitis?	**Yes:** Approve treatment for up to 1 year.	**No:** Go to #8.
~~6.~~8. Is the diagnosis rheumatoid arthritis (ICD-9 714.xx) or psoriatic arthropathy (ICD-9 696.0) and the product requested FDA approved for rheumatoid arthritis (see table above)?	**Yes:** Go to #9.	**No:** Go to #12.

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Approval Criteria		
~~7.~~9. Has the patient had a trial and inadequate response to methotrexate or other first line DMARDs (leflunomide, sulfasalazine, hydroxychloroquine, penicillamine) and a disease duration of ≥6 months? **OR** An intolerance or contraindication to oral DMARDs?	**Yes:** Go to #10.	No: Pass to RPh; deny for medical appropriateness.
~~8.~~10. Is the request for tofacitinib?	**Yes:** Go to #11.	**No:** Approve treatment for up to 1 year.
~~9.~~11. Has the patient had a trial and inadequate response or intolerance to 1 or more biologic TIM (Humira, Enbrel, Cimzia, Simponi,Orencia)?	**Yes:** Approve treatment for up to 1 year.	**No:** Pass to RPh; deny for medical appropriateness.
~~10.~~12. Is the diagnosis Crohn's disease (ICD-9 555) or ulcerative colitis (ICD-9 556.0-556.9) and the product requested FDA approved for the indication (see table above)?	**Yes:** Go to #13.	**No:** Pas to RPh; deny for medical appropriateness.
~~11.~~13. Has the patient had a trial and inadequate response to conventional therapy including immunosuppressive therapy (mercaptopurine, azathioprine) and/or corticosteroid treatments? **OR**~~,~~ Has an intolerance or contraindication~~s~~ to conventional therapy?	**Yes:** Approve treatment for up to 1 year.	**No:** Pass to RPh; deny for medical appropriateness.

P&T/DUR Review: *7/15; 9/14; 8/12*
Implementation: *TBD; 9/27/14; 2/21/13*

Topical Antipsoriasis Drugs

Goal(s):

- Cover topical antipsoriasis drugs only for covered OHP diagnoses. Moderate/Severe psoriasis treatments are covered on the OHP. Treatments for mild psoriasis (696.1-696.2, 696.8), seborrheic dermatitis (690.XX), keroderma (701.1-701.3) and other hypertrophic and atrophic conditions of skin (701.8, 701.9) are not covered.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs
- TC = 92 and HIC = L1A, L5F, L9D, T0A

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis for seborrheic dermatitis (690.XX), keroderma (701.1-701.3) or other hypertrophic and atrophic conditions of skin (701.8, 701.9)?	**Yes:** Pass to RPh; deny, not covered by the OHP.	**No:** Go to #3.
3. Is the diagnosis Psoriasis? (ICD-9: 696.1-696.2, 696.8)	**Yes:** Go to #4.	**No:** Go to #7.
4. Is the Psoriasis Moderate/Severe? Defined as: • At least 10% body surface area involved or with functional impairment? • Hand, foot or mucous membrane involvement	**Yes:** Go to #5.	**No:** Pass to RPh; deny, not covered by the OHP.
~~5. Is the product requested a non-preferred biologic agent approved for plaque psoriasis?~~	~~**Yes:** Go to #6.~~	~~**No:** Go to #7.~~
~~6. Has the patient tried and not had an adequate response to standard systemic therapies, including cyclosporine or methotrexate or acitretin, or the person is intolerant of or has a contraindication to these treatments?~~	~~**Yes**: Approve for length of treatment; maximum 1 year.~~	~~**No:** Pass to RPH. Deny for medical appropriateness.~~

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Approval Criteria		
5. Is the product requested preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #6.
6. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives. Approve for length of treatment; maximum 1 year.	**No:** Approve for length of treatment; maximum 1 year.
7. RPH only: All other indications need to be evaluated as to whether they are above the line or below the line diagnosis.	**If above the line or clinic provides supporting literature:** approve for length of treatment.	**If below the line:** Deny, not funded by the OHP.

P&T/DUR Review: *7/15; 1/15; 09/10; 9/09; 3/09; 5/07; 2/06*
Implementation: *TBD; 9/13; 6/12; 9/10; 1/10; 7/09; 6/07; 9/06*

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

New Drug Evaluation: Pirfenidone capsules, oral

Month/Year of Review: July 2015
Generic Name: Pirfenidone
PDL Class: Pulmonary Fibrosis

End Date of Literature Search: January 2015
Brand Name (Manufacturer): Esbriet™ (Genentech)
Dossier Received: No

Research Questions:

- Is there evidence of efficacy for pirfenidone in the treatment of idiopathic pulmonary fibrosis (IPF) as demonstrated by clinical improvement in outcomes such mortality, functional status (e.g., exercise tolerance), quality of life or symptoms (e.g., acute exacerbations)? If so, is there direct comparative evidence with other treatments for IPF?
- Is there evidence of acceptable adverse effects for pirfenidone in comparison to other treatments for IPF?
- Are there subgroups of patients that may receive greater benefit or harm from pirfenidone therapy?

Conclusions and Recommendations:

- Studies used for approval of pirfenidone were the CAPACITY studies (004 and 006) and the ASCEND trial.[1-2] There is low to moderate strength of evidence that pirfenidone slows decline of percent-predicted forced vital capacity (FVC) relative to placebo. CAPACITY study 004 demonstrated a significant benefit in the primary efficacy endpoint of change in percent-predicted FVC from baseline to week 72 with pirfenidone 2,403 mg/day (-8.0%) compared to placebo (-12.4%) with an absolute difference of 4.4% (95% CI, 0.7% to 9.1%; p=0.001).[1] However, a subsequent study (CAPACITY study 006) did not demonstrate improvement with pirfenidone treatment, prompting the FDA to require the ASCEND trial.[1,2] In the ASCEND trial, the magnitude of treatment effect was estimated by comparing the distribution of patients in the pirfenidone group with those in the placebo group across two thresholds of change at week 52: a composite outcome of absolute ≥10% decline in percent-predicted FVC or death (pirfenidone 16.5% vs. placebo 31.8%; p<0.001; NNT of 7 for 1 year), or no decline in the percent-predicted FVC (pirfenidone 22.7% vs. placebo 9.7%; p<0.000001; NNT of 8 for 1 year).[2]
- There is low quality evidence that pirfenidone may reduce mortality in patients with IPF. There was a consistent but non-significant trend in decreased mortality in all Phase 3 trials that appeared to correlate with slower decline in FVC. Pooled 72-week trial data from two Phase 3 trials and 52-week data from another Phase 3 trial (n=1,247) demonstrated a trend in decreased all-cause mortality favoring pirfenidone relative to placebo (hazard ratio [HR] 0.69, 95% CI, 0.46 to 1.05, p=0.08).
- There is insufficient quality evidence that pirfenidone improves progression-free survival when it is defined as a composite endpoint of ≥10% decline in percent-predicted FVC, ≥15% decline in percent-predicted DLco, or death. The CAPACITY studies had conflicting results but the favorable trend in this composite outcome was primarily driven by decreased decline in FVC compared to placebo (HR 0.64, 95% CI, 0.44 to 0.95; p=0.023). In the ASCEND trial, 52% of patients in the pirfenidone group compared to 41% in the placebo group achieved progressive-free survival at week 52 (HR 0.57; 95% CI, 0.43 to 0.77;

p<0.001), which was alternatively defined as the time to first occurrence of any of the following: a decrease of 10% or more in predicted FVC, a decrease in 50 m or more in 6MWT or death. [1,2]

- There is low quality evidence that pirfenidone slows decline in the 6-minute walk test (6MWT) relative to placebo.[1,2] The absolute difference from placebo ranged from 16-32 meters (52.5 to 105 feet, or 17.5 to 35 yards), but it is unclear whether this is a clinically meaningful difference.[1,2]
- There is low quality evidence that pirfenidone does not improve dyspnea scores over 52 to 72 weeks compared to placebo.
- There are no head-to-head studies and therefore insufficient evidence to compare other treatments for IPF to pirfenidone. Patients in the clinical trials received pirfenidone as monotherapy and did not take concomitant treatment for IPF.
- There is moderate quality evidence pirfenidone commonly causes gastrointestinal-related adverse effects, as well as dermatologic photosensitivity reactions or rash.[3] Patients discontinued pirfenidone due to adverse reactions at a higher rate compared to placebo (14.6% vs. 9.6%, respectively). Discontinuations were primarily due to rash/photosensitivity and nausea.[3] Elevated liver enzymes (AST/ALT) were more common with pirfenidone compared to placebo and will require monitoring and may require dose reduction or interruption of pirfenidone therapy in affected patients.
- Recommend requiring a prior authorization for pirfenidone to assure appropriate utilization.

Background:

Idiopathic pulmonary fibrosis is a type of fibrosing interstitial pneumonia originally thought to be due to chronic inflammation. More recently abnormal wound healing has been implicated in the pathogenesis. In most IPF cases the etiology is unknown; however a link to cigarette smoking and environmental factors has been described. Familial pulmonary fibrosis accounts for less than 5% of IPF cases and genetic factors have been seen in sporadic cases of IPF.[4] IPF is chronic, progressive and unpredictable with a median survival rate of 2-3 years after diagnosis. Estimates of prevalence range from 2-29 cases per 100,000 in the population at large.[4] IPF is usually diagnosed between the ages of 40-70 years and is slightly more common in men than women. The diagnosis of IPF requires a detailed patient history to rule out other interstitial lung diseases. Most patients can be diagnosed based upon a specific interstitial pneumonia pattern seen on high-resolution computerized tomography (HRCT) of the chest. Patients may also be diagnosed by a specific combination of HRCT and surgical lung biopsy pattern.[4] Common symptoms of IPF are: chronic exertional dyspnea, cough, bibasilar inspiratory crackles and finger clubbing.[4] Staging of IPF is not currently used in practice to direct clinical decision making and there are no corresponding changes in percent-predicted FCV associated with different stages.[4] Indicators of disease progression are worsening respiratory symptoms, declining pulmonary function tests and acute respiratory decline.

Mortality is the most relevant endpoint for IPF studies and is the ideal endpoint for assessing efficacy of IPF therapy[5] Other clinically meaningful outcomes include acute exacerbation of IPF (usually measured by worsening dyspnea), all-cause non-elective hospitalizations and quality of life.[6] However, endpoints commonly studied in clinical trials include FVC and diffusion capacity for carbon monoxide (DLco) as a surrogate endpoint for lung function; 6-minute-walk test (6MWT) as a surrogate endpoint for functional status; HRCT imaging features; and biomarkers.[6,7] There is no consensus on the most appropriate surrogate outcomes to be used in IPF trials and there are no validated surrogate endpoints.[6] Further, it is uncertain what magnitude of difference for FVC or 6MWT constitutes a clinically meaningful change for patients with IPF.[5] Progression-free survival, usually assessed by combining decline in FVC and death, is a composite endpoint used in some IPF trials. The World Health Organization – Quality of Life Questionnaire (WHO-QoL) and St. George's Hospital Respiratory Questionnaire (SGRQ), which measure distress due to respiratory symptoms, are also used to measure the impact of IPF on patients' quality of life.

Multiple features have been identified with increased mortality in IPF patients (Table 1).[5] Predictors of disease progression and mortality have been demonstrated with FVC changes. Decreased survival rates have been associated with declining FVC rates of 5-10% or more, and a sign of disease progression is indicated by a decrease in FVC of ≥10%.[4,6,9] Limited evidence suggests that small decreases in FVC (5-10%) is associated with poor outcomes. A decline in the 6MWT has also been correlated with increased mortality in patients with IPF.[9] Retrospective cohort studies have suggested a decline of 30 meters (m) in the

6MWT to be a clinically meaningful threshold.[6] Standards in conducting the 6MWT are lacking, making interpretation of this test result difficult, though it is thought to be a robust indicator of functional exercise capacity.[6,11]

The joint American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) evidence-based guideline on the diagnosis and management of IPF was updated in 2011.[4] Treatment recommendations and corresponding evidence designation, using the GRADE methodology, is presented in table 2. A wide range of medical therapies for IPF have been explored but none have clearly demonstrated a clinical benefit in IPF. A Cochrane review found no randomized controlled trials (RCTs) to assess the benefits of corticosteroid monotherapy in patients with IPF.[12] Observational cohort studies have failed to find a mortality benefit in patients treated with corticosteroids.[12] Treatment with azathioprine and prednisone has been studied in patients with IPF without demonstrating definitive benefits and is not currently recommended. Cyclophosphamide treatment in IPF has failed to show mortality benefits and is also not recommended. The use of everolimus failed to show improved efficacy in patients with IPF and may cause harm. A study of anticoagulant use in patients with IPF was discontinued early due to excess deaths in the warfarin group with a low probability of benefit from treatment.[14] Bosentan was studied in patients with IPF in the BUILD-1 and BUILD-3 trials but was not shown to improve outcomes and is therefore not recommended.[15,16] Ambrisentan, macitentan, sildenafil, interferon-gamma, etanercept and imatinib have been studied in IPF patients without benefit. The ATS/ERS/JRS/ALAT guideline weakly recommends against the use of pirfenidone but suggests it could be considered an option for patients who realize the expected benefits are small and there are risks of adverse reactions (ASCEND results not included in guideline).[4] The use of pirfenidone in IPF is weakly recommended by the Spanish Society of Pneumology and Thoracic Surgery (SEPAR).[17] French practical guidelines and National Institute for Health and Care Excellence (NICE) recommend pirfenidone in patients with mild to moderate IPF (FVC ≥50%).[18,19] The only treatment shown to improve survival in IPF patients is lung transplantation.[4] Pirfenidone and nintedanib are currently the only drugs approved by the FDA for IPF, with the evidence for their use presented below.

Table 1. ATS/ERS/JRS/ALAT Statement on Selected Features Associated with Increased Risk of Mortality in IPF.[8]

Baseline Factors	**Longitudinal Factors**
Level of dyspnea	Decrease in FVC ≥10% absolute value
DLco <40% predicted	Decrease in DLco by ≥15% absolute value
Desaturation ≤88% during 6MWT	Worsening of fibrosis on HRCT
Extent of honeycombing on HRCT	
Pulmonary hypertension	
Definitions of abbreviations: 6MWT= 6-minute walk-test; DLco = diffusion capacity for carbon monoxide; HRCT = high-resolution computer tomography.	

Raghu G, Collard H, Egan J, et al. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guideline for Diagnosis and Management. Am J Respir Crit Care Med 2011;183:788-824.

Table 2. ATS/ERS/JRS/ALAT Treatment Recommendations.[4]

	Treatment	Evidence Grade
Recommendation AGAINST the use of treatment in IPF is STRONG	Corticosteroid Monotherapy	Very low
	Colchicine	Very low
	Cyclosporine A	Very low
	Combined corticosteroid and immune-modulator therapy	Low
	Interferon γ 1b	High
	Bosentan	Moderate
	Etanercept	Moderate
Recommendation AGAINST the use of treatment in IPF is weak	Combined acetylcysteine and azathioprine and prednisone	Low
	Acetylcysteine monotherapy	Low
	Anticoagulation	Very low
	Pirfenidone	Low
Recommendation for therapy in IPF patients is STRONG	Long-term oxygen therapy	Very low
Recommendation for procedure in IPF patients is STRONG	Lung transplantation	Very low
Recommendation AGAINST procedure in patients with respiratory failure due to IPF is WEAK	Mechanical ventilation	Low
Recommendation for procedure in IPF patients is WEAK	Pulmonary rehabilitation	Low
Recommendation for therapy in IPF patients with acute exacerbations is WEAK	Corticosteroids	Very low
Recommendation AGAINST the treatment of associated IPF conditions is WEAK	Pulmonary hypertension	Very low
Recommendation for therapy in IPF patients is WEAK	Asymptomatic gastroesophageal reflux	Very low

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

Clinical Efficacy:

Pirfenidone was initially studied in a Phase 3, double-blind, randomized, controlled trial of 275 Japanese patients with mild IPF assessing pirfenidone 600 mg three times daily, pirfenidone 400 mg three times daily or placebo.[20] Study enrollment was dependent upon desaturation results using the 6MWT, which is a measure that has not been validated in IPF. There were also less current smokers in the high dose pirfenidone group (4.6%) compared to placebo (12.5%). Both doses of pirfenidone were superior to placebo for the primary endpoint of change in VC from baseline to week 52 (-90 mL, -80 mL and -160 mL, respectively). Progression of disease, as indicated by VC, was low in all groups with decline ranging from 3-6% from baseline assessment. Progression-free survival, defined as death or ≥10% decline in VC from baseline, was only statistically significant between the high dose pirfenidone group compared to placebo (p=0.0280).[19]

In the U.S., the FDA approved pirfenidone based on two of three randomized clinical trials demonstrating efficacy of improved FVC with consistent numerical trends in improved all-cause mortality compared to placebo in mild to moderate IPF patients.

The first two trials were CAPACITY 004 and CAPACITY 006, which were identical double-blind, placebo-controlled, randomized trials of 72 weeks' duration.[1] In study 004, 435 IPF patients 40-80 years of age were randomized in a 2:1:2 ratio to pirfenidone 801 mg three times daily, pirfenidone 399 mg three times daily (used as a reference only) or placebo.[1] Study 006 included 344 patients randomized in a 1:1 ratio to pirfenidone 801 mg three times daily or placebo.[1] In both trials, pirfenidone was given in three divided doses with food and titrated over 2 weeks. Patient populations were similar with the majority of patients being

white males with mild to moderate IPF and few comorbidities or concomitant lung disorders. Patients in study 006 had a shorter baseline walk distance and higher utilization of supplemental oxygen compared to study 004; however, baseline percent predicted FVCs were similar. Other IPF treatments were prohibited, though immunosuppressant drugs were briefly allowed for acute exacerbations of IPF, acute respiratory decompensation or progression of IPF. In both trials, the primary endpoint was absolute change in percent-predicted FVC from baseline to week 72. Key secondary endpoints included: time to worsening of IPF (defined as time to acute IPF exacerbation, IPF-related death, lung transplantation, or respiratory hospitalization, whichever came first), change in progressive-free survival (defined as time to first occurrence of either: ≥10% absolute decline in percent-predicted FVC, or ≥15% absolute decline in percent-predicted DLco, or death), change in dyspnea, and change in 6MWT, all analyzed from baseline to week 72. All-cause mortality and IPF-associated mortality were exploratory endpoints.

In study 004, pirfenidone reduced decline in percent-predicted FVC compared to placebo by -8.0% and -12.4%, respectively, which was a statistically significant difference.[1] The clinical significance of this difference is unknown, though a decline in FVC greater than 10% has been associated with disease progression and increased mortality.[4,5,8] There were significantly less patients who experienced a percent-predicted decline in FVC ≥10% compared to placebo (NNT of 7 for 72 weeks). Pirfenidone was associated with an increase in progression-free survival, a composite endpoint of ≥10% decline in percent-predicted FVC, ≥15% decline in percent-predicted DLco, or death, which was primarily driven by decline in FVC, compared to placebo (HR 0.64, 95% CI, 0.44 to 0.95; p=0.023). However, changes in dyspnea scores and the 6MWT were not statistically different between pirfenidone and placebo.

Study 006 did not yield results consistent with study 004 despite enrolling similar patients and using the same methodology. There was no statistically significant difference in the primary endpoint of mean change of percent-predicted FVC at week 72 between pirfenidone (-9.0%) and placebo (-9.6%).[1] The number of patients with a categorical change in ≥10% percent-predicted FVC and difference in progression-free survival were also not significantly different between the pirfenidone and placebo groups. The only key secondary endpoint that favored pirfenidone was an improved 6MWT of 32 m (105 feet, or 35 yards) at week 72 compared to placebo (p=0.0009).

If the primary efficacy analyses from both study 004 and study 006 each showed efficacy, then the secondary outcome variables were to be analyzed using pooled data from both studies.[5]However, because that was not achieved, the pooled data will not be presented. Still, it is important to note exploratory analyses of pooled overall all-cause mortality data and mortality due to IPF showed a beneficial trend with pirfenidone, though pooling the data still did not have enough statistical power to demonstrate a significant difference from placebo.[5]

The FDA required a third clinical trial demonstrating efficacy with pirfenidone before drug approval could be granted, and so the ASCEND trial was conducted.[1,5] The study design of the ASCEND trial was similar to the CAPACITY trials with an important difference in study duration: the ASCEND trial was 52 weeks instead of 72 weeks. Other differences included inclusion of patients with lower percent-predicted DLco, higher FEV1/FVC ratio and longer time since IPF diagnosis.[2] The primary endpoint was similar to the CAPACITY trials, an absolute change in percent predicted FVC from baseline at week 52, but this outcome was rather reported as two distinct measures: 1) a composite of the proportion of patients with an absolute decline of 10% or more in the percent-predicted FVC or death, or 2) the proportion of patients with no decline in the percentage of the predicted FVC. Key secondary endpoints were also similar to the CAPACITY trials.

Pirfenidone was associated with decreased decline in percent-predicted in FVC versus placebo (p<0.001).[3] Decline in percent predicted FVC of ≥10% or death at week 52 was 16.5% for pirfenidone and 31.8% for placebo (p<0.001). However, the difference was largely due to ≥10% decline in FVC. Patients with no decline in percent-predicted FVC was higher in patients treated with pirfenidone compared to placebo with a NNT of 8 over 1 year. The absolute difference of 27 m (88 feet, or 30 yards) in the 6MWT favored pirfenidone, but the clinically meaningful benefit of the result is unclear. Fifty-two percent of patients in the pirfenidone

group compared to 41% in the placebo group achieved progressive-free survival at week 52 (HR 0.57; 95% CI, 0.43 to 0.77; p<0.001), which was defined as the time to first occurrence of any of the following: a decrease of 10% or more in predicted FVC, a decrease in 50 m or more in 6MWT or death.[3]

Mortality is the most relevant endpoint for IPF studies and is the ideal endpoint for assessing efficacy of an IPF therapy.[5] Mortality data in the CAPACITY and ASCEND trials were analyzed in various ways by the drug sponsor and by the FDA.[5] Mortality was evaluated differently between the CAPACITY trials and the ASCEND trial. In the CAPACITY trials, mortality was assessed for about 120 weeks, from the time the first patient was enrolled until the last patient enrolled finished 72 weeks of treatment.[5] All-cause mortality in the CAPACITY trials numerically favored pirfenidone but the difference was not statistically significant (HR 0.85; 95% CI, 0.53 to 1.37; p=0.51). However, when mortality data were pooled and assessed only during the treatment period (i.e., 72 weeks), there was a statistically significant difference in IPF-related mortality that favored pirfenidone (HR 0.45; 95% CI, 0.24 to 0.95).[5] However, the results should be interpreted with caution as it was limited to by assessment while on treatment (typical method to assess mortality as an adverse event), the nature of the post-hoc analysis, and lack of adjudication of cause of death, which resulted in inconsistent analysis of the data.[5] In the ASCEND trial, mortality was only assessed for 52 weeks and cause of death was adjudicated.[5] All-cause mortality benefit also numerically favored pirfenidone but was not statistically demonstrated. When all-cause mortality data were pooled between all Phase 3 trials (72 weeks for the CAPACITY trials and 52 weeks for the ASCEND trial), the trend continued to favor pirfenidone versus placebo, but the sample size was still not large enough to demonstrate a statistically significant difference (HR 0.69; 95% CI, 0.46 to 1.05; p=0.08).[5] However, if pre-specified censoring rules by the drug manufacturer were applied to the data (pooled mortality data of all 3 trials was truncated at 52 weeks), mortality was statistically benefitted pirfenidone versus placebo (3.5% vs. 6.7%, respectively; HR 0.52; 95% CI, 0.31 to 0.87; p=0.01; NNT of 31 for 1 year).[2,5]

Clinical Safety:

The adverse events identified as events of interest in the Phase 3 trials are liver-related adverse events, gastrointestinal adverse events, rash and photosensitivity, dizziness and falls, and carcinogenicity.[5] However, none of these adverse events resulted in death and resolved upon permanent discontinuation of pirfenidone. In the overall safety database, ALT and AST elevations were infrequent, but occurred in a larger proportion of patients on pirfenidone than on placebo. The most common adverse reactions occurring in at least 10% of patients receiving pirfenidone were primarily gastrointestinal or dermatologic in nature. Prominent gastrointestinal adverse events were nausea, gastrointestinal reflux, vomiting and anorexia. Common dermatologic adverse events included rash (30%) and photosensitivity (9%) but there were no cases of Stevens-Johnson syndrome, erythema multiforme or toxic epidermal necrolysis, and no cases were life-threatening or led to hospitalization.[5] Dizziness was also often reported in patients receiving pirfenidone, with 5.4% of cases of dizziness associated with falls.[5] Adverse effects were deemed to be dose-related. Severe adverse reactions were similar in the pooled pirfenidone and placebo groups, 33% and 31%, respectively.[1] Discontinuations due to adverse events was higher in the pirfenidone treated groups compared to placebo, with rates ranging from 14%-20%.[1,2,19] The number of cancers in the studies were balanced across treatment groups, but the studies were too small to exclude a definitive cancer risk and the animal carcinogenicity study was positive for pirfenidone.[5] Common adverse events that occurred at a rate of at least 10% and occurred more commonly than placebo are listed in Table 3.

Table 3. Common Adverse Events Occurring in ≥10% of Pirfenidone-treated Patients and Occurring More Commonly than Placebo in Phase 3 Clinical Trials.[3]

Adverse Event	% of Patients (0 to 118 Weeks)	
	Pirfenidone 2403 mg/day (n=623)	Placebo (n=624)
Nausea	36%	16%
Rash/Photosensitivity	30%	10%
Abdominal Pain	24%	15%
Diarrhea	26%	20%
Fatigue	26%	20%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-esophageal Reflux Disease	11%	7%

Pharmacology and Pharmacokinetic Properties:[3]

Parameter	
Mechanism of Action	In vitro studies show regulation of the activity of transforming growth factor (TGF) β and tumor necrosis factor (TNF) α. Mechanism in IPF is unknown.
Oral Bioavailability	Has not been determined in humans.
Distribution and Protein Binding	Pirfenidone binds to human plasma proteins, primarily to serum albumin. The mean binding at concentrations seen in clinical trials is 58%.
Elimination	80% in the urine
Half-Life	3 hours
Metabolism	Liver by CYP1A2 and multiple other CYP enzymes

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Mortality
2) Hospitalizations
3) Disease Progression (FVC, VC)
4) Functional Status (e.g., exercise tolerance (6MWT)
5) Quality of life
6) Symptom improvement (e.g., acute exacerbations)

Primary Study Endpoint:
1) Change in percent predicted FVC or VC

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity /Applicability
1. Noble, et al. (CAPACITY - 004)[1,5] DB, PG, PC, RCT Phase 3	1. Pirfenidone 801 mg TID (PIR) 2. Pirfenidone 399 mg TID (PIR2) 3. Placebo (P) Randomized 2:1:2 72 weeks	Demographics: Age: 67 years Men: 72% White: 96% Predicted FVC: 76% 6MWT: 413 m Current Smokers: 4% Key Inclusion Criteria: Age 40-80 years; Dx of IPF in previous 48 months; No improvement in disease severity over past year; Predicted FVC ≥50%; Predicted DLco ≥35%; Either predicted FVC or predicted DLco of ≤90%; 6MWT ≥150 m. Key Exclusion Criteria: Concomitant tx for IPF; Obstructive airway disease; Connective tissue disease; Wait list for lung transplant	ITT: 1. 174 2. 87 3. 174 Attrition*: 1. 51 (29%) 2. 22 (25%) 3. 39 (22%) *Excludes death or lung trans-plantation	**Primary Endpoint**: (week 72) Change in %-predicted FVC from baseline: PIR: -8.0% vs. PIR2: -10.2% vs. P: -12.4% PIR vs. P: ARR 4.4% (95% CI, 0.7 to 9.1%; P=0.001) **Key Secondary Endpoints**: (week 72) ≥10% decline %-predicted FVC: PIR 20% vs. P 35% ARR 14.4% (95% CI, 7.4 to 21.3; P=0.001) Progression-free Survival (≥10% decline %-predicted FVC, ≥15% decline %-predicted DLco or death): PIR 138 (79.3%) vs. P 116 (66.7%) HR 0.64 (95% CI, 0.44 to 0.95; p=0.023) Worsening IPF (time to acute exacerbation, death, lung transplant or hospitalization for respiratory problem): PIR (NR) vs. P (NR) HR 0.84 (95% CI, 0.50 to 1.42; p=0.515) Mean change in Dyspnea (UCSD SoBQ, scale 0-120): PIR +12.1 vs. P +15.2 ARR -3.1 (95% CI, -8.5 to 2.3; p=0.509) Mean change in 6MWT: PIR -60.4 m vs. P -76.8 m ARR 16.4 m (95% CI, -10.9 to 43.7 m; p=0.171)	NA 14.4%/7 NA NS NS NS	Serious Adverse Events: PIR: 28% PIR2: 41% P: 28% p-value NR Discontinuations due to adverse effects: PIR: 15% P: 9% Pooled analysis w/ CAPACITY 006; p-value NR Nausea: PIR: 35% PIR2: 25% P: 18% p-value NR Rash: PIR: 31% PIR2: 17% P: 10% p-value NR Photosensitivity: PIR: 14% PIR2: 7% P: 1% AST/ALT 3x ULN: PIR 4.1% P: 0.6% Pooled analysis w/ CAPACITY 006; p-value NR	NA NA NA NA NA	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: Randomized by independent statistician via computer-generated permuted block code and stratified by region; groups allocated via interactive voice response system. Groups well matched. Performance: All personnel involved in the study were masked to group assignment until after final database lock. Detection: States ITT analysis performed; power/sample size calculations not reported; appropriate statistical tests applied; unclear if data assessor blinded. Attrition: Overall attrition high, with higher attrition in PIR group. Imputed missing data as average value, or worst rank outcome for death. **Applicability**: Patients: Patients with mild to moderate IPF; nearly all patients white; 48% diagnosed w/ IPF within last year; 65% were former smokers; 16% required supplemental oxygen; 65% enrolled from U.S. Intervention: The 2403 mg/day regimen based on 1800 mg/day dose used in Japanese studies to the predicted body weight of US citizens. A second regimen of 1197 mg/day only summarized descriptively. PIR dose titrated over 2 weeks. No data on final mean dose of PIR considering dose-adjustments were permitted for intolerance during study. Adherence was high (>80%). Comparator: Placebo control appropriate. Outcomes: Change in FVC is an accepted surrogate endpoint but it is unknown what magnitude of change affects mortality. Significant difference in progression-free survival primarily driven by the criterion of decline in FVC. Post-hoc analysis of pooled data from CAPACITY 006 demonstrated a favorable overall all-cause mortality trend with PIR vs. P (8% vs. 10%; HR 0.77; 95% CI, 0.47 to 1.28; p=0.315) and favorable IPF-related mortality trend with PIR vs. P (5% vs. 8%; HR 0.62; 95% CI, 0.35 to 1.13; p=0.117); no adjudication was performed. Setting: 110 centers in 13 countries (USA n=64). Drug sponsor participated in the study design, data collection, data analysis and writing the report.

2. Noble, et al. (CAPACITY - 006)[1,5] DB, PG, PC, RCT Phase 3	1. Pirfenidone 801 mg TID (PIR) 2. Placebo (P) Randomized 1:1 72 weeks	Demographics: Age: 67 years Men: 72% White: 99% % Predicted FVC: 74% 6MWT: 389 m Current Smokers: PIR 0% vs P 5% Key Inclusion Criteria: See CAPACITY 004 Key Exclusion Criteria: See CAPACITY 004	ITT: 1. 171 2. 173 Attrition*: 1. 47 (27%) 2. 40 (23%) * Excludes death or lung trans-plantation	**Primary Endpoint**: (week 72) Change in %-predicted FVC from baseline: PIR: -9.0% vs. P: -9.6% ARR 0.6% (95% CI, -3.5 to 4.7%; p=0.50) **Key Secondary Endpoints**: (week 72) FCV decline ≥10%: PIR 23% vs. P 27% ARR 3.8% (95% CI, -2.7 to 10.2) P=0.440 Progression-free Survival (time to ≥10% decline in %-predicted FVC, ≥15% decline in %predicted DLco or death): PIR 126 (73.7) vs. P 123 (71.9%) HR 0.84 (95% CI, 0.58 to 1.22; p=0.355) Worsening IPF (time to acute exacerbation, death, lung transplant or hospitalization for respiratory problem): PIR (NR) vs. P (NR) HR 0.73 (95% CI, 0.43 to 1.24; p=0.248) Mean change in Dyspnea (UCSD SoBQ, scale 0-120): PIR +11.9 vs. P +13.9 ARR -2.0 (95% CI, -7.6 to 3.6; p=0.604) Mean change in 6MWT: PIR -45.1 m vs. P -76.9 m ARR +31.8 m (95% CI, 3.2 to 60.4; p=0.0009)	 NS NS NS NS NS NA	Serious Adverse Events: PIR: 32% P: 28% p-value not reported Discontinuations due to adverse effects: PIR: 15% P: 9% Pooled analysis w/ CAPACITY 004; p-value NR Nausea: PIR: 65 (38%) P: 28 (16%) p-value not reported Rash: PIR1: 58 (34%) P: 22 (13%) p-value not reported Photosensitivity: PIR: 10% P: 2% p-value not reported AST/ALT 3x ULN: PIR 4.1% P: 0.6% Pooled analysis w/ CAPACITY 004; p-value NR	 NA NA NA NA NA	**Quality Rating**: **Internal Validity (Risk of Bias)**: Selection: No current smokers in the pirfenidone group yet 8 in the placebo group; otherwise, see CAPACITY 004. Performance: See CAPACITY 004. Detection: See CAPACITY 004. Attrition: See CAPACITY 004. **Applicability**: Patients: Patients with mild to moderate IPF; nearly all patients white; 62% were former smokers; ; 28% required supplemental oxygen. Intervention: See CAPACITY 004 Comparator: See CAPACITY 004 Outcomes: No statistically significant difference between PIR and P in primary endpoint of change in FVC. No statistically significant difference in key secondary endpoints progression-free survival, worsening IPF, or change in dyspnea scores; unaware of individual outcomes of composite secondary endpoints. It is uncertain what constitutes a clinically meaningful change in 6MWT. Post-hoc analysis of pooled data from CAPACITY 004 demonstrated a favorable overall all-cause mortality trend with PIR vs. P (8% vs. 10%; HR 0.77; 95% CI, 0.47 to 1.28; p=0.315) and favorable IPF-related mortality trend with PIR vs. P (5% vs. 8%; HR 0.62; 95% CI, 0.35 to 1.13; p=0.117); no adjudication was performed. Setting: See CAPACITY 004

3. King, et al. (ASCEND)[2,5] DB, PG, PC, RCT Phase 3	1. Pirfenidone 801 mg TID w/ meals (PIR) 2. Placebo (P) 52 weeks	Demographics: Age: 68 years Men: 79% % Predicted FVC: 68% 6MWT: 418 m Current smokers: Not reported Key Inclusion Criteria: Age 40-80 years; Dx of IPF; Predicted FVC 50-90%; DLco 30-90%; FEV_1 /FVC ≥0.80 6MWT ≥150 m Key Exclusion Criteria: FEV1/FVC ratio <0.8 after administration of bronchodilator; Absolute increase of ≥12% and an increase of 200 mL in predicted FEV1 and /or FVC after bronchodilator use compared to bronchodilator use at screening; Connective tissue disease; Asthma or COPD; Expected lung transplant ≤1 year; Severe hepatic or renal disease; Unstable cardiac or pulmonary disease; Concomitant tx for IPF unless needed for another indication	ITT: 1. 278 2. 277 Attrition*: 1. 72 (26%) 2. 55 (20%) * Does not include death or lung trans-plantation	**Primary Endpoint**: (week 52) ≥10% decline %-predicted FCV or death: PIR 46 (16.5%) vs. P 88 (31.8%) ARR 15.3% (95% CI, 8.1 to 22.1%; p<0.001) No decline %-predicted FVC: PIR 63 (22.7%) vs. P 27 (9.7%) ARR 13% (95% CI, 7.0 to 19.0%; p<0.000001) **Key Secondary Endpoints**: (week 52) Mean change in 6MWT: PIR -33.6 m vs. P -60.2 m ARR 26.7 m (p=0.04) Post-hoc analysis: Decrease of ≥50 m in 6MWT or death: PIR 72 (25.9%) vs. P 99 (35.7%) (p=0.04) ARR 9.8% (CI not provided) Progression-free Survival (≥10% decline %-predicted FVC, ≥50 m decrease 6MWT, or death): PIR 144 (51.8%) vs. P 113 (40.8%) HR 0.57 (95% CI, 0.43 to 0.77; p<0.001) Mean change in Dyspnea (UCSD SoBQ, scale 0-120): Data NR but p=NS Post-hoc analysis: Increase ≥20 points in UCSD SoBQ: PIR 81 (29.1%) vs. P 100 (36.1%) (p=0.16) All-cause mortality: PIR 11 (4%) vs. P 20 (7.2%) HR 0.55 (95% CI 0.26 to 1.15, p=0.10) Mortality from IPF: PIR 3 (1.15) vs. P 7 (2.5%) HR 0.44 (95% CI, 0.11 to 1.72; p=0.23)	15.3%/7 13%/8 NA 9.8%/10 11%/9 NS NS NS	Serious Adverse Events*: PIR: 52 (18.7%) P: 56 (20.2%) p-value NR *Excludes worsening IPF Discontinuations due to adverse effects: PIR 40 (14.4%) P 30 (10.8%) p-value NR AST/ALT 3x ULN: PIR 8 (2.9%) P 2 (0.7%) p-value NR Nausea: PIR 100 (36%) P 37 (13.4%) p-value NR Gastrointestinal Reflux: PIR 36 (11.9%) P 18 (6.5%) p-value NR Anorexia: PIR 44 (15.8%) P 18 (6.5%) P-value NR Rash: PIR 78 (28.1) P 24 (8.7%) p-value NR	NA NA NA NA NA NA NA	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: Patients were randomized by permuted-block design via a computer generated randomization code and the study drug was assigned by means of an interactive voice-response system. Both groups well matched. Performance: Described as double-blind and both treatments were "visually equivalent". Detection: True ITT analysis performed; power/sample size calculations not described; appropriate statistical tests applied; data assessor blinded to allocation when FVC, DLco and mortality data analyzed. Attrition: Overall attrition high, with higher attrition in PIR group. Imputed missing data as average value, or worst rank outcome for death. **Applicability**: Patients: Patients had mild to moderate IPF; majority of patients were white males; 63% were former smokers. Intervention: PIR dose titrated over 2 weeks. No data on final mean dose of PIR since dose adjustments were permitted for intolerance during study. Adherence was high (>80%). Comparator: Placebo control appropriate. Outcomes: Change in FVC is an accepted surrogate endpoint but it is unknown what magnitude of change affects mortality. It is uncertain what constitutes a clinically meaningful change in 6MWT. Significant difference in progression-free survival primarily driven by the criterion of 6MWT and decline in FVC. Pooled all-cause mortality data from ASCEND and CAPACITY trials when analyzed by the FDA do not demonstrate a significant difference between PIR (7.1%) vs. P (9.3%) (HR 0.75; 95% CI, 0.50 to 1.11; p=0.14). Pooled mortality data provided by the drug sponsor, which utilized more strict censoring rules, showed a more favorable but still non-significant trend (PIR (6.1%) vs. P (8.7%); HR 0.69; 95% CI, 0.46 to 1.05; p=0.08). Setting: 127 sites and 9 countries (USA n=87). Drug sponsor participated in the study design and writing the final manuscript.

4. Taniguchi, et al. 2010[19] DB, PG, PC, RCT Phase 3	1. Pirfenidone 600 mg TID (PIR1) 2. Pirfenidone 400 mg TID (PIR2) 3. Placebo (P) Randomized 2:1:2 52 weeks	Demographics: Age: 65 years Men: 81% VC: 2.437 L 6MWD: NR Current Smokers: 12% Key Inclusion Criteria: Age 20-75 years; Diagnosis of IPF; SpO2 desaturation of ≥5% difference between resting SpO_2 and the lowest SpO_2 during a 6MET; and Lowest SpO_2 during the 6MET of ≥85% while breathing air. Key Exclusion Criteria: Improved symptoms in the previous 6 months; Use of immuno-suppressants or oral corticosteroids at a dose >10 mg/day during the preceding 3 months; Chronic or acute respiratory illness	mITT: 1. 108 2. 55 3. 104 Attrition: 1. 40 (37%) 2. 15 (27%) 3. 31 (30%)	**Primary Endpoint**: (52 weeks) Change in VC from baseline: PIR1: -0.09 (0.02) L PIR2: -0.08 (0.03) L P: -0.16 (0.02) L PIR1 vs P: Adjusted mean 0.07 L (0.03), p=0.0416 PIR2 vs P: Adjusted mean 0.09 L (0.04), p=0.0394 PIR1 vs. PIR2: p=NS **Key Secondary Endpoints**: (52 weeks) Progression-free survival (death or ≥10% decline in VC): PIR1: 45 (42.5%) PIR2: 26 (47.3%) P: 40 (38.5%) PIR1 vs. P: ARR 3.2%% (no CI); p=0.028 PIR2 vs. P: ARR 8.8%% (no CI); p=0.066 PIR1 vs. PIR2: ARR 5.6% (no CI); p=0.91	NA NA NA 19.7%/6 NA NA	Photosensitivity: PIR1: 56 (51.4%) PIR2: 29 (52.7%) P: 24 (22.4%) PIR1 vs P: (p<0.01) PIR2 vs P: (p<0.01) Anorexia: PIR1: 18 (16.5%) PIR2: 6 (10.9%) P: 3 (2.8%) PIR1 vs. P: (p<0.01) PIR2 vs. P: (p=0.06) Discontinuations due to adverse effects: PIR1: 20 (18.3%) PIR2: 11 (20%) P: 14 (13.1%) p-value NR	29.0%/3 30.3%/3 13.7%/7 NA NA	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: Selection: Patients randomized with a modified minimization method, including some random allocation based on biased coin design to balance baseline SpO_2. Imbalance in allocation of current smokers, with less allocated to the PIR1 group. Performance: Described as double-blind with matching placebo. Detection: Statistical assumptions to power study provided; appropriate statistical tests used. No details on blinding of outcome data assessors. Modified ITT performed as 8 patients excluded after randomization. Confidence intervals not provided for outcomes. Attrition: Overall attrition high. Used LOCF imputation for missing data, which can bias results when studying progressive diseases. **Applicability**: Patients: All Japanese patients; 92% of patients were treatment naïve with relatively mild functional impairment based on PFTs. Intervention: Doses titrated over 2 weeks to pirfenidone 600 mg TID and pirfenidone 400 mg TID. Comparator: Placebo control appropriate. Outcomes: VC and progression-free survival are appropriate endpoints. Only high dose pirfenidone was associated with a significant improvement in progression free survival and decreased disease progression. Serious adverse events other than those resulting in treatment discontinuation not reported. Small changes in outcomes and lack of reported confidence intervals makes assessment of clinical applicability of results difficult. Setting: 73 centers in Japan.

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; DLco = carbon monoxide diffusing capacity; dx = diagnosis; FEV_1 = forced expiratory volume in one second, HRCT = high-resolution CT; IPF = idiopathic pulmonary fibrosis; ITT = intention to treat; m = meters; LOCF = last observation carried forward; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; PFT = pulmonary function test; PG = parallel group; PIR = pirfenidone; PP = per protocol; SoB = shortness of breath; SpO_2 = oxygen saturation measured by pulse oximetry; SSD = sum of squared differences; TID = three times daily; tx = treatment; UCSD SoBQ = University of California, San Diego Shortness of Breath Questionnaire; scores range from 0 to 120, with larger scores indicating greater shortness of breath (minimally clinically important difference, 5 – 11 points); ULN = upper limit of normal; 6MET = 6-min steady-state exercise test ; 6MWT = 6-min walk test

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Appendix 1: Highlights of Prescribing Information

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

ESBRIET® (pirfenidone) capsules, for oral use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

ESBRIET is a pyridone indicated for the treatment of idiopathic pulmonary fibrosis (IPF). (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage: 801 mg (three capsules) three times daily taken with food. (2)
- Upon initiation of treatment, the daily dosage should be titrated to the full dosage of nine capsules per day over a 14-day period as follows:

Treatment days	Dosage
Days 1 through 7	1 capsule three times a day with meals
Days 8 through 14	2 capsules three times a day with meals
Days 15 onward	3 capsules three times a day with meals

- Consider temporary dosage reduction, treatment interruption, or discontinuation for management of adverse reactions. (2.3, 5.1, 5.2, 5.3)
- Prior to treatment, conduct liver function tests. (2.1)

DOSAGE FORMS AND STRENGTHS

Capsules: 267 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Elevated liver enzymes: ALT, AST, and bilirubin elevations have occurred with ESBRIET. Monitor ALT, AST, and bilirubin before and during treatment. Temporary dosage reductions or discontinuations may be required. (2.1, 5.1)
- Photosensitivity and rash: Photosensitivity and rash have been noted with ESBRIET. Avoid exposure to sunlight and sunlamps. Wear sunscreen and protective clothing daily. Temporary dosage reductions or discontinuations may be required. (5.2)
- Gastrointestinal disorders: Nausea, vomiting, diarrhea, dyspepsia, gastro-esophageal reflux disease, and abdominal pain have occurred with ESBRIET. Temporary dosage reductions or discontinuations may be required. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥10%) are nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastro-esophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact InterMune at 1-888-486-6411 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Moderate (e.g., ciprofloxacin) and strong inhibitors of CYP1A2 (e.g., fluvoxamine) increase systemic exposure of ESBRIET and may alter the adverse reaction profile of ESBRIET. Discontinue fluvoxamine prior to administration of ESBRIET or reduce to one capsule three times a day. Consider dosage reduction with use of ciprofloxacin. (7.1)

USE IN SPECIFIC POPULATIONS

- Hepatic Impairment: Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed. ESBRIET is not recommended for use in patients with severe hepatic impairment. (8.6, 12.3)
- Renal Impairment: Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed. ESBRIET is not recommended for use in patients with end stage renal disease on dialysis. (8.7, 12.3)
- Smokers: Decreased exposure has been noted in smokers which may alter the efficacy profile of ESBRIET. (8.8)

Idiopathic Pulmonary Fibrosis (IPF) Agents

Goal: To optimize the evidence-based use of drugs for the treatment of IPF.

Length of Authorization: Up to 1 year

Requires PA:

- Non-preferred drugs

Preferred Alternatives:

- None at this time

Approval Criteria		
1. Does the patient have a diagnosis of idiopathic pulmonary fibrosis (ICD-9 516.31)?	Yes: Go to #2	No: Pass to RPH; Deny for medical appropriateness.
2. Is the treatment prescribed by a pulmonologist?	Yes: Go to #3	No: Pass to RPH; Deny for medical appropriateness.
3. Does the patient have a forced vital capacity (FVC) >50%?	Yes: Go to #4	No: Pass to RPH; Deny for medical appropriateness.
4. Is the patient a current smoker?	Yes: Pass to RPH; Deny for medical appropriateness. Efficacy of approved drugs for IPF may be altered in smokers due to decreased exposure (see prescribing information).	No: Go to #5
5. Are pirfenidone and nintedanib concurrently prescribed in this patient?	Yes: Pass to RPH; Deny for medical appropriateness. Safety and efficacy of concomitant therapy has not been established.	No: Approve for up to 12 months.
Renewal Criteria		
Is there evidence of disease progression (≥10% decline in percent-predicted FVC within the previous 12 months?	Yes: Pass to RPH; Deny for medical appropriateness.	No: Approve for up to 12 months.

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P&T/DUR Review: *3/15 (KS)*
Implementation: ***TBD***

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

New Drug Evaluation: Nintedanib capsules, oral

Month/Year of Review: July 2015
Generic Name: Nintedanib
PDL Class: Idiopathic Pulmonary Fibrosis Agents

End Date of Literature Search: January 2015
Brand Name (Manufacturer): Ofev™ (Boehringer Ingelheim Pharmaceuticals)
Dossier Received: Yes

Research Questions:

- Is there evidence of efficacy for nintedanib in the treatment of idiopathic pulmonary fibrosis (IPF) as demonstrated by clinical improvement in outcomes such mortality, functional status (e.g., exercise tolerance), quality of life or symptoms (e.g., acute exacerbations)? If so, is there direct comparative evidence with other treatments for IPF?
- Is there evidence of acceptable adverse effects for nintedanib in comparison to other treatments for IPF?
- Are there subgroups of patients that may receive greater benefit or harm from nintedanib therapy?

Conclusions and Recommendations:

- There is insufficient evidence comparing nintedanib to other treatment for IPF. Current evidence is based on two placebo-controlled studies (INPULSIS-1 and INPULSIS-2).
- There is insufficient evidence that nintedanib reduces mortality in patients with IPF.[1]
- There is moderate strength of evidence from the INPULSIS trials (n=1066) that nintedanib slows disease progression based on surrogate outcomes as demonstrated by changes in forced vital capacity (FVC). Adjusted annual rate of change in FVC were significantly superior in the nintedanib groups compared to placebo in both studies.[1] INPULSIS-1 reported a significant benefit in FVC decline ≤10% with a number needed to treat (NNT) of 7. Results were not significant for this outcome in INPULSIS-2.
- There is low strength of evidence that nintedanib improved quality of life based results of the INPULSIS-2 study that showed less deterioration in scores of patients taking nintedanib compared to placebo, 2.80 points vs. 5.48 points, p=0.02.[1] Clinical benefit on quality of life resulting from a difference of 2.69 points between groups is unknown. There was no significant difference in quality of life scores in INPULSIS-1.[1]
- There is low strength of evidence that incidence of acute exacerbations were significantly improved in the nintedanib group compared to placebo in INPULSIS-2. In INPULSIS-1 no significant difference between groups was demonstrated.[1]
- Common adverse reactions experienced by patients in the nintedanib group were diarrhea, nausea, abdominal pain and vomiting. Diarrhea occurred in over 60% of the patients and was the most common adverse reaction leading to discontinuations in INPULSIS-1 and INPULSIS-2, 4.5% and 4.3%, respectively.[1,2] Elevated liver enzymes 3-4-times the upper limit of normal occur at higher incidence with nintedanib than placebo, and may require dosage reduction or interruption.

- Recommend establishing prior authorization criteria for nintedanib to limit use to appropriate patients. See **Appendix 2**.

Background:

Idiopathic pulmonary fibrosis is a type of fibrosing interstitial pneumonia originally thought to be due to chronic inflammation. More recently abnormal wound healing has been implicated in the pathogenesis. In most IPF cases the etiology is unknown; however a link to cigarette smoking and environmental factors has been described. Familial pulmonary fibrosis accounts for less than 5% of IPF cases and genetic factors have been seen in sporadic cases of IPF.[4] IPF is chronic, progressive and unpredictable with a median survival rate of 2-3 years after diagnosis. Estimates of prevalence range from 2-29 cases per 100,000 in the population at large.[4] IPF is usually diagnosed between the ages of 40-70 years and is slightly more common in men than women. The diagnosis of IPF requires a detailed patient history to rule out other interstitial lung diseases. Most patients can be diagnosed based upon a specific interstitial pneumonia pattern seen on high-resolution computerized tomography (HRCT) of the chest. Patients may also be diagnosed by a specific combination of HRCT and surgical lung biopsy pattern.[4] Common symptoms of IPF are: chronic exertional dyspnea, cough, bibasilar inspiratory crackles and finger clubbing.[4] Staging of IPF is not currently used in practice to direct clinical decision making and there are no corresponding changes in percent-predicted FCV associated with different stages.[4] Indicators of disease progression are worsening respiratory symptoms, declining pulmonary function tests and acute respiratory decline.

Mortality is the most relevant endpoint for IPF studies and is the ideal endpoint for assessing efficacy of IPF therapy.[5] Other clinically meaningful outcomes include acute exacerbation of IPF (usually measured by worsening dyspnea), all-cause non-elective hospitalizations and quality of life.[6] However, endpoints commonly studied in clinical trials include FVC and diffusion capacity for carbon monoxide (DLco) as a surrogate endpoint for lung function; 6-minute-walk test (6MWT) as a surrogate endpoint for functional status; HRCT imaging features; and biomarkers.[6,7] There is no consensus on the most appropriate surrogate outcomes to be used in IPF trials and there are no validated surrogate endpoints.[6] Further, it is uncertain what magnitude of difference for FVC or 6MWT constitutes a clinically meaningful change for patients with IPF.[5] Progression-free survival, usually assessed by combining decline in FVC and death, is a composite endpoint used in some IPF trials. The World Health Organization – Quality of Life Questionnaire (WHO-QoL) and St. George's Hospital Respiratory Questionnaire (SGRQ), which measure distress due to respiratory symptoms, are also used to measure the impact of IPF on patients' quality of life.

Multiple features have been identified with increased mortality in IPF patients (Table 1).[5] Predictors of disease progression and mortality have been demonstrated with FVC changes. Decreased survival rates have been associated with declining FVC rates of 5-10% or more, and a sign of disease progression is indicated by a decrease in FVC of ≥10%.[4,6,9] Limited evidence suggests that small decreases in FVC (5-10%) is associated with poor outcomes. A decline in the 6MWT has also been correlated with increased mortality in patients with IPF.[9] Retrospective cohort studies have suggested a decline of 30 meters (m) in the 6MWT to be a clinically meaningful threshold.[6] Standards in conducting the 6MWT are lacking, making interpretation of this test result difficult, though it is thought to be a robust indicator of functional exercise capacity.[6,11]

The joint American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) evidence-based guideline on the diagnosis and management of IPF was updated in 2011.[4] Treatment recommendations and corresponding evidence designation, using the GRADE methodology, is presented in table 2. Wide ranges of medical therapies for IPF have been explored but none have clearly demonstrated a clinical benefit in IPF. A Cochrane review found no randomized controlled trials (RCTs) to assess the benefits of corticosteroid monotherapy in patients with IPF.[12] Observational cohort studies have failed to find a mortality benefit in patients treated with corticosteroids.[12] Treatment with azathioprine and prednisone has been studied in patients with IPF without demonstrating definitive benefits and is not currently recommended. Cyclophosphamide treatment in IPF has failed to show mortality benefits and is also not recommended. The use of everolimus failed to show improved efficacy in patients with IPF and may cause harm. A study of anticoagulant use in patients with IPF was discontinued early due to excess deaths in the warfarin group with a low probability of benefit from treatment.[14] Bosentan was studied in patients with IPF in the BUILD-1 and BUILD-3 trials but was not shown to improve outcomes and is

therefore not recommended.[15,16] Ambrisentan, macitentan, sildenafil, interferon-gamma, etanercept and imatinib have been studied in IPF patients without benefit. The ATS/ERS/JRS/ALAT guideline weakly recommends against the use of pirfenidone but suggests it could be considered an option for patients who realize the expected benefits are small and there are risks of adverse reactions (ASCEND results not included in guideline).[4] The use of pirfenidone in IPF is weakly recommended by the Spanish Society of Pneumology and Thoracic Surgery (SEPAR).[17] French practical guidelines and National Institute for Health and Care Excellence (NICE) recommend pirfenidone in patients with mild to moderate IPF (FVC ≥50%).[18,19] The only treatment shown to improve survival in IPF patients is lung transplantation.[4] Pirfenidone and nintedanib are currently the only drugs approved by the FDA for IPF, with the evidence for their use presented below.

Table 1. ATS/ERS/JRS/ALAT Statement on Selected Features Associated with Increased Risk of Mortality in IPF.[8]

Baseline Factors	**Longitudinal Factors**
Level of dyspnea	Decrease in FVC ≥10% absolute value
DLco <40% predicted	Decrease in DLco by ≥15% absolute value
Desaturation ≤88% during 6MWT	Worsening of fibrosis on HRCT
Extent of honeycombing on HRCT	
Pulmonary hypertension	
Definitions of abbreviations: 6MWT= 6-minute walk-test; DLco = diffusion capacity for carbon monoxide; HRCT = high-resolution computer tomography.	

Raghu G, Collard H, Egan J, et al. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guideline for Diagnosis and Management. Am J Respir Crit Care Med 2011;183:788-824.

Table 2. ATS/ERS/JRS/ALAT Treatment Recommendations.[4]

	Treatment	**Evidence Grade**
Recommendation AGAINST the use of treatment in IPF is STRONG	Corticosteroid Monotherapy	Very low
	Colchicine	Very low
	Cyclosporine A	Very low
	Combined corticosteroid and immune-modulator therapy	Low
	Interferon γ 1b	High
	Bosentan	Moderate
	Etanercept	Moderate
Recommendation AGAINST the use of treatment in IPF is weak	Combined acetylcysteine and azathioprine and prednisone	Low
	Acetylcysteine monotherapy	Low
	Anticoagulation	Very low
	Pirfenidone	Low
Recommendation for therapy in IPF patients is STRONG	Long-term oxygen therapy	Very low
Recommendation for procedure in IPF patients is STRONG	Lung transplantation	Very low
Recommendation AGAINST procedure in patients with respiratory failure due to IPF is WEAK	Mechanical ventilation	Low
Recommendation for procedure in IPF patients is WEAK	Pulmonary rehabilitation	Low
Recommendation for therapy in IPF patients with acute exacerbations is WEAK	Corticosteroids	Very low
Recommendation AGAINST the treatment of associated IPF conditions is WEAK	Pulmonary hypertension	Very low
Recommendation for therapy in IPF patients is WEAK	Asymptomatic gastroesophageal reflux	Very low

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

Clinical Efficacy:
Nintedanib was studied in two double blind, placebo-controlled, phase 3, randomized trials in 717 patients and lasting 52 weeks. Both studies, INPULSIS-1 and INPULSIS-2, were conducted in the same manner with the same methodology.[1] Patients were randomized to nintedanib 150 mg orally twice daily or placebo for 52 weeks. The dose could be decreased to 100 mg twice daily if needed for the management of adverse events. The primary endpoint was the annual rate of decline in FVC. Secondary endpoints were absolute change from baseline in FVC, FVC response (decline in the percentage of predicted FVC not more than 5 percentage points and decline not more than 10 percentage points at week 52), time to the first acute exacerbation and change from baseline in the total score on the St. George's Respiratory Questionnaire (SGRQ). The SGRQ measures a total score of 0 to 100, with higher scores correlated with worse health-related quality of life. Randomized controlled trial in IPF patients have demonstrated between group differences in SGRQ total scores ranging from -3.3 to -6.[18] In patients with chronic obstructive pulmonary disease, the minimal important difference is 4 points.[19] However, the minimal important difference in patients with IPF has not been determined.

Patients in INPULSIS-1 had mild to moderate IPF, were predominately men and were a mean age of 67 years.[1] A majority of participants were former smokers (70%). In INPULSIS-1, the adjusted annual rate of change in FVC was less with nintedanib compared to placebo, -114.7 mL/year vs. -239.9 mL/year, respectively ($p<0.001$). The absolute percent predicted change in FVC favored nintedanib, with an absolute difference from placebo of 3.2% (95% CI 2.1 to 4.3; $P<0.001$). The number of patients that had less than 10% decline in FVC at 52 weeks was significantly higher in the nintedanib group compared to placebo with a NNT of 7. Incidence (percent) of first investigator reported acute exacerbation was not significantly different between nintedanib and placebo groups (HR 1.15, 95% CI, 0.54 to 2.42; p=0.67). In addition, there was no significant difference in quality of life as seen in SGRQ scores between the groups at 52 weeks.

The patient demographics in INPULSIS-2 were similar to patients enrolled in INPULSIS-1.[1] Nintedanib was statistically superior to placebo based on the surrogate endpoint of adjusted annual rate of change in FVC (absolute difference 93.7 mL/year, 95% CI 44.8 to 142.7; $p<0.001$). The difference in the adjusted absolute mean change from baseline in percent predicted FVC was 3.1%, favoring nintedanib treatment ($p<0.001$). Nintedanib and placebo groups were not significantly different in the number of patients with ≤10 % decline in FVC at 52 weeks. Results showed nintedanib to be superior to placebo in cumulative incidence (percent) of first investigator reported acute exacerbation (HR 0.38, 95% CI, 0.19 to 0.77; p=0.005). Nintedanib was associated with a significant improvement in SGRQ score compared to placebo with an absolute difference -2.69 (95% CI -4.95 to 0.43; p=0.02). However, it is unknown if such a small difference is clinically significant.[18,19]

Prespecified pooled data of INPULSIS-1 and INPULSIS-2 showed a statistically significant benefit of nintedanib over placebo for the surrogate endpoint of annual rate of FVC change, with a difference of -109.9 mL (95% CI 75.9 to 144.0 mL).[1] Absolute mean change from baseline in FVC, from pooled data, showed a significant advantage with nintedanib therapy over placebo (difference 110.6 mL, 95% CI 83.2 to 137.9 mL; $p<0.001$). A significant FVC response (patients with an absolute decline in % predicted FVC of no more than 5% or no more than 10% at week 52) favored the nintedanib groups compared to placebo in pooled analysis data. Time to first acute exacerbation was not significantly different in the pooled nintedanib group compared to placebo (HR 0.64, 95% CI 0.39 to 1.05; p=0.08). In a prespecified pooled analysis, death from any cause, death due to respiratory cause, and death that occurred between randomization and 28 days after the last dose of the study drug were not significantly different between groups.

Conclusions of clinical efficacy for nintedanib are limited to only two, small phase 3 studies using a surrogate primary endpoint for analysis. The INPULSIS studies were fair-good quality with high levels of overall attrition that could potentially influence results. Wide confidence intervals seen with the primary endpoint suggest an imprecise prediction in the true treatment effect. The clinically meaningful endpoints of time to first acute exacerbation and quality of life improvements were only significant in IMPULSIS-2. The clinical importance of increased myocardial infarctions seen with nintedanib will need further investigation.

Clinical Safety:
The most common adverse reactions occurring ≥5% are: diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight decreased and hypertension (Table 2).[2] Diarrhea was the most common adverse event leading to discontinuations; fourteen patients randomized to nintedanib in both studies versus no patients in the placebo group in INPULSIS-1 and 1 patient in the placebo group in INPULSIS-2. Serious adverse events were similar between groups in both trials. Elevated liver enzymes, at 3-4 times the upper limit of normal, were more common in patients taking nintedanib compared to placebo. Myocardial infarction was reported in more often in pirfenidone treated patients compared to placebo, 1.5% vs. 0.4%, respectively.

Table 3. Adverse Reactions Occurring in ≥5% of Pirfenidone-treated Patients More commonly Than Placebo[2]

Adverse Reaction	Pirfenidone 150 mg (n=723)	Placebo (n=508)
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal Pain	15%	6%
Vomiting	12%	3%
Liver enzyme elevation	14%	3%
Decreased appetite	11%	5%
Headache	8%	5%
Weight decreased	10%	3%
Hypertension	5%	4%

5

Pharmacology and Pharmacokinetic Properties:[2]

Parameter	
Mechanism of Action	Works by inhibiting receptor tyrosine kinases (RTK) and non-receptor tyrosine kinases (nRTKs), which are involved in the pathogenesis of IPF.
Oral Bioavailability	4.7%
Distribution and Protein Binding	Bi-phasic disposition kinetics and high protein binding (97.8%).
Elimination	Urinary excretion 0.05%
Half-Life	9.5 hours
Metabolism	Hydrolytic cleavage by esterases and subsequent glucuronidation by UGT enzymes. CYP-dependent metabolism accounted for 5% of the

	total.

Abbreviations: CYP – cytochrome P450.

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Mortality
2) Hospitalizations
3) Disease Progression (FVC, VC)
4) Exercise tolerance (6MWD)
5) Quality of life
6) Acute exacerbations and symptoms

Primary Study Endpoint:
1) Adjusted annual rate of change in FVC

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. Richeldi, et al (INPULSIS-1)[1] PC, DB, RCT, Phase 3 52 weeks	1. Nintedanib 150 mg twice daily (N) 2. Placebo (P)	Demographics: Men: 81% Age: 67 years FVC: 2,801 mL Predicted DLco: 48% Key Inclusion Criteria: • Age >40 years; • IPF dx previous 5 years; • FVC ≥50% of predicted value; • DLco 30-79% of predicted value • HRCT of the chest previous 12 months; • Prednisone ≤15 mg/day, or equivalent, allowed if dose stable x8 weeks before screening.	ITT: 1.309 2.204 PP: 1.229 2. 163 Attrition: 1. 105 (34%) 2. 41 (20%)	Primary Endpoint: Adjusted Annual Rate of Change in FVC: N: -114.7 mL/year P: -239.9 mL/year Difference 125.3 mL/year (95% CI 77.7 to 172.8) P<0.001 Secondary Endpoints: Mean Change in SGRQ Score from baseline at week 52: N: +4.34 points P: +4.39 points Absolute difference -0.05 (95% CI -2.50 to 2.40) P=0.97 Mean Change from Baseline % predicted FVC: N: -2.8 % P: -6.0 %	NA NA	Diarrhea: N: 190 (61.5%) P: 38 (18.6%) p-value not reported Serious Adverse Events: N: 96 (31.1%) P: 55 (27.0%) p-value not reported Elevated Liver Enzymes*: N: 15 (4.9%) P: 1 (0.5%) p-value not reported Adverse Events Leading to Discontinuations: N: 65 (21.0%) P: 22 (10.8%) p-value not reported * ALT/AST 3-4x ULN.		**Quality Rating**: Fair - Good **Internal Validity (Risk of Bias)**: Selection: Interactive telephone and web-based response system. Performance: Double-blind design and treatment was masked with identical packaging. Detection: Outcome assessors were blinded. Attrition: Attrition was high overall (27%). Modified ITT analysis was used. **Applicability**: Patient: Population representative of patients with IPF. A majority (70%) of patients were former smokers. 27% required dose reduction to 100 mg BID compared to 5% w/ placebo. Intervention: new drug. Comparator: Placebo-controlled; no active control Outcomes: Annual rate of decline in FVC is an FDA accepted surrogate endpoint. Data on long-term health outcomes are lacking. Setting: Patients recruited from 205 outpatient sites in 24 countries.

		Key Exclusion Criteria: • Treatments for IPF other than prednisone or equivalent; • Anticoagulant or high-dose antiplatelet therapy; • abnormal labs; • Cardiac disease; • Lung transplant candidates.		Absolute difference 3.2% (95% CI 2.1 to 4.3) P<0.001 FVC decline ≤10 percentage points: N: 218 (70.6%) P: 116 (56.9%) Odds Ratio 1.91 (95% CI 1.32 to 2.79) P<0.001	14/7			**Analysis**: Absolute changes in FVC from baseline were small in both groups, suggesting enrolled patients had less progressive IPF.
2. Richeldi, et al (INPULSIS-2)[1] PC, DB, RCT, Phase 3 52 weeks	1. Nintedanib 150 mg twice daily (N) 2. Placebo (P)	Demographics: Men: 78% Age: 67 years FVC: 2,646 mL Predicted DLco: 46.7% Key Inclusion Criteria: See INPULSIS-1 Key Exclusion Criteria: See INPULSIS-2	ITT: 1. 329 2. 219 PP: 1. 246 2. 169 Attrition: 1. 83 (25%) 2. 50 (23%)	Primary Endpoint: Adjusted Annual Rate of Change in FVC: N: -113.6 mL/year P: -207.3 mL/year Absolute difference 93.7 mL/year (95% CI 44.8 to 142.7) P<0.001 Secondary Endpoints: Mean Change in SGRQ Score from baseline at week 52: N: +2.80 points P: +5.48 points Absolute difference -2.69 (95% CI -4.95 to 0.43) P=0.02 Mean Change from Baseline % predicted FVC: N: -3.1% P: -6.2% Absolute difference 3.1% (95% CI 1.9 to 4.3) P<0.001 FVC decline ≤10 percentage	NA NA NA	Diarrhea: N: 208 (63.2%) P: 40 (18.3%) p-value not reported Serious Adverse Events: N: 98 (29.8%) P: 72 (32.9%) p-value not reported Elevated Liver Enzymes*: N: 17 (5.2%) P: 2 (0.9%) p-value not reported Adverse Events Leading to Discontinuations: N: 58 (17.6%) P: 33 (15.1%) p-value not reported * ALT/AST 3-4x ULN.		**Quality Rating**: Fair - Good **Internal Validity (Risk of Bias)**: Selection: Interactive telephone and web-based response system. Performance: Double-blind design and treatment was masked with identical packaging. Detection: Outcome assessors were blinded. Attrition: Attrition overall was high (24%). Modified ITT analysis was used. **Applicability**: Patient: A majority of participants were former smokers (65%). 29% required dose reduction to 100 mg BID compared to 3% w/ placebo. Intervention: new drug. Comparator: Placebo-controlled; no active control Outcomes: Annual rate of decline in FVC is an FDA accepted surrogate endpoint. Data on long-term health outcomes are lacking. Setting: Patients recruited from 205 outpatient sites in 24 countries. **Analysis**: Population representative of patients with IPF. Absolute changes in FVC from baseline were small in both groups, suggesting enrolled patients had less progressive IPF.

				points: N: 229 (69.6%) P: 140 (63.9%) Odds Ratio 1.29 (95% CI 0.89 to 1.86) P=0.18	NS			

Abbreviations [alphabetical order]: ALT/AST = alanine aminotransferase/aspartate aminotransferase; ARR = absolute risk reduction; BID = twice daily; CI = confidence interval; DLco = carbon monoxide diffusing capacity; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; ITT = intention to treat; mITT = modified intention to treat; mL= milliliters; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol; ULN = upper limit of normal.

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Appendix 1: Highlights of Prescribing Information

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

OFEV® (nintedanib) capsules, for oral use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

OFEV is a kinase inhibitor indicated for the treatment of idiopathic pulmonary fibrosis (IPF). (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage: 150 mg twice daily approximately 12 hours apart taken with food. (2.2)
- Consider temporary dose reduction to 100 mg, treatment interruption, or discontinuation for management of adverse reactions. (2.3, 5.1, 5.2, 6)
- Prior to treatment, conduct liver function tests. (2.1, 5.1)

DOSAGE FORMS AND STRENGTHS

Capsules: 150 mg and 100 mg (3)

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Elevated liver enzymes: ALT, AST, and bilirubin elevations have occurred with OFEV. Monitor ALT, AST, and bilirubin before and during treatment. Temporary dosage reductions or discontinuations may be required. (2.1, 5.1)
- Gastrointestinal disorders: Diarrhea, nausea, and vomiting have occurred with OFEV. Treat patients at first signs with adequate hydration and antidiarrheal medicine (e.g., loperamide) or anti-emetics. Discontinue OFEV if severe diarrhea, nausea, or vomiting persists despite symptomatic treatment. (5.2)
- Embryofetal toxicity: Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.3)
- Arterial thromboembolic events have been reported. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. (5.4)
- Bleeding events have been reported. Use OFEV in patients with known bleeding risk only if anticipated benefit outweighs the potential risk. (5.5)
- Gastrointestinal perforation has been reported. Use OFEV with caution when treating patients with recent abdominal surgery. Discontinue OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk. (5.6)

ADVERSE REACTIONS

Most common adverse reactions (≥5%) are: diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight decreased, hypertension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Coadministration of P-gp and CYP3A4 inhibitors may increase nintedanib exposure. Monitor patients closely for tolerability of OFEV. (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. (8.3)
- Hepatic impairment: Monitor for adverse reactions and consider dose modification or discontinuation of OFEV as needed for patients with mild hepatic impairment. OFEV is not recommended for use in patients with moderate or severe hepatic impairment. (8.6, 12.3)
- Renal impairment: The safety and efficacy of OFEV have not been studied in patients with severe renal impairment and end-stage renal disease. (8.7, 12.3)
- Smokers: Decreased exposure has been noted in smokers which may alter the efficacy profile of OFEV. (8.8)

Idiopathic Pulmonary Fibrosis (IPF) Agents

Goal: To optimize the correct use of agents used for the treatment of IPF.

Length of Authorization: Up to 1 year with annual renewal

Requires PA:

- Non-preferred drugs

Preferred Alternatives:

- None at this time

Approval Criteria		
1. Does the patient have a diagnosis of idiopathic pulmonary fibrosis (IPF) (ICD-9 516.31)?	Yes: Go to #2	No: Pass to RPH; Deny for medical appropriateness.
2. Is the treatment prescribed by a pulmonologist?	Yes: Go to #3	No: Pass to RPH; Deny for medical appropriateness.
3. Does the patient have a forced vital capacity (FVC) >50%?	Yes: Go to #4	No: Pass to RPH; Deny for medical appropriateness.
4. Is the patient a smoker?	Yes: Pass to RPH; Deny for medical appropriateness. Efficacy of approved agents for IPF may be altered in smokers due to decreased exposure (see prescribing information).	No: Go to #5
5. Are pirfenidone and nintedanib concurrently prescribed in this patient?	Yes: Pass to RPH; Deny for medical appropriateness. Safety and efficacy of concomitant therapy has not been established.	No: Approve for up to 12 months.
Renewal Criteria		
Is there evidence of disease progression (≥10% decline in percent-predicted FVC within the previous 12 months?	Yes: Pass to RPH; Deny for medical appropriateness.	No: Approve for up to 12 months.

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P&T/DUR Review: *3/15 (KS)*
Implementation: ***TBD***

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

Class Review: Intranasal Allergy Drugs

Month/Year of Review: July 2015

Purpose for Class Review:
Prior authorization (PA) with clinical criteria has been in place for intranasal corticosteroids, antihistamines and mast cell stabilizers since 2002. However, these criteria have not been reviewed by the P&T committee since 2008. These drugs have received FDA approval for use in seasonal and/or perennial allergic rhinitis, which is not funded by the Oregon Health Plan (OHP). An updated evidence-based review of these intranasal inhalers for OHP-funded conditions is therefore needed to determine the appropriateness of the current criteria.

Research Questions:
- For adults and children with conditions funded by the OHP, which conditions have nasal inhalers been studied to treat?
- Do nasal corticosteroids, antihistamines or mast cell stabilizers differ in effectiveness when used to treat conditions funded by the OHP?
- Do nasal corticosteroids, antihistamines or mast cell stabilizers differ in safety when used to treat conditions funded by the OHP?
- Are there subgroups of patients based on demographics (e.g., age, race, gender), concomitant comorbidities and medications, or pregnancy status, for which one nasal inhaler is more effective or associated with fewer harms?

Conclusions:
- There is moderate quality evidence intranasal corticosteroids are effective in managing asthma-related outcomes in patients who are not concurrently receiving an orally inhaled corticosteroid. An improvement in forced expiratory volume in 1 second (FEV1) (2.10%; 95% CI, 0.21 to 3.99%), asthma-related symptom scores (0.69; 95% CI, 0.04 to 1.25), and use of rescue asthma medication (standardized mean difference [SMD] 0.22; 95% CI, 0.04 to 0.39) was observed in patients receiving an intranasal corticosteroid relative to placebo. However, in patients already on an orally inhaled corticosteroid, there is moderate strength of evidence the addition of an intranasal corticosteroid does not offer any additional benefit in any asthma-related outcome.[1]
- There is low quality evidence that intranasal corticosteroids reduce apneas and hypoapneas, without improving nadir oxygen saturation, by demonstration of improvement in the Apnea Hypopnea Index (AHI) following short-term therapy in children and adults with obstructive sleep apnea (OSA).[2,3] The AHI is calculated by dividing the number of apnea events by the number of hours of sleep. There is also low quality evidence intranasal corticosteroids do not result in complete cessation of apneas or hypoapneas, do not improve subjective sleep quality, and do not prolong total sleep time in treated patients.[2,3]
- There is moderate quality evidence that patients receiving intranasal corticosteroids are more likely to experience resolution or improvement in symptoms of acute sinusitis at 21 days of treatment compared to placebo (73% versus 66.4%; risk ratio (RR) 1.11; 95% CI, 1.04 to 1.18).[4] The efficacy of intranasal corticosteroids for acute sinusitis appears to be delayed as there is moderate quality evidence that use of intranasal corticosteroids for a period of less than 21 days does not result in any difference in resolution or improvement in symptoms of acute sinusitis compared to placebo.[5]

- There is moderate quality evidence that when compared to placebo, topical corticosteroids improve symptom scores in patients with chronic rhinosinusitis (SMD -0.37; 95% CI, -0.60 to -0.13, p=0.002) and results in greater response to therapy (RR 1.69; 95% CI, 1.21 to 2.37, p=0.002). Subgroup analyses by topical delivery method revealed more benefit when the corticosteroid was administered directly to the sinuses than with simple nasal delivery (p=0.04).[6]
- Evidence is insufficient to draw any conclusions about comparative effectiveness, efficacy, or safety between intranasal corticosteroid formulations for management of asthma-related outcomes, obstructive sleep apnea, acute sinusitis and chronic rhinosinusitis.
- Evidence is insufficient for the intranasal use of antihistamines or mast cell stabilizers for any indication other than allergic rhinitis.
- There is moderate quality evidence that intranasal corticosteroids, antihistamines and mast cell stabilizers are not associated with increased serious harms compared to placebo. However, use of intranasal corticosteroids in growing children may be associated with increased risk for growth suppression.[7]

Recommendations:

- Create a PDL for "Intranasal Allergy Drugs" and prefer at least one intranasal corticosteroid due to evidence of effectiveness for OHP-funded conditions. Preference will be based on comparative costs in the executive session.
- Permit use of non-preferred intranasal allergy drugs with evidence of effectiveness for OHP-funded conditions, as outlined in the modified PA criteria in **Appendix 3**.

Background:

Each intranasal formulation of drugs within the corticosteroid, antihistamine and mast cell stabilizer classes have demonstrated benefit, and received FDA approval, for allergic rhinitis (see **Table 1**).[8] However, treatment of allergic and chronic rhinitis and nasal polyps are not currently funded by the OHP.

Intranasal formulations of these drugs are well tolerated and are associated with various topical adverse effects in 5-10% of patients regardless of the formulation.[9] The most common of these adverse side effects include dryness, burning, hoarseness, sneezing, and aftertaste. A common precaution for intranasal corticosteroids includes potential reduction in growth velocity in children.[7]

Intranasal use of antihistamines and mast cell stabilizers has not been adequately studied in conditions outside of allergic rhinitis. However, intranasal corticosteroids have been studied and used for several other conditions that are currently funded by the OHP. For example, allergic rhinitis and asthma are often comorbid diseases. An epidemiologic association between allergic rhinitis and asthma has been consistently demonstrated across patient populations. Given the association, it is hypothesized that reducing inflammation in the upper airway with an intranasal corticosteroid may improve asthma symptoms.[1] Attempts have also been made to reduce frequency of episodes of OSA by changing the characteristics of the upper airway using topical therapies such as intranasal corticosteroids.[2] Acute sinusitis is frequently caused by a viral infection and is a common reason for primary care visits. Inflammation of nasal mucosa plays an essential role in the development of sinusitis. In addition to treating seasonal and perennial rhinitis, corticosteroids might be beneficial in reducing inflammation in the treatment of sinusitis.[4] Lastly, chronic rhinosinusitis (CRS) is a group of disorders characterized by chronic inflammation of the mucosa of the nose and paranasal sinuses, with symptoms that persist for more than 12 weeks without complete resolution of symptoms. Anti-inflammatory therapies, including intranasal corticosteroids, play a significant role in the treatment of CRS.[6] The efficacy and safety of intranasal corticosteroids for the management of these conditions will therefore be reviewed.

Table 1. Indications and Dosing.[8]

Drug Name (Trade Name)	FDA Indication(s)	Formulation	OTC
Intranasal Antihistamines			
Azelastine (ASTEPRO, generic)	Allergic Rhinitis ≥6 mo	0.125 and 0.1876 mg/spray	NO
Olopatadine (*generic*, PATANSASE)	Allergic Rhinitis ≥6 yo	0.665 mg/spray	NO
Intranasal Corticosteroids			
Azelastine-Fluticasone propionate (DYMISTA)	Allergic Rhinitis ≥6 yo	0.125 mg-0.05 mg/spray	NO
Beclomethasone (BECONASE AQ)	Allergic, non-allergic rhinitis ≥6 yo	0.042 mg/spray	NO
Beclomethasone (QNASL)	Allergic rhinitis ≥4 yo	0.04 and 0.08 mg/spray	NO
Budesonide (*generic*, RHINOCORT, RHINOCORT ALLERGY)	Allergic Rhinitis ≥6 yo	0.032 mg/spray	YES
Ciclesonide (OMNARIS)	Allergic Rhinitis ≥6 yo	0.05 mg/spray	NO
Ciclesonide (ZETONNA)	Allergic Rhinitis ≥12 yo	0.037 mg/spray	NO
Flunisolide (*generic*)	Allergic Rhinitis ≥6 yo	0.025 and 0.029 mg/spray	NO
Fluticasone furoate (VERAMYST)	Allergic Rhinitis ≥2 yo	0.0275 mg/spray	NO
Fluticasone propionate (FLONASE, FLONSASE ALLERGY RELIEF, *generic*)	Allergic Rhinitis ≥4 yo	0.5 mg/spray	YES
Mometasone (NASONEX)	Allergic Rhinitis ≥2 yo; Nasal Polyps ≥18 yo	0.05 mg/spray	NO
Triamcinolone (*generic*; NASACORT ALLERGY 24 HOUR)	Allergic Rhinitis ≥2 yo	0.055 mg/spray	YES
Intranasal Mast Cell Stabilizers			
Cromolyn (*generic*)	Allergic Rhinitis ≥2 yo	5.2 mg/spray	YES

Abbreviations: mo = months of age; OTC = over-the-counter; yo = years of age

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls in conditions funded by the OHP were conducted. The Medline search strategy used for this review is available in **Appendix 1**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will only be emphasized if evidence is insufficient from preferred sources.

Systematic Reviews:

Asthma

A systematic review[1] with meta-analysis sought to assess the impact of intranasal corticosteroids on asthma outcomes in patients with allergic rhinitis and comorbid asthma. There were 18 eligible studies (n=1,659) identified that met inclusion criteria. All trials were placebo-controlled, single- or double-blinded RCTs or appropriate crossover trials, evaluating the efficacy of intranasal corticosteroids in adults or children which assessed at least one asthma-specific clinical outcome measure. Ten studies assessed primarily adult patients, 5 only recruited pediatric patients, and 3 studies enrolled both adults and children into the trials. The included studies appeared to have an overall low risk of bias. Ten of the 18 trials measured changes in FEV1. Pooling data from these trials found a significant improvement in percent-predicted FEV1 of 2.10% (95% CI, 0.21% to 3.99%) with use of an intranasal corticosteroid but a non-significant improvement in change in FEV1 when expressed in Liters (0.09 L; 95% CI, 0.04 to 0.22 L). Subgroup analyses demonstrated that there was a more pronounced treatment effect in patients who did not receive concurrent treatment with an orally inhaled corticosteroid (SMD = 0.31; 95% CI, 0.04 to 0.58), whereas an intranasal corticosteroid treatment had no impact on FEV1 in patients who received a concurrent orally inhaled corticosteroid (SMD 0.04; 95% CI, -0.15 to 0.22). No difference was found when morning oral peak expiratory flow (PEF) was assessed, whether patients were concurrently receiving an orally inhaled corticosteroid or not. In trials reporting asthma symptom scores using various scales, a significant improvement in symptom scores of 0.69 (95% CI, 0.04 to 1.25) were demonstrated in patients receiving intranasal corticosteroids versus placebo. However, similar to other subgroup analyses, there was no statistical difference between those receiving an intranasal corticosteroid and those receiving placebo in patients who concurrently received an orally inhaled corticosteroid. When quality of life was assessed, there was a non-significant improvement demonstrated in patients who received an intranasal corticosteroid compared to patients who received placebo (mean difference = -0.04 QoL units; 95% CI, -0.42 to 0.49). Lastly, a significant improvement in use of rescue medication (i.e., albuterol) was demonstrated in patients who received intranasal corticosteroids versus placebo (SMD 0.22; 95% CI, 0.04 to 0.39). But again, similar to other subgroup analyses, the difference was more profound in patients who did not concurrently take an orally inhaled corticosteroid (SMD 0.29; 95% CI, 0.01 to 0.58), and the difference was lost in patients who did receive an orally inhaled corticosteroid (SMD 0.00; 95% CI, -0.14 to 0.15).[1]

Obstructive Sleep Apnea

A systematic review[3] evaluated the evidence of anti-inflammatory drugs as treatment for OSA in children. Only two placebo-controlled RCTs were identified that specifically investigated the efficacy of intranasal corticosteroids (fluticasone and budesonide). The authors excluded a substantial number of potentially useful trials from the review because of the absence of polysomnographic assessment (sleep study) to ascertain the presence and severity of OSA. The first trial showed a statistically significant reduction of the Apnea Hypopnea Index (AHI) following six weeks of fluticasone (the AHI is calculated by dividing the number of apnea events by the number of hours of sleep). Users of fluticasone experienced a significantly greater reduction in AHI after six weeks compared to placebo. However, the study was small (n=25) and was terminated prematurely. Other study limitations were that treatment resulted only in a reduction of apneas and hypopneas, not in their complete cessation. In addition, the nadir oxygen saturation did not change following treatment. Thus, the children may have continued to have sleep-related hypoxia of the same magnitude as before treatment. Lastly, this study investigated neither sustained treatment effect over the long-term nor potential long-term harms, such as growth suppression. The second trial also reported a significant reduction in AHI with budesonide compared to placebo but did not analyze the patients as randomized. There were other methodological issues as well; baseline imbalances were not accounted for in the analysis and there was a higher number of withdrawals in the placebo group. The evidence from the two studies primarily applies to children with mild to moderate OSA. In these patients, intranasal fluticasone may have a short-term beneficial effect on the AHI in children with mild to moderate OSA but the evidence is very limited so far. [3]

A second systematic review[2] evaluated drug therapy for OSA in adults. The review identified one placebo-controlled crossover trial (n=24) evaluating intranasal fluticasone in patients with OSA and concurrent allergic rhinitis. In the study, fluticasone led to a significantly lower AHI compared with placebo (23.3 versus 30.3; p<0.05). For reference, scores between 15 and 29 are categorized as *moderate* sleep apnea while scores of 30 or higher are categorized as *severe* sleep apnea. No significant differences in subjective sleep quality, total sleep time and nocturnal oxygen saturation were apparent. Participants reported an increase in daytime alertness but no validated scale was used. From these data, intranasal fluticasone can reduce apnea in adult patients with mild OSA and co-existing rhinitis, but more evidence of long-term effectiveness is lacking.[2]

Acute Sinusitis

A systematic review[4] examined whether intranasal corticosteroids are effective in relieving symptoms of acute sinusitis in adults and children. Eligible studies were RCTs comparing intranasal corticosteroids of any dose to placebo or no intervention in adults and children with acute sinusitis. Acute sinusitis was defined by clinical diagnosis and confirmed by radiological evidence or nasal endoscopy. The primary outcome was the proportion of patients with either resolution or improvement of symptoms. Four double-blind, randomized, placebo-controlled studies of 15 or 21 days' duration involving 1,943 patients with acute sinusitis met the inclusion criteria. Results of 3 trials were combined for meta-analysis (the fourth study was not included due to high attrition, use of non-parametric tests, and inability to extract data), patients receiving intranasal corticosteroids were more likely to experience resolution or improvement in symptoms (73% vs. 66.4%; RR 1.11; 95% CI, 1.04 to 1.18).[4]

A second systematic review with meta-analysis[5] evaluated RCTs comparing intranasal corticosteroids with placebo in children or adults who had clinical signs and symptoms acute sinusitis or rhinosinusitis. Six studies (n=2,495) met inclusion criteria, all of which had adequate allocation concealment, blinding, and comparability of groups; however, 3 studies did not report the method of randomization. In 5 RCTs that assessed resolution or improvement of symptoms at days 14 to 21, intranasal corticosteroids had a modest clinical benefit, with a risk difference of 0.08 (95% CI, 0.03 to 0.13). However, this benefit was driven by studies of 21 days' duration; there was no significant difference found in studies of 14 or 15 days' duration. In studies that reported symptom relief, patients who received intranasal corticosteroids had significantly greater improvement in facial pain, congestion, rhinorrhea, headache and post-nasal drip compared to patients who received placebo (all p<0.05). Adverse events were mild or moderate in severity but there were no significant differences of reported events between patients who took intranasal corticosteroids (23%) and patients who took placebo (23%).[5]

Chronic Rhinosinusitis

A systematic review[6] assessed the effects of topical corticosteroid treatment in patients with chronic rhinosinusitis (CRS) without nasal polyps. The primary outcome was sinonasal symptoms, which was measured by symptom scores, proportion of patients showing improvement of symptoms, or quality of life measures. A meta-analysis of symptom improvement data was performed, including subgroup analysis by topical delivery methods. Eligible studies for inclusion were all randomized trials in which a topically administered corticosteroid was compared with either a placebo, no treatment, or an alternative topically administered corticosteroid for the treatment of CRS without polyps in patients of any age. Ten studies (590 patients) met the inclusion criteria. The trials were of low (six trials) and medium (four trials) risk of bias. When compared to placebo, topical corticosteroids improved symptom scores (SMD -0.37; 95% CI, -0.60 to -0.13, p=0.002) and had a greater proportion of responders (RR 1.69; 95% CI, 1.21 to 2.37, p=0.002). Subgroup analyses by topical delivery method revealed more benefit when the corticosteroid was administered directly to the sinuses than with simple nasal delivery (p=0.04). There were no differences between the groups in quality of life or adverse events.[6]

Guidelines:
The American Academy of Pediatrics has published a clinical practice guideline on the management of OSA in children.[10] Within the guideline, the panel addresses use of intranasal corticosteroids. The guideline suggests intranasal corticosteroids are an option for children with mild OSA (AHI <5 per hour) in whom adenotonsillectomy is contraindicated or for mild post-operative OSA (Evidence Quality: *B*; Recommendation Strength: *Option*). Though studies demonstrate the use of intranasal corticosteroids decreases the degree of OSA, residual OSA may often remain. Indeed, some children may not have an adequate response to intranasal corticosteroids and it is unknown whether the therapeutic effect persists long-term. The panel agreed based on the evidence that intranasal corticosteroids provide a less invasive treatment than surgery or CPAP and, therefore, may be preferred in some cases despite inferior efficacy and lack of long-term efficacy data.[10]

Clinical Trials:

Several potentially relevant abstracts were reviewed from the literature search.

After further review, 5 trials of intranasal corticosteroids were potentially relevant: 3 trials evaluated subjects with asthma and 2 trials evaluated subjects with sleep apnea. One of the sleep apnea studies was not randomized. However, because high-quality systematic reviews for this population are already available, these studies are presented as abstracts in **Appendix 2**.

No studies were identified that evaluated intranasal antihistamines or mast cell stabilizers for OHP-funded conditions. A Medline search of current non-preferred oral antihistamines found inconsistent evidence for these drugs in improving asthma-related outcomes. Oral antihistamines were not effective in patients with OSA. There is insufficient evidence for use of oral antihistamines for other conditions funded by the OHP. For completeness, identified studies are presented as abstracts in **Appendix 2**. Oral antihistamines designated as preferred on the PDL are available without prior authorization.

References:

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Appendix 1: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2015

1 exp Beclomethasone/ 1421
2 exp Budesonide/ 3044
3 ciclesonide.mp. 273
4 flunisolide.mp. 191
5 fluticasone.mp. 3128
6 mometasone.mp. 662
7 exp Triamcinolone Acetonide/ or exp Triamcinolone/ 3835
8 exp Nasal Absorption/ or exp Nasal Sprays/ or nasal.mp. 58239
9 exp Administration, Intranasal/ 8152
10 8 or 9 62254
11 1 or 2 or 3 or 4 or 5 or 6 or 7 11265
12 10 and 11 1138
13 exp Asthma/ 60783
14 exp Sleep Apnea Syndromes/ or exp Sleep Apnea, Central/ or exp Sleep Apnea, Obstructive/ 19814
15 exp Sinusitis/ 9419
16 13 or 14 or 15 89228
17 12 and 16 243

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2015

1 azelastine.mp. 327
2 olopatadine.mp. 254
3 exp Cromolyn Sodium/ 768
4 exp Sleep Apnea Syndromes/ 19814
5 exp Sinusitis/ 9419
6 exp Asthma/ 60783
7 exp Nasal Absorption/ or exp Nasal Sprays/ or nasal.mp. 58239
8 exp Administration, Intranasal/ 8152
9 1 or 2 or 3 1311
10 4 or 5 or 6 89228
11 7 or 8 62254
12 9 and 10 and 11 15

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to May Week 4 2015

1 exp Cetirizine/ 1152
2 exp Loratadine/ 1014
3 fexofenadine.mp. 693
4 levocetirizine.mp. 277
5 desloratadine.mp. 454
6 1 or 2 or 3 or 4 or 5 2655
7 exp Asthma/ 108998
8 exp Bronchial Hyperreactivity/ 6928
9 exp Inflammation/ and exp Orbital Diseases/ 1264
10 exp Frontal Sinusitis/ or exp Sphenoid Sinusitis/ or exp Ethmoid Sinusitis/ or exp Sinusitis/ or exp Maxillary Sinusitis/ 16762
11 exp Sleep Apnea Syndromes/ 25245
12 exp Granulomatosis with Polyangiitis/ 5953
13 7 or 8 or 9 or 10 or 11 or 12 159158
14 azelastine.mp. 595
15 olopatadine.mp. 266
16 exp Cromolyn Sodium/ 3989
17 14 or 15 or 16 4799
18 6 or 17 7365
19 13 and 18 2103
20 limit 19 to (english language and humans and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 673

Intranasal Corticosteroids, Asthma

Baiardini I, Villa E, Rogkakou A, et al. Effects of mometasone furoate on the quality of life: a randomized placebo-controlled trial in persistent allergic rhinitis and intermittent asthma using the Rhinasthma questionnaire. *Clinical & Experimental Allergy*. 2010;41:417–423.

BACKGROUND: Allergic rhinitis, especially when persistent (PER) and associated with asthma heavily impairs patients' quality of life (QoL). OBJECTIVE: This study assessed the effect of mometasone furoate nasal spray (MFNS) on the QoL of patients with PER and asthma, using the Rhinasthma questionnaire (EUDRACT n. 2007-004683-45). METHODS: Patients with moderate/severe PER and intermittent asthma were randomized to MFNS (alcohol-free) 200 mg/day or placebo for 28 days. Rhinasthma was completed at baseline and at weeks 2 and 4. The total five symptom score (T5SS) for rhinitis, the asthma symptom score and the sum of the two [global symptoms score (GSS)] were recorded daily. The primary outcome was the change in the Rhinasthma global summary (GS) at the end of treatment. Secondary end-points were (a) the change from baseline to end of treatment of each Rhinasthma factor: upper airways (UAs), lower airways (LAs) and respiratory allergy impact; (b) the change from baseline to end of treatment of the T5SS and of the GSS and (c) the use of rescue medication. RESULTS: Fifty-two adults were randomized. Compared with placebo, MFNS produced a significant change in the Rhinasthma GS (-10.4 vs. 0.4; P<0.01). MFNS also achieved a significant improvement of the UA (-16.6 vs. 0.1; P<0.001), LA (-10.8 vs. 1.1; P<0.001) and GSS (-6.7 vs. -3.1; P=0.019). The change of the T5SS was greater in the MFNS group but did not reach statistical significance. Conclusion In patients with PER rhinitis and intermittent asthma, MFNS improves the QoL and the burden of respiratory symptoms. Treating rhinitis may affect the asthma-related QoL.

Kersten E, van Leeuwen J, Brand P, et al. Effect of an Intranasal Corticosteroid on Exercise Induced Bronchoconstriction in Asthmatic Children. *Pediatric Pulmonology*. 2012;47:27-35.

RATIONALE: Allergic rhinitis and exercise induced bronchoconstriction (EIB) are common in asthmatic children. The aim of this study was to investigate whether treatment of allergic rhinitis with an intranasal corticosteroid protects against EIB in asthmatic children. METHODS: This was a double-blind, randomized, placebo-controlled, parallel group study. Subjects aged 12–17 years, with mild-to-moderate asthma, intermittent allergic rhinitis and >10% fall in FEV1 at a screening exercise challenge were randomized to 22 ±3 days treatment with intranasal fluticasone furoate or placebo. The primary outcome was change in exercise induced fall in FEV1. Secondary outcomes were changes in the area under the curve (AUC), asthma control questionnaire (ACQ), pediatric asthma quality of life questionnaire (PAQLQ), and exhaled nitric oxide (FeNO). RESULTS: Twenty-five children completed the study. Mean exercise induced fall in FEV1 (±SD) decreased significantly (95% CI, 0.7-18.2%; P=0.04) in the fluticasone furoate group from 28.4 ±15.8% to 19.0 ±13.8%, compared to the placebo group (27.4 ±16.0% to 27.4 ±19.2%). The change in AUC was not significantly different between treatment groups. However, within the fluticasone furoate group the AUC decreased significantly (P=0.01). Although total PAQLQ score did not improve, the activity limitation domain score improved significantly within the fluticasone furoate group (P=0.03). No significant changes were observed in FeNO and ACQ. CONCLUSION: Treatment of allergic rhinitis in asthmatic children with an intranasal corticosteroid reduces EIB and tends to improve quality of life.

Scichilone N, Arrigo R, Paterno A, et al. The Effect of Intranasal Corticosteroids on Asthma Control and Quality of Life in Allergic Rhinitis with Mild Asthma. *Journal of Asthma*. 2011;48:41-47.

BACKGROUND. The mechanisms through which rhinitis affects asthma have not been completely elucidated. We explored whether the effect of nasal treatment on asthma control and respiratory-related quality of life (HRQoL) is mediated by inflammatory changes of the upper and lower airways. METHODS. Allergic

rhinitics with mild asthma were randomized to a 14-day treatment period with either nasal budesonide 100 mcg, 1 puff per nostril twice a day, or placebo. Clinical, functional, and biological evaluations were performed before and after treatment. RESULTS. Twenty subjects (M/F: 10/10; age: 31 ±15 years; mean ±SD) were enrolled, and a total of 17 individuals completely participated in the study. Lung function was within the normal range. The total asthma control test (ACT) score was 20 ±5.3 and the RHINASTHMA Global Summary (GS) was 44 ± 15. The percentage proportion of eosinophils in nasal lavage was 9.9% and significantly correlated with spirometric parameters reflecting peripheral airway function (for FEF_{50}: r=0.48, p=0.03; for FEF_{25}: r=0.47, p=0.03). The pH of the exhaled breath condensate (EBC) was 7.33 ±0.4. After nasal treatment, the percentage proportion of eosinophils fell significantly (p=0.002), and changes in percentage proportion of eosinophils were associated with changes both in the ACT score (r=0.76, p=0.04) and in the RHINASTHMA GS (r=0.77, p=0.02). The increase in the pH of the EBC was not associated with changes in the ACT score or with the RHINASTHMA GS. CONCLUSIONS. These findings confirm that, in subjects with allergic rhinitis with mild asthma, nasal inflammation impacts on asthma control and HRQoL. The improved control of respiratory symptoms obtained with nasal corticosteroids seems to be mediated by functional changes in the peripheral airways.

Intranasal Corticosteroids, Sleep Apnea

Lavigne F, Petrof B, Johnson J, et al. Effect of topical corticosteroids on allergic airway inflammation and disease severity in obstructive sleep apnoea. *Clinical & Experimental Allergy*. 2013;43:1124-1133.

BACKGROUND: The incidence of sleep-related breathing disorders is correlated with lower and upper airway inflammatory diseases, such as asthma and allergic rhinitis. We hypothesized that corticosteroids treatment would lead to a greater reduction in disease severity in obstructive sleep apnea syndrome (OSAS) patients with concomitant allergic rhinitis vs. non-allergic OSAS patients by reducing the level of inflammation in upper airway tissues. OBJECTIVE: This study was performed to determine whether treatment with intranasal corticosteroids could reduce upper airway inflammation and improve sleep parameters in obstructive sleep apnea syndrome patients with or without concomitant allergic rhinitis. METHODS: Obstructive sleep apnea syndrome patients with (n=34) or without (n=21) documented allergic rhinitis voluntarily enrolled in the study and were assessed at baseline and after corticosteroids treatment for 10-12 weeks. Sleep studies were performed and biopsies were obtained from the inferior turbinate, nasopharynx, and uvula. The apnea-hypopnea index, sleep quality, and level of daytime alertness were determined, and immunocytochemistry was used to phenotype tissue inflammation. RESULTS: Standard sleep indices improved following treatment in the entire cohort of obstructive sleep apnea syndrome patients, with greater improvement seen in the allergic rhinitis group. Allergic rhinitis patients demonstrated significantly improved O2 saturation and a lower supine apnea-hypopnea index score after corticosteroid treatment; similar improvements were not seen in the non-allergic rhinitis group. Eosinophilia was detected at all three sites in the allergic rhinitis group, but not in the non-allergic rhinitis group. Following treatment, fewer eosinophils and CD4 lymphocytes were documented at all three biopsy sites in the allergic group; the reduction in inflammation was less apparent in the non-allergic rhinitis group. CONCLUSION: This study has provided important molecular and clinical evidence regarding the ability of corticosteroids to reduce upper airway inflammation and improve obstructive sleep apnea syndrome morbidity patients with concomitant allergic rhinitis.

Strobel W, Schlageter M, Andersson M, et al. Topical nasal steroid treatment does not improve CPAP compliance in unselected patients with OSAS. *Respiratory Medicine*. 2011; 105:310-315.

BACKGROUND: Continuous positive airways pressure (CPAP) for treatment of obstructive sleep apnea (OSA) can produce troublesome nasal symptoms (i.e. congestion, rhinorrhea) that may reduce the compliance of CPAP. Topical nasal steroids are often prescribed to reduce these side effects, although scientific data are scarce supporting any benefits of this treatment for CPAP-induced nasal side effects. OBJECTIVE: To study whether a topical nasal steroid can reduce

CPAP-induced nasal symptoms and improve CPAP adherence during the initial phase of OSA treatment. METHODS: A randomized, double-blinded, placebo-controlled study with fluticasone propionate 100 mg/nasal cavity twice daily Treatment was started 10 days prior to and continued throughout the first 4 weeks of CPAP. Sixty-three patients who were selected for CPAP treatment participated. Nasal symptoms were recorded, nasal patency was assessed and lung function was measured with a peak flow meter. The patients' adherence to CPAP was recorded by the CPAP device. RESULTS: Total nasal symptoms increased from baseline to 4 wks after CPAP use for both nasal treatments ($p<0.05$). No differences in total nasal symptoms between treatments were seen ($p=1$), and no differences in nasal peak flow values after treatment were seen ($p=0.11$). Moreover, there were no differences in CPAP use between the treatments. CONCLUSION: fluticasone propionate as a nasal topical steroid does not reduce CPAP-induced unwanted nasal side effects, and has no beneficial effect on CPAP compliance during the first four weeks of treatment in unselected patients with OSAS.

Oral Antihistamines, Asthma

Lu S, Liu N, Dass B, et al. A Randomized Study Comparing the Effect of Loratadine Added to Montelukast with Montelukast, Loratadine, and Beclomethasone Monotherapies in Patients with Chronic Asthma. *Journal of Asthma*. 2009; 46:465-469. DOI: 10.1080/02770900902846323.

BACKGROUND. Loratadine added to montelukast has been suggested to improve endpoints of asthma. Objective. This study investigated the additive effects of concomitant montelukast and loratadine when compared with montelukast, loratadine, and inhaled beclomethasone monotherapies in asthma. METHODS. Patients (n=406) were 15 to 65 years of age with a forced expiratory volume in 1 second (FEV1)-predicted of 50% to 85%, FEV1 reversibility ≥15%, and a minimal level of daytime symptoms and β-agonist use. This three-part 2X2 crossover-study consisted of two double-blind 6-week treatment periods where patients were administered once daily oral montelukast 10 mg, loratadine 10 mg, montelukast 10 mg + loratadine 10 mg, or twice daily inhaled beclomethasone 200 mcg. A subsequent 48-week extension study compared montelukast+loratadine with beclomethasone. The primary endpoint was the percentage change from baseline in FEV1. RESULTS. Over 6 weeks of double-blind treatment, significant improvements ($p<0.05$) in the primary endpoint of FEV1 were seen for montelukast+loratadine versus loratadine (least-square mean percentage-point difference of 5.8%), beclomethasone versus montelukast+loratadine (2.35%), montelukast versus loratadine (5.94%), and beclomethasone versus montelukast (4.65%); a numerical improvement ($p = 0.054$) was seen for montelukast+loratadine versus montelukast (1.60%). Significant improvements for montelukast+loratadine versus montelukast were seen in some secondary endpoints (evening peak expiratory flow, nocturnal asthma symptom score, nocturnal awakenings, and asthma-specific quality of life) but not others. Significant improvements in most endpoints except daytime asthma symptoms score were seen for montelukast+loratadine versus loratadine. In the extension study, both montelukast+loratadine and beclomethasone improved several endpoints. All treatments were generally comparable in the percentage of patients with clinical and laboratory adverse experiences. CONCLUSION. In this study, the addition of loratadine to montelukast produced a small numerical, but not statistically significant, improvement in FEV1 and, in general, no consistent improvement in other asthma endpoints. No improvement of montelukast+loratadine versus beclomethasone was seen in any endpoint.

Ngamphaiboon J, Wirawarn T, Thongkaew T. Prevention of recurrent wheezing in young children by loratadine compared with ketotifen. *Journal of the Medical Association of Thailand*. 2009;92:351-355.

BACKGROUND: Various trials showed benefit of the prophylactic agent ketotifen in prevention of recurrent wheezing in young children, but no such clinical trial with loratadine or comparison trial is available. OBJECTIVE: To study the efficacy and safety of loratadine syrup compared with ketotifen and placebo in prevention of recurrent wheezing in young children. METHODS: Randomized double-blind placebo controlled trial on 90 recurrent wheezing children aged less than 6 years old was done. Children were randomized to receive loratadine, ketotifen syrup, or placebo with dose of 0.25 mL/kg once a day for four months. Blood biochemistry (CBC, LFT) and EKG were performed pre and post treatment period. Assessment of symptoms--wheezing and night cough including use of

bronchodilators was done daily via patient diary card. Subjects were asked to do monthly visits to the clinic for physical examination. At those visits, the doctors questioned the patients about adverse event. RESULTS: Of the 90 children enrolled, 12 dropped out. Thus, 27 children remained in the loratadine, 26 in the placebo, and 25 in the ketotifen group. The demographic data were comparable among the three treatment groups. It was noted that wheezing decreased significantly at 2 months in the ketotifen (p = 0.008) and at 3 months in the loratadine (p = 0.029) but not in the placebo group. Coughing at night decreased significantly at 3 months in both the loratadine (p = 0.005) and the ketotifen (p = 0.036) group. The use of bronchodilator drug was significantly decreased at 2 months in the ketotifen (p = 0.028) and placebo (p = 0.025) group, and at 3 months in the loratadine (p = 0.009) group. Only a few patients had mild adverse events in all groups. CONCLUSION: Loratadine and ketotifen are safe and effective significantly in prevention of recurrent wheezing in young children.

Manjra A, Nel H, Maharaj B. Effect of Desloratadine on Patients with Allergic Rhinitis and Exercise-Induced Bronchoconstriction: A Placebo Controlled Study. *Journal of Asthma*. 2009;46:156-159.

BACKGROUND. Exercise induced broncho-constriction (EIB) is a significant problem in asthmatic patients. The link between allergic rhinitis and asthma is now well established. Patients with allergic rhinitis may have EIB. OBJECTIVE. This study compared the effects of desloratadine and placebo on EIB in a group of patients with allergic rhinitis and EIB. METHODS. This was a double blind placebo controlled, randomized, crossover study. Exercise challenge tests were performed before and after 7 days of treatment with either 5 mg desloratadine or placebo. Patients then underwent a washout period for 7 days and were crossed over to receive either 5 mg desloratadine or placebo. The exercise challenge tests were repeated. RESULTS. Desloratadine had no effect on the reduction in percentage fall in FEV1, the AUC (0–60 min) and the time to recovery. CONCLUSIONS. Desloratadine has no effect in attenuating the broncho-constriction caused by exercise in patients with allergic rhinitis and exercise induced broncho-constriction.

Pasquali M, Baiardini I, Rogkakou A. Levocetirizine in persistent allergic rhinitis and asthma: effects on symptoms, quality of life and inflammatory parameters. Clinical and Experimental Allergy. 2006;36:1161-67.

BACKGROUND: Levocetirizine (LCZ) has been shown to be effective in allergic rhinitis. We evaluated its clinical efficacy, antinflammatory actions and its effects on quality of life (QoL) with a specific instrument in the asthma–rhinitis comorbidity. METHODS: Fifty adult patients with persistent rhinitis with/without asthma were enrolled. After a 1-week run-in for baseline evaluation, they were randomized to LCZ or placebo for 8 weeks. Cromolyn and salbutamol were permitted on demand. Rhinoconjunctivitis and asthma symptoms were evaluated by diary cards. QoL was assessed by the specific Rhinasthma questionnaire and the generic SF-36 at different time-points. Nasal scrapings and lavages were also performed for inflammatory cell count and mediator assessment. RESULTS: Ten patients dropped out for unrelated reasons and the remaining completed the study with no side-effect. Symptoms began to decrease in the active group at the second week of treatment when the difference with the placebo group became significant (0.05) and so remained until the end of the trial. Starting from 2 weeks of therapy, there was a significant decrease vs. baseline in all the four components of the Rhinasthma questionnaire only in the active group. The intergroup comparison became significant (P=0.05) at 4 weeks. The SF-36 detected only sporadic differences between groups. Eosinophils and neutrophils in nasal scraping were significantly decreased in the LCZ group vs. baseline at all times. Nasal mediators were under the detection limits and no analysis could be performed. In the active group, only two patients used rescue medications compared with 13 patients in the placebo group. CONCLUSIONS: LCZ is clinically effective and capable of improving the rhinitis–asthma-related QoL.

Davis B, Todd D, Cockcroft W. Effect of combined montelukast and desloratadine on the early asthmatic response to inhaled allergen. *Journal of Allergy & Clinical Immunology*. 2005;116:768-72.

BACKGROUND: The early asthmatic response (EAR) to inhaled allergen results from IgE-mediated release of multiple mast-cell mediators, including leukotrienes and histamine, both of which cause bronchoconstriction. Combination therapy directed at blocking the effects of both mediators might protect against the EAR

better than either therapy alone. OBJECTIVE: We sought to evaluate the effect of desloratadine and montelukast, administered alone and in combination, on the EAR to inhaled allergen. METHODS: Ten adults with mild-to-moderate atopic asthma participated in a randomized, 4-way crossover study design comparing placebo, 5 mg of desloratadine, 10 mg of montelukast, and the combination administered at 26 hours and 2 hours before each allergen challenge conducted at least 7 days apart. The primary end point was the concentration of allergen that resulted in a 20% decrease in FEV1 (PC20). RESULTS: The geometric mean allergen PC20 (mean log +/- SEM) for combination therapy, montelukast, desloratadine, and placebo was 697 U/mL (2.8433 +/- 0.3253), 338 U/mL (2.5295 +/- 0.2979), 123 U/mL (2.0883 +/- 0.2102), and 104 U/mL (2.0166 +/- 0.2553), respectively (n = 9; P < .00001, ANOVA). Montelukast increased the allergen PC20 4.8-fold, and combination therapy increased the allergen PC20 8.9-fold. The effect of the combination was greater than that with montelukast alone (P < .02). Desloratadine treatment was no different than placebo. CONCLUSIONS: The early response to inhaled allergen was unchanged after desloratadine therapy and partially inhibited with montelukast therapy. The combination of desloratadine and montelukast provided superior efficacy to either blocker administered alone. Investigations into the possible mechanisms of the enhanced inhibition are necessary.

Orhan F, Baki A. The bronchodilatory effects of loratadine, terbutaline, and both together versus placebo in childhood asthma. *Journal of Investigational Allergology & Clinical Immunology*. 2003;13:189-92.

AIM: To assess the bronchodilatory effect of loratadine in children with mild-to-moderate asthma and to determine whether loratadine interacts with terbutaline. METHODS: The effect on pulmonary functions of a 10 mg oral dose of loratadine, with and without inhaled terbutaline powder (0.5 mg), was determined in 13 patients with a mean (SE) age of 10.63 (0.77) years (range from eight to 17 years) at 11 time points during 8 h in a randomized, double-blind, placebo controlled, crossover study. Forced expiratory volume in 1 s (FEV1) was the primary measure of efficacy. RESULTS: Although loratadine alone produced an increase in FEV1 relative to baseline, this was not statistically significant ($p > 0.05$). Terbutaline with, and without loratadine, significantly increased FEV1 from 1 to 5 h according to baseline ($p<0.004$). When compared with the placebo, loratadine significantly increased FEV1 from 150 min to 8 h ($p<0.05$). Also, terbutaline alone, or in combination with loratadine, significantly increased FEV1 from 30 min to 7 h ($p<0.004$, from 30 min to 5 h; $p<0.05$, between 6-7 h). Although the mean increase in FEV1, with terbutaline + loratadine in combination, was greater than with terbutaline alone, the difference was not significant ($p>0.05$). CONCLUSION: Loratadine has a mild bronchodilatory effect in the study period and does not interfere with the bronchodilatory effect of terbutaline in childhood asthma.

Baena-Cagnania C, Bergerb W, DuBuske L, et al. Comparative Effects of Desloratadine versus Montelukast on Asthma Symptoms and Use of ß2-Agonists in Patients with Seasonal Allergic Rhinitis and Asthma. *Int Arch Allergy Immunol*. 2003;130:307-313. DOI: 10.1159/000070218

BACKGROUND: Asthma and seasonal allergic rhinitis (SAR) are recognized as manifestations of a single airway disease. Desloratadine has demonstrated efficacy in treating SAR symptoms, including nasal obstruction. METHODS: Safety and efficacy of desloratadine and montelukast each were assessed in a double-blind, placebo-controlled trial of patients with SAR and symptoms of asthma, who were assigned randomly to once-daily treatment with desloratadine 5 mg, montelukast 10 mg, or placebo for 4 weeks. Change from baseline of AM/PM reflective total asthma symptom severity scores (TASS), FEV1, individual asthma symptom scores, and β2-agonist usage were assessed. RESULTS: Desloratadine and montelukast each were associated with statistically significant reductions from baseline in the mean TASS averaged over the 4-week period ($p \leq 0.022$ vs. placebo). Individual asthma symptom scores also improved significantly for both therapies ($p \leq 0.05$). Patients treated with desloratadine or montelukast demonstrated improvement from baseline in FEV1 versus placebo; significant improvement was seen in a subset of patients with baseline FEV1 <80% of predicted normal (both $p<0.05$). Both active therapies significantly reduced β2-agonist use (both $p<0.01$). Improvements for both therapies were comparable for all efficacy parameters; they were tolerated well with adverse event profiles similar to placebo. CONCLUSIONS: Asthma symptoms and ß2-agonist were improved significantly in patients with concomitant SAR and asthma treated with desloratadine

5 mg as well as montelukast 10 mg once daily. Both therapies significantly improved FEV1 in a subset of patients with FEV1 <80% of predicted normal at entry. Improvements in asthma symptoms were comparable for both active treatment groups.

Oral Antihistamines, Sleep Apnea

Acar M, Cingi C, Sakallioglu O, et al. The effects of mometasone furoate and desloratadine in obstructive sleep apnea syndrome patients with allergic rhinitis. Am *J Rhinol Allergy*. 2013;27:e113-e116. DOI 10.2500/ajra.2013.27.3921

BACKGROUND: Allergic rhinitis (AR) and obstructive sleep apnea syndrome (OSAS) are worldwide prevalent diseases. These diseases impair patient quality of life. The aim of this study was to investigate and compare the efficacy of treatment of AR on OSAS by objective and subjective methods. METHODS: The study group was composed of 80 OSAS patients with AR between the ages of 30 and50 years. The patients were admitted with the complaint of snoring, and they were asked about AR-related symptoms (nasal discharge, nasal itching, sneeze, and nasal obstruction). Daytime somnolence was measured by the Epworth sleepiness scale (ESS). Sleep parameters on polysomnography tests before and after treatment were compared, and the effects of different AR treatment protocols on sleep quality were evaluated. RESULTS: When pretreatment and posttreatment apnea–hypopnea index (AHI) values of the groups were compared, the most significant difference was observed in the nasal steroid (Ns) plus antihistamine (Ah) group ($p<0.05$). The ESS results were significantly decreased in the Ns and Ns+Ah groups after treatment ($p<0.05$). AHI oxygen saturation <90% were significantly decreased in the Ns and Ns+Ah groups after treatment ($p<0.05$). CONCLUSION: Nasal obstruction due to nasal congestion causes increases in airway resistance and can lead to development of OSAS. We concluded that treating AR with Ns has both positive effects on OSAS and daily activity. However, adding Ah to this treatment did not show improved effects compared with placebo treatment.

Intranasal Allergy Drugs

Goals:

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

Length of Authorization:

6 months

Requires PA:

- Non-preferred intranasal corticosteroids
- Intranasal antihistamines
- Intranasal cromolyn sodium

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Will the prescriber consider switching to a preferred product? *Note: preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.*	Yes: Inform provider of covered alternatives.	No: Go to #3
3. Is the prescribed drug an intranasal corticosteroid?	Yes: Go to #4	No: Pass to RPh; deny for medical appropriateness or not funded by OHP.
4. Does the patient have asthma or reactive airway disease exacerbated by chronic/allergic rhinitis (493.xx)?	Yes: Go to #5	No: Go to #6

Approval Criteria		
5. Does the drug profile show the patient is currently receiving an orally inhaled corticosteroid (ICS)?	Yes: Pass to RPh; deny for medical appropriateness. Note: asthma-related outcomes are not improved by the addition of an intranasal corticosteroid to an orally inhaled corticosteroid.	No: Approve for 6 months.
6. Does patient have other co-morbid conditions or complications that are funded by the OHP? • Chronic Sinusitis (473.xx) • Acute Sinusitis (461.xx) • Sleep Apnea (327.20; 327.21; 327.23; 327.29; 780.51; 780.53; 780.57)	Yes: Document ICD-9 code(s) and approve for 6 months.	No: Go to #7
7. RPh only: Is the diagnosis funded by the OHP?	Funded: Deny for medical appropriateness. (e.g., COPD, Obstructive Chronic Bronchitis, or other Chronic Bronchitis [496; 490; 491.0; 491.1; 491.2x; 491.8; 491.9]) Use clinical judgment to APPROVE for 1 month starting today to allow time for appeal. Message: "The request has been denied because it is considered medically inappropriate; however, it has been APPROVED for 1 month to allow time for appeal."	Not Funded: Deny, not funded by the OHP. (e.g., allergic rhinitis (477.x), chronic rhinitis (472.0), allergic conjunctivitis (372.14), upper respiratory infection (465.9), acute nasopharyngitis (common cold) (460), urticaria (708.x), etc.)

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

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Class Update with New Drug Evaluation: Oral Antifungals

Month/Year of Review: July 2015
New Drug: isavuconazole (a.k.a. isavunconazonium sulfate)
Current Status of PDL Class: See Appendix 1.

Date of Last Review: March 2013
Brand Name (Manufacturer): Cresemba™ (Astellas Pharma US, Inc.)
Dossier Received: Yes[1]

Research Questions:

- Is there any new evidence of effectiveness or safety for oral antifungals since the last review that would change current PDL or prior authorization recommendations?
- Is there evidence of superior clinical cure rates or morbidity rates for invasive aspergillosis and invasive mucormycosis for isavuconazole over currently available oral antifungals?
- Is there evidence of superior safety or tolerability of isavuconazole over currently available oral antifungals?
- Is there evidence of superior effectiveness or safety of isavuconazole for invasive aspergillosis and invasive mucormycosis in specific subpopulations?

Conclusions:

- There is low level evidence that griseofulvin has lower mycological cure rates and higher relapse rates than terbinafine and itraconazole for adult onychomycosis.[2] There is high level evidence that terbinafine has more complete cure rates than itraconazole (55% vs. 26%) for adult onychomycosis caused by dermatophyte with similar discontinuation rates for both drugs.[2] There is low level evidence itraconazole has higher complete cure rates than terbinafine (92% vs. 40%) for *Candida* onchomycosis.[2]
- Ketoconazole is associated with increased risk of liver injury, adrenal insufficiency and drug interactions.[3]
- There is high level evidence that voriconazole and posaconazole prevent more fungal infections in high risk hematology patients than fluconazole and itraconazole (OR= 0.47, 95% CI 0.32 – 0.69, I^2=0%, p=0.0001) with no difference in overall mortality or withdrawal due to adverse events.[4]
- There is moderate level evidence that isavuconazole is non-inferior to voriconazole to reduce all-cause mortality at 42 days from invasive aspergillosis in adult patients with hematologic malignancy (18.6% vs. 20.2%; adjusted absolute risk difference (AARD) = -1.0%; 95% CI -8.0%, 5.9%, Δ 10%).[5]
- There is low level evidence from a very small (n=37), open-label, non-comparative phase 3 trial that isavuconazole is effective for mucormycosis.[5]
- There is insufficient comparative safety data for isavuconazole to draw conclusions.[5]
- There are no data regarding use of isavuconazole in specific populations (e.g. elderly, pediatrics).[5]

Recommendations:

- Update the prior authorization criteria to reflect changes to the OHP prioritized list **(Appendix 5).**
- Maintain open access to fluconazole due to high level of evidence for multiple indications (including pediatric candidiasis).
- Maintain clinical prior authorization requirement for griseofulvin, itraconazole and terbinafine due to limited role outside of non-funded onychomycosis.
- Make ketoconazole non-preferred due to increased risk of hepatotoxicity, adrenal insufficiency and drug interactions.
- Consider allowing open access to either or both (depending on comparative pricing in executive session) voriconazole and posaconazole for hematology, oncology and infectious disease specialty prescribers to cover invasive aspergillosis. All other prescribers would continue to require a clinical prior authorization.
- Evaluate comparative pricing of other products in executive session for appropriate PDL placement.

Purpose for Class Update:

Isavuconazole (Cresemba™) was approved by the United States Food and Drug Administration (FDA) in March 2015 for invasive aspergillosis and invasive mucormycosis in adults.[6] This review evaluates its place in therapy and reconsiders current coverage policies in light of any new evidence and changes to the Oregon Health Plan (OHP) prioritized list.[7]

Previous Conclusions and Recommendations (2010):

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events
- Recommend inclusion of at least one medication from this group
- Recommend including nystatin for pediatric use

Background:

The oral antifungal class was ranked 82nd by net OHP fee-for-service drug costs in Q1-2015 ($21,000). Generic fluconazole was associated with 78% of claims and generic nystatin 18% of claims. **Appendix 1** provides a summary of FDA approved and off-label indications for oral and buccal antifungals as reported in Micromedex™.[8] The OHP prioritized list ranks candidiasis of the mouth, skin and nail at line 590, dermatophytosis of the scalp, hand, body at line 547, and dermatophytosis of the nail, groin and foot at line 495.[7] The funding line is currently line 476.[7] Many of these indications are funded on line 141 if they occur in an immunocompromised host.[7] But, notably, onychomycosis is not on line 141 and is not funded except under the co-morbidity rules.[7]

Superficial dermatophyte infections (i.e. ringworm) of the skin and scalp are very common occurring at a 10-20% lifetime incidence in the general population.[9] These specific infections are characterized by itchy, red skin lesions.[10] The majority of cases are caused by *Epidermophyton, Trichophyton* and *Microsporum* which survive on keratin.[11] They can be spread via close person-to-person contact or contact with infected pets. The infections are named by location (e.g. tinea capitis and tinea pedis).[11] Topical antifungals (except nystatin) are recommended and effective for treatment[11] but oral antifungals are indicated for immunocompromised patients.[10] Secondary bacterial infections are a potential complication.[10] Tinea unguium (i.e. onychomycosis) is a dermatophyte infection of the nails though *Candida* accounts for 5–10% of all cases.[2] It is a cosmetic concern but can also cause mild to moderate pain resulting in difficulty in wearing footwear and walking.[2,12] It can serve as a reservoir for fungi that spreads to feet, hands and groin and may increase the risk of secondary bacterial infection for immunocompromised patients.[12] Topical antifungals are not generally effective for onychomycosis and even oral therapy has a high rate of initial treatment failure.[12] Recurrence rates are 40%-70%.[2]

Oral candidiasis (i.e. thrush) is the most common fungal infection in humans with reported asymptomatic carrier rates of up to 75%.[13] The highest rates of symptomatic disease are in patients with impaired immune systems (e.g. patients infected with human immunodeficiency virus [HIV], patients on the extremes of age, and oncology chemotherapy or organ transplant patients).[13] Other risk factors include use of inhaled corticosteroids or use of broad spectrum antibiotics.[13] Complications of oral candidiasis are uncommon but mouth pain may lead to nutritional deficit.[13] Topical therapies (troches, buccal tablets or suspensions) can be effective for mild disease but systemic fluconazole is recommended for all patients (including children).[13] Relapse rates in clinical trials range from 28-75% of patients.[13]

The incidence of invasive fungal infections has increased in the last decade, likely because of the increasing number of patients at risk due to advances in oncology chemotherapy, hematopoietic stem cell transplant and organ transplant.[14] Candidiasis and aspergillosis are the most common pathogens.[14] Mucormycosis is still rare but increasing in prevalence.[14] Other systemic fungal infections include by histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, paracoccidioidomycosis, and sporotrichosis.[14] Generally, in the immunocompetent host, these cause mild or asymptomatic disease but can become invasive in immunocompromised hosts.[14] *Fusarium* and *Cryptococcus* species are additional opportunistic fungi.[14]

Candida infections "range from non–life-threatening mucocutaneous disorders to invasive disease that can involve any organ."[15] Most severe cases affect immunocompromised or critically ill patients where mortality rates are highest.[15] The Infectious Diseases Society of America (IDSA) published evidence-graded treatment guidelines for localized (e.g. vulvovanginal, urinary tract, or esophageal) and systemic infections, including complications such as endocarditis and meningitis, in 2009.[15] Fluconazole is recommended as initial treatment for most localized and systemic infections in immunocompetent adults and children due to its good bioavailability, penetration into the central nervous system and intraocular pentration.[15] The other azole antifungals (itraconazole and voriconazole) demonstrate similar activity against *Candida.*[15] Central nervous system infections or infections in immunocompromised patients require initial treatment with intravenous antifungals (e.g. caspofungin, micafungin or amphotericin B) but recommendations include a step down to oral fluconazole upon improvement.[15] All azoles and flucytosine should be avoided in pregnant women due to documented birth defect risks.[15] Fluconazole is an initial recommendation for antifungal prophylaxis for adult and pediatric patients at high risk of candidiasis (e.g. organ transplant patients, intensive care patients in units with high rates of candidiasis, patients with chemotherapy-induced neutropenia and stem cell transplant patients with neutropenia).[15]

Aspergillus species are associated with allergic bronchopulmonary aspergillosis, which occurs almost exclusively in patients with cystic fibrosis or asthma and is generally treated with steroids.[16] Oral azole antifungals may be used to reduce steroid doses.[16] Other clinical forms of aspergillosis include chronic infection, which affects patients with underlying lung disease, and invasive pulmonary aspergillosis affecting patients with prolonged neutropenia, advanced HIV infection, inherited immunodeficiency and patients who have undergone allogeneic hematopoietic stem cell transplantation or lung transplantation.[16,17] It is the most common fungal pathogen in febrile neutropenic patients.[17] Invasive disease focuses in the lungs and sinuses but may disseminate.[17] Voriconazole is recommended as primary treatment for most patients though; few randomized trials have been performed.[17] Posaconazole or itraconazole are recommended for prophylaxis in high-risk patients.[17]

Mucormycosis, caused by fungi commonly found in soils and decaying vegetation (e.g. *Rhizopus, Mucor, Lichtheimia*), is responsible for serious rhino-orbital-cerebral and pulmonary infections in immunocompromised hosts and diabetics with ketoacidosis.[18,19] *Rhizopus* thrives in high glucose, acidic conditions.[18] It also prefers a high iron environment which is accentuated in the presence of deferoxime and the iron-chelates it produces.[18] While rare (0.4 – 1.7 cases per million/year), it is highly fatal (24-49%).[19] Mucormycosis appears more prevalent after natural disasters (e.g. tornados), in combat zones and is associated with penetrating trauma.[18,19] Current treatment recommendations include surgical debridement and amphotericin B.[18]

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

Systematic Reviews:

Onychomycosis
A fair quality systematic review of oral onychomycosis therapy published in December 2013 included 46 placebo or active RCTs of terbinafine, fluconazole, itraconazole, posaconazole, griseofulvin, and ketoconazole and compared clinical or mycological cure rates.[20] Study rigor was not reported. There was no formal pooling of results but the authors concluded fluconazole, itraconazole and terbinafine were effective. Terbinafine produced the "best result" when dermatophyte was the pathogen and the azoles were recommended for *Candida* infections.[20]

Gupta and Paquet published a fair quality qualitative systematic review of oral onychomycosis therapy in children that included 26 publications.[21] Case reports (18) and retrospective studies (3) were also included because of the lack of information in this population.[21] Interventions included terbinafine, itraconazole, griseofulvin and fluconazole.[21] Sample sizes were very small (1 – 19).[21] Outcomes were converted to "complete cure", defined as 100% visual clearing of the nail or negative fungal culture, in order to pool the data.[21] Overall, oral therapy resulted in a complete cure rate in 70.8% of patients (n=151).[21] The authors concluded systemic antifungals for pediatric onychomycosis was safe and effective.[21]

Aspergillosis
Cochrane published a systematic review of the effectiveness and safety of antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis.[22] Four trials were identified but no studies met the inclusion criteria.

Antifungal prophylaxis in hematology patients
Ping et al. published a good quality meta-analysis comparing oral first generation azoles (fluconazole and itraconazole) to oral second generation azoles (voriconazole and posaconazole) for prophylaxis of fungal infections in hematology patients.[4] Four RCTs (n=2267) were included that reported proved or probable invasive fungal infections as the outcome.[4] Second generation azoles reduced the odds of fungal infection (OR= 0.47, 95% CI 0.32 – 0.69, I^2=0%, p=0.0001).[4] There was no difference between the regimens on overall mortality or withdrawal due to adverse events.[4]

New Guidelines:

Onychomycosis

British Association of Dermatologists (BAD) produced a good quality guideline for management of onychomycosis that was intended for implementation by the British National Health Service.[2] Twelve weeks of itraconazole and 12-16 weeks of terbinafine are recommended first line treatment for adult toenail onychomycosis based upon at least one high-quality meta-analysis, systematic review or RCT.[2] Terbinafine has reported better complete cure rates (100% absence of clinical signs and negative mycology results) than itraconazole (55% vs. 26%) and lower relapse rates (23%-21% vs. 53%-48%) for dermatophyte onychomycosis.[2] Itraconazole is considered more effective for *Candida* onychomycosis.[2] Terbinafine is well tolerated but there have been rare reports of Stevens–Johnson syndrome, and serious hepatic toxicity in patients with existing liver disease.[2] Reported adverse effects of itraconazole included hepatitis and prolonged QT interval. Discontinuation was similar for both drugs and lower if either was given as a pulse regimen rather than continuously.[2] Fluconazole is recommended for patients unable to tolerate itraconazole or terbinafine based upon at least one high-quality systematic review of case–control or cohort studies.[2] Griseofulvin has poor oral bioavailability unless taken with fatty foods, lower mycological cure (negative mycology results but clinical signs remain) rates (30–40%) and higher relapse rates so, is not recommended unless other drugs are unavailable or contraindicated based upon well-conducted case–control or cohort studies with a low risk of confounding, bias or chance.[2] Reported adverse effects included nausea and rashes in 8–15% of patients.[2] The BAD also provide recommendations in special populations.[2] Onychomycosis is present in up to 33% diabetics and considered a predictor for the development of diabetic foot ulcers.[2] There is reportedly a prevalence of 30% in HIV patients.[2] Terbinafine is recommended for both cases due to lower risk of drug interactions and high efficacy.[2] Recommendations for children are similar to adults but with lower levels of evidence.

Invasive fungal infections in cancer patients

The Infectious Diseases Working Party of the German Society of Hematology and Oncology updated treatment recommendations for fungal infections in cancer patients.[23] The guideline focused on patients with solid tumors or hematologic malignancies and includes treatment of acute invasive infections caused by *Aspergillus, Candida, Cryptococcus, Scedosporium, Fusarium, Zygomycetes,* and *Trichosporon.* The literature search end date was June 2012.[23] IDSA evidence levels were used: I- at least 1 properly conducted RCT, II- at least 1 well-designed, non-randomized controlled clinical trial or dramatic results of uncontrolled experiments, III – expert opinion.[23] Intravenous therapies are frequently required for initial therapy with step-down to oral therapies when clinically indicated. Oral therapies include: voriconazole (level I) is recommended for invasive aspergillosis and posaconazole is second-line treatment (level II).[23] Voriconazole or fluconazole is recommended (level I) for candidemia in non-neutropenic patients.[23] Posaconazole is recommended first-line for mucormycosis (level III).[23] Voriconazole is recommended for the very rare *Scedospoirum* and *Trichosporon* infections and fusariosis (level III).[23] Posaconazole is recommended for *Scedospoirum* (level III).[23]

Mucormycosis

The European Conference on Infections in Leukemia published diagnosis and treatment guidelines for mucormycosis.[24] Evidence is very limited because of the rarity of the disease. The guidelines apply to all patients (hematologic and non-hematologic) because existing studies are in mixed populations.[24] A consensus based approach was used using IDSA evidence levels where possible: I- at least 1 properly conducted RCT, II- at least 1 well-designed, non-randomized controlled clinical trial or dramatic results of uncontrolled experiments, III – expert opinion.[24] The conference attendees acknowledge relationships with multiple manufacturers and the conference was funded by an unrestricted grant from Astellas Pharma, Gilead Sciences, Mercke Sharp Dohme, Pfizer and Schering Plough.[24] Amphotericin B deoxycholate is recommended (level II) and is FDA-approved for mucormycosis. Posaconazole is recommended second-line (level II) and for maintenance treatment (level III) using data from 2 separate but overlapping compassionate use protocols (n=104).[24] Overall, 73% of patients survived 1

month post-therapy for the infection. Isavuconazole *in vitro* activity is mentioned in the guidelines but clinical data were not available at the time of publication.[24]

European Society for Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology published joint clinical guidelines for the diagnosis and management of mucormycosis.[19] The methods for evidence gathering, grading (IDSA) and consensus approach were published for transparency.[19] Multiple industry funding declarations encompass more than one complete page of the publication.[19] Posaconazole is recommended for prophylaxis in neutropenic or graft versus host disease patients in an "outbreak situation" (level III) but the authors acknowledge this is a contrived situation.[19] Posaconazole is recommended second-line for treatment (level II) based upon the compassionate use data mentioned above and only if liposomal amphotericin B in not effective or not tolerated.[19] Isavuconazole is not mentioned in the guidelines.

Hyalohyphomycosis

European Society for Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology published joint clinical guidelines for a heterogeneous group of mycoses defined by the presence of hyaline hyphae.[19] This includes the genera of *Fusarium, Scedosporium, Acremonium, Scopulariopsis, Purpureocillium* and *Paecilomyces* which are increasingly affecting severely immunocompromised patients.[19] The guideline covers epidemiology, clinical spectrum, diagnosis and therapy, mainly for species associated with the genera *Fusarium* and *Scedosporium*. The methods for evidence gathering, grading (IDSA) and consensus approach were published for transparency.[19] Voriconazole is recommended first-line treatment for both species (level II) with posaconazole recommended for *Fusarium* salvage treatment (level II).[19]

New Safety Alerts:

Ketoconazole – 7/26/2013[3]

The FDA updated the label to limit the use of oral ketoconazole due to potentially fatal liver injury, risk of drug interactions and adrenal gland problems. It should only be used for treatment of fungal infections when alternative antifungal therapies are not available or not tolerated. The black box warning was revised to include a contraindication in patients with liver disease. Serious liver damage has occurred in patients on high doses for short duration and low doses for long duration with no other obvious signs of liver injury. Ketoconazole may cause adrenal insufficiency by decreasing the production of corticosteroids.

New Formulations or Indications:

No new indications or formulations identified.

Randomized Controlled Trials:

50 potentially relevant clinical trials were identified from the literature search. After further review, 0 trials were relevant head-to-head comparisons of oral antifungals and were therefore excluded.

NEW DRUG EVALUATION:

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

ClinicalTrials.gov lists 29 studies but, the majority is pharmacokinetic and drug interaction studies.[25] There is 1 Phase 2/3 study listed (NCT00413439 – prophylaxis in chemotherapy patients, n=18) and 3 phase 3 (NCT00413218 - invasive *Candida* treatment, n=450; NCT00634049 aka VITAL – renally impaired aspergillosis treatment, n=150; NCT00412893 aka SECURE – invasive aspergillosis treatment, n=527).[25] NCT00412893 has results posted.[25] No published placebo-controlled trials of isavuconazole were identified (see **Appendix 4)**. The manufacturer's dossier identifies a New England Journal of Medicine publication of the SECURE trial is pending.[1] The FDA Summary Review identified 2 Phase 3 studies, one in patients with invasive aspergillosis (presumably SECURE) and another in patients with invasive fungal disease including invasive mucormycosis (presumably VITAL).[5] The FDA narrative[5] is summarized below.

Clinical Efficacy[5]:
Isavuconazole 200 mg intravenous (IV) loading dose 3 times per day for 2 days followed by 200 mg IV or orally once a day was compared to voriconazole 6 mg/kg IV every 12 hours for 24 hours followed by 4 mg/kg IV or orally every 12 hours in a randomized, double-blind, non-inferiority study of invasive aspergillosis treatment. Patients were treated for 7 days after resolution of all clinical signs of infection, or a maximum of 84 days. The non-inferiority delta was 10% for the primary endpoint for all-cause mortality through day 42 and was judged to be reasonable by the FDA reviewer. Patients were adults, primarily with hematologic malignancy. Patients with a creatinine clearance of less than 50mL/min were excluded. The trial enrolled 527 patients but excluded 11 because they did not take the study drug, leaving 258 in each group. After randomization, patients were screened against criteria for proven, probable, possible or no invasive fungal disease. An additional 244 patients were excluded from the modified intention-to-treat (mITT) population because they did not meet the criteria for proven or probable invasive fungal disease. The mITT population consisted of 123 isavuconazole and 108 voriconazole patients. Using the ITT, the rate of all-cause mortality at day 42 was 18.6% in the isavuconazole group compared to 20.2% in the voriconazole group, with an adjusted absolute risk difference (AARD) of -1.0% (95% CI -8.0%, 5.9%), thus meeting the non-inferiority delta. This was confirmed with the mITT (AARD = -2.7% 95% CI -13.65, 8.2%).

The second trial was an open-label, non-comparative trial for treatment of invasive fungal disease caused by *Aspergillus* in patients with renal impairment or caused by rare filamentous fungi. Only the rare filamentous fungi results were used by the FDA for the invasive mucormycosis indication. Survival status was recorded at Days 42, 84 and 4 weeks after the last dose of isavuconazole, with Day 42 designated by the FDA as the most relevant endpoint. The mITT-*Mucorales* population included patients classified as having infection due *Mucorales* only (n=37). The all-cause mortality at day 42 was 14/37 (37.8%). These results were compared to 2 epidemiologic reports (n=22, n=241) where untreated mucormycosis mortality ranged from 95% to 97%. Patients were also matched to 3 controls who received amphotericin B from the Fungiscope Registry Database. The results of the matched control mortality comparison were: isavuconazole 7/21 (33.3%; 95% CI 14.6%, 57.0%) and amphotericin B 13/33 (39.4%; 95% CI 22.9%, 57.9%).

Clinical Safety[5]:
The safety database consists of 1692 subjects, including 1145 healthy volunteers from Phase 1 and 2 studies. The mean duration of exposure was 60 days. The SECURE trial treatment-emergent adverse events were more common in the voriconazole group (59.8%) than the isavuconazole group (42.4%, $p < 0.001$) and fewer isavuconazole patients withdrew due to adverse events (14.4% versus 22.8%, p=0.017).[1] Exclusion criteria from the SECURE study included hepatic dysfunction, patients with creatinine clearance of < 50ml/min, chronic aspergillosis, aspergilloma or allergic aspergillosis, previous antifungal therapy of more

than 4 days, CD4 counts < 200 cells/mm or AIDS, mechanical ventilation or a case that is unlikely to survive 30 days.[1] Data are still insufficient to draw definite conclusions about the relative safety of isavuconazole in a clinical setting.

Pharmacology and Pharmacokinetic Properties[26]:

Parameter	
Mechanism of Action	"Isavuconazole inhibits the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14-alpha-demethylase. This enzyme is responsible for the conversion of lanosterol to ergosterol. An accumulation of methylated sterol precursors and a depletion of ergosterol within the fungal cell membrane weakens the membrane structure and function. Mammalian cell demethylation is less sensitive to isavuconazole inhibition."[26]
Oral Bioavailability	98% (with or without food)
Distribution and Protein Binding	Volume of distribution ~450 liters; 99% protein bound, predominantly to albumin
Elimination	46.1% feces; 45.5% urine
Half-Life	130 hours
Metabolism	prodrug isavuconazonium sulfate is rapidly hydrolyzed in blood to isavuconazole; isavuconazole is CYP 3A4 and 3A5 substrate

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Appendix 1: Oral Antifungal Agents and Indications[8]

PDL	Generic	Dermatomycosis*	Onychomycosis^	Oropharyngeal candidiasis*	Candidiasis	Aspergillosis	Other fungal infections	Prophylaxis in high-risk patients (adult)
Y	CLOTRIMAZOLE (TROCHE)			FDA				FDA: candidiasis (oropharyngeal)
Y	FLUCONAZOLE (ORAL)	off-label	off-label	FDA	FDA: esophagus, urogenital, sepsis off-label: other sites		FDA: cryptococcal meningitis off-label: blastomycosis coccidioidomycosis cryptococcosis (pulmonary) histoplasmosis sporotrichosis (lymphocutaneous)	FDA: candidiasis off-label: candidiasis (pediatric) histoplasmosis coccidioidomycosis
Y	KETOCONAZOLE (ORAL)						FDA if intolerant or failed other therapies: blastomycosis, coccidioidomycosis, chromoblastomycosis, histoplasmosis, paracoccidioidomycosis	
Y	NYSTATIN (SUSP)			FDA				off-label: candidiasis (oropharyngeal)
Y	NYSTATIN (ORAL)				FDA: gastrointestinal			
N	FLUCYTOSINE (ORAL)			FDA	FDA		FDA: cryptococcosis, cryptococcal meningitis off-label: cryptococcosis (pulmonary)	
N	GRISEOFULVIN	FDA	FDA					
N	ITRACONAZOLE (ORAL)	off-label	FDA	FDA	FDA: esophagus	FDA	FDA: blastomycosis, histoplasmosis off-label: chromoblastomycosis, coccidioidomycosis, cryptococcosis, cryptococcal meningitis paracoccidioidomycosis, sporotrichosis	off-label: candidiasis(oropharyngeal) coccidioidomycosis, histoplasmosis
N	MICONAZOLE (BUCCAL)			FDA				
N	POSACONAZOLE (ORAL)			FDA	FDA: disseminated off-label: esophagus	FDA	off-label: fusarium	off-label: candidiasis (esophagus)
N	TERBINAFINE (ORAL)	FDA	FDA					
N	VORICONAZOLE (ORAL)			off-label	FDA: esophagus, sepsis, disseminated	FDA	FDA: scedosporium, apiospermum & fusarium species off-label: blastomycosis	off-label: aspergillosis

*Not funded by OHP unless present in immunocompromised host; ^Not funded by OHP

Appendix 2: Abstracts of Clinical Trials - No head to head RCTs of oral antifungals identified.

Appendix 3: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

CRESEMBA® (isavuconazonium sulfate)
Capsules for oral administration
For Injection for intravenous administration
Initial U.S. Approval: 2015

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

CRESEMBA is an azole antifungal indicated for use in the treatment of:

- Invasive aspergillosis (1.1).
- Invasive mucormycosis (1.2).

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

- CRESEMBA for injection must be administered through an in-line filter over a minimum of 1 hour (2.1).
- Loading Dose: 372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) every 8 hours for 6 doses (48 hours) via oral (2 capsules) or intravenous administration (1 reconstituted vial) (2.2).
- Maintenance Dose: 372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) once daily via oral (2 capsules) or intravenous administration (1 reconstituted vial) starting 12 to 24 hours after the last loading dose (2.2).
- Capsules can be taken with or without food (2.2).

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

- CRESEMBA capsules contain 186 mg of isavuconazonium sulfate (equivalent to 100 mg of isavuconazole) (3).
- CRESEMBA for injection is supplied in a single-dose vial as a sterile lyophilized powder containing 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) (3).

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

- Hypersensitivity to CRESEMBA (4).
- Coadministration with strong CYP3A4 inhibitors, such as ketoconazole or high-dose ritonavir (4, 7).
- Coadministration with strong CYP3A4 inducers, such as rifampin, carbamazepine, St. John's wort, or long acting barbiturates (4, 7).
- Use in patients with familial short QT syndrome (4).

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

- Hepatic Adverse Drug Reactions: Serious hepatic reactions have been reported. Evaluate liver-related laboratory tests at the start and during the course of CRESEMBA therapy (5.1).
- Infusion-related reactions were reported during intravenous administration of CRESEMBA. Discontinue the infusion if these reactions occur (5.2).
- Hypersensitivity Reactions: Serious hypersensitivity and severe skin reactions, such as anaphylaxis or Stevens Johnson syndrome, have been reported during treatment with other azole antifungal agents. Discontinue CRESEMBA for exfoliative cutaneous reactions (5.3).
- Embryo-Fetal Toxicity: Do not administer to pregnant women unless the benefit to the mother outweighs the risk to the fetus. Inform pregnant patients of the hazard (5.4).
- Drug Interactions: Review patient's concomitant medications. Several drugs may significantly alter isavuconazole concentrations. Isavuconazole may alter concentrations of several drugs (5.5, 7, 12.3).
- Drug Particulates: Intravenous formulation may form insoluble particulates following reconstitution. Administer CRESEMBA through an in-line filter (2.4, 5.6).

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

Most frequent adverse reactions: nausea, vomiting, diarrhea, headache, elevated liver chemistry tests, hypokalemia, constipation, dyspnea, cough, peripheral edema, and back pain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

- CYP3A4 inhibitors or inducers may alter the plasma concentrations of isavuconazole (7).
- Appropriate therapeutic drug monitoring and dose adjustment of immunosuppressants (i.e., tacrolimus, sirolimus, and cyclosporine) may be necessary when co-administered with CRESEMBA (7).
- Drugs with a narrow therapeutic window that are P-gp substrates, such as digoxin, may require dose adjustment when administered concomitantly with CRESEMBA (7).

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

- Pregnancy: CRESEMBA should only be used if the benefits to the mother outweigh the risk to the fetus. Inform pregnant woman of risk (8.1).
- Mothers should not breast feed children while taking CRESEMBA (8.3).
- Use in patients with severe hepatic impairment only when the benefits outweigh the risks; clinical monitoring for CRESEMBA-related adverse reactions is recommended (8.7).

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

Revised: 03/2015

Appendix 4: Medline Search Strategy

Database(s): Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to May Week 1 2015
Search Strategy:

#	Searches	Results
1	exp fluconazole/ or exp itraconazole/ or exp voriconazole/	11748
2	exp clotrimazole/ or exp miconazole/	3117
3	exp Ketoconazole/	5093
4	exp Nystatin/	2962
5	exp Flucytosine/	2442
6	Griseofulvin/	2931
7	antifungal agents/ or exp fluconazole/ or exp flucytosine/ or exp griseofulvin/ or exp itraconazole/ or exp ketoconazole/ or exp miconazole/ or exp nystatin/ or exp voriconazole/	56350
8	POSACONAZOLE.mp.	1372
9	TERBINAFINE.mp.	1996
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	57439
11	exp blastomycosis/ or exp candidiasis/ or exp candidiasis, chronic mucocutaneous/ or exp candidiasis, cutaneous/ or exp candidiasis, invasive/ or exp candidiasis, oral/ or exp coccidioidomycosis/ or exp cryptococcosis/ or exp meningitis, cryptococcal/ or blastomycosis/ or candidiasis, chronic mucocutaneous/ or candidiasis, cutaneous/ or chromoblastomycosis/ or exp hyalohyphomycosis/ or exp aspergillosis/ or exp fusariosis/ or exp paracoccidioidomycosis/ or exp sporotrichosis/ or tinea/ or onychomycosis/ or exp tinea capitis/ or exp tinea favosa/ or exp tinea pedis/ or exp tinea versicolor/ or exp fungemia/ or exp candidemia/ or exp histoplasmosis/ or exp aspergillosis, allergic bronchopulmonary/ or exp neuroaspergillosis/ or exp trichosporonosis/ or exp zygomycosis/ or exp mucormycosis/	71615
12	10 and 11	19985
13	limit 12 to (english language and humans and yr="2013 -Current")	1295
14	limit 13 to (meta analysis or systematic reviews)	50

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Database(s): Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to May Week 1 2015
Search Strategy:

#	Searches	Results
1	exp fluconazole/ or exp itraconazole/ or exp voriconazole/	11748
2	exp clotrimazole/ or exp miconazole/	3117
3	exp Ketoconazole/	5093
4	exp Nystatin/	2962
5	exp Flucytosine/	2442
6	Griseofulvin/	2931
7	antifungal agents/ or exp fluconazole/ or exp flucytosine/ or exp griseofulvin/ or exp itraconazole/ or exp ketoconazole/ or exp miconazole/ or exp nystatin/ or exp voriconazole/	56350
8	POSACONAZOLE.mp.	1372
9	TERBINAFINE.mp.	1996
10	exp blastomycosis/ or exp candidiasis/ or exp candidiasis, chronic mucocutaneous/ or exp candidiasis, cutaneous/ or exp candidiasis, invasive/ or exp candidiasis, oral/ or exp coccidioidomycosis/ or exp cryptococcosis/ or exp meningitis, cryptococcal/ or blastomycosis/ or candidiasis, chronic mucocutaneous/ or candidiasis, cutaneous/ or chromoblastomycosis/ or exp hyalohyphomycosis/ or exp aspergillosis/ or exp fusariosis/ or exp paracoccidioidomycosis/ or exp sporotrichosis/ or tinea/ or onychomycosis/ or exp tinea capitis/ or exp tinea favosa/ or exp tinea pedis/ or exp tinea versicolor/ or exp fungemia/ or exp candidemia/ or exp histoplasmosis/ or exp aspergillosis, allergic bronchopulmonary/ or exp neuroaspergillosis/ or exp trichosporonosis/ or exp zygomycosis/ or exp mucormycosis/	71615
11	isavuconazole.mp.	78
12	1 or 2 or 4 or 5 or 6 or 7 or 8 or 9 or 11	57440
13	10 and 12	19985
14	limit 13 to (english language and humans and yr="2013 -Current" and (clinical trial, phase iii or randomized controlled trial))	55

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50. Benjamin DK Jr, Hudak ML, Duara S, et al. Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: a randomized clinical trial. *JAMA.* 2014;311(17):1742-9. doi:10.1001/jama.2014.2624 EXCLUDED - COMPARISON

Database(s): Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to May Week 1 2015
Search Strategy:

#	Searches	Results
1	isavuconazole.mp.	78
2	BAL4815.mp.	11
3	1 or 2	82
4	limit 3 to (english language and humans)	61
5	limit 4 to (clinical trial, all or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)	6

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Antifungals

Goal(s):

- Approve use of antifungals only for covered diagnoses. Minor fungal infections of skin, such as dermatophytosis and candidiasis are only funded when complicated by an immunocompromised host.

Length of Authorization:

See criteria

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Table 1 – Examples of FUNDED indications (1/1/~~06~~15)

ICD-9	Description
112.1	Candidiasis of vulva and vagina
~~112.2~~	~~Candidiasis of other urogenital sites~~
112.4	Candidiasis of the lung
112.5	Disseminated Candidiasis
112.8x	Candidiasis of other specified sites
114.0-114.9	Coccidiomycosis various sites
115.00-115.99	Histoplamosis
116.0-116.2	Blastomycosis
117.xx	Rhinosporidosis, Sporotrichosis, Chromoblastomycosis, Aspergillosis, Mycotis Mycetomas, Cryptococcosis, Allescheriosis, Zygomycosis, Dematiacious Fungal Infection, Mycoses Nec and Nos
118.xx	Mycosis, Opportunistic
518.6	Bronchopulmonary Aspergillus, Allergic
616.xx (except 616.0)	Inflammatory disease of cervix vagina and vulva
681.xx	Cellulitis and abscess of finger and toe
771.7	Neonatal Candida infection

Table 2 – Examples of NON-FUNDED indications (1/1/15~~06~~)

ICD-9	Description
690.10 – 690.8	Erythematosquamous dermatosis
691.0	Diaper or napkin rash
691.8	Other atopic dermatitis and related conditions
692.0 – 692.70, 692.74, 692.79-692.9	Contact dermatitis and other eczema
695.0,695.10, 695.11, 695.19, 695.2-695.4, 695.50-695.59, 695.89-695.9	ERYTHEMATOUS CONDITIONS
697.0-697.9	Lichen Planus
706.0,706.1	ROSACEA; ACNE
110.1	Dermatophytosis of nail (onychomycosis)
111.0	Pityriasis versicolor
111.2	Tinea blanca
111.3	Black piedra
111.8	Dermatomycoses nec
111.9	Dermatomycosis nos
112.3	Cutaneous candidiasis
112.9	Candidiasis site nos
782.1	Nonspecif skin erupt nec

Table 3 – Criteria driven diagnoses (1/1/15~~06~~)

ICD-9	Description
110.0	Dermatophytosis of scalp and beard (tinea capitis/ tinea barbae)
~~110.1~~	~~Dermatophytosis of nail (onychomycosis)~~
110.2	Dermatophytosis of hand (tinea manuum)
110.3	Dermatophytosis of groin and perianal area (tinea cruris)
110.4	Dermatophytosis of foot (tinea pedis)
110.5	Dermatophytosis of body (tinea corporis / tinea imbricate)
110.6	Deep seated dermatophytosis
110.8-110.9	Dermatophytosis of other specified sites - unspecified site
111.1	Tinea nigra
112.0	Candidiasis of mouth

112.2	Candidiasis of other urogenital sites

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis funded by OHP? (See examples in Table 1).	Yes: Go to #3.	No: Go to #4.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety.	Yes: Inform provider of covered alternatives in class.	No: Approve for 3 months or course of treatment.
4. Is the diagnosis not funded by OHP? (See examples in Table 2).	Yes: Pass to RPH: Deny, (Not Funded by OHP).	No: Got to #5.
5. Is the diagnosis funded by OHP if criteria are met? (See examples in Table 3).	Yes: Go to #6.	No: Go to #8.
6. Is the client immunocompromised (examples below)? • Does the client have a current (not history of) diagnosis of cancer **AND** is currently undergoing Chemotherapy or Radiation? Document therapy and length of treatment. **OR** • Does the client have a diagnosis of HIV/AIDS? **OR** • ~~Does client have diagnosis of diabetes that requires anti-diabetic medications e.g. Insulin, metformin, glyburide, or any drug in the therapeutic class of Diabetic Therapy? Document medication(s).~~ **~~OR~~** • Does client have sickle cell anemia? • Poor nutrition, elderly or chronically ill • Other conditions as determined and documented by a RPh.	Yes: Record ICD-9 code. Approve as follows: (Immunocompromised client) ~~ORAL~~ ~~• Toenails = 12 weeks. Max 1 course per year.~~ ~~• Fingernails = 6 weeks. Max 1 course every 6 months.~~ ORAL & TOPICAL • Course of treatment. • If length of therapy is unknown, approve for 3 months.	No: Go to #7.

Approval Criteria		
7. Is client currently taking an immunosuppressive drug? Document drug. **Pass to RPH for evaluation if drug not in list.** Immunosuppressive drugs include but are not limited to: azathioprine / leflunomide basiliximab / mercaptopurine cyclophosphamide / methotrexate cyclosporine / mycophenolate etanercept / rituximab everolimus / sirolimus hydroxychloroquine / tacrolimus infliximab ~~azathioprine / Imuran~~ ~~basiliximab / Simulect~~ ~~cyclosporine / Sandimmune, Neoral~~ ~~sirolimus / Rapamune~~ ~~tacrolimus / Prograf~~ ~~methotrexate (MTX) / Rheumatrex~~ ~~hydroxychloriquin / Plaquenil~~ ~~etanercept / Enbrel~~ ~~leflunomide / Arava~~	Yes: Approve as follows: (Immunocompromised client) ~~ORAL~~ ~~• Toenails = 12 weeks. Max 1 course per year.~~ ~~• Fingernails = 6 weeks. Max 1 course every 6 months.~~ ORAL & TOPICAL • Course of treatment. • If length of therapy is unknown, approve for 3 months.	No: Pass to RPH; Deny, (Not Funded by the OHP)

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Approval Criteria

~~7.~~8. RPH only: All other indications need to be evaluated to see if they are above or below the line diagnosis:

- If above the line fungal code, then it may be approved for treatment course with prn renewals. If length of therapy is unknown, approve for 3 months intervals only.

- If below the line: Deny, (Not Funded by the OHP).
  - Deny Non-fungal diagnosis (Medical Appropriateness)
  - Deny Fungal ICD-9 codes that do not appear on the OHP list pending a more specific diagnosis code (Not Funded by the OHP).
  - Forward any fungal ICD-9 codes not found in the Tables 1, 2, or 3 to the Lead Pharmacist. These codes will be forwarded to DMAP to be added to the Tables for future requests.

P&T / DUR Review: *Jul 2015 (kk), 09/16/10 (KS/DO); 2/23/06; 11/10/0; 9/15/05; 5/12/05*
Implemented *TBA; 1/1/11; 7/1/06; 11/1/0; 9/1/0*

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Class Update: Calcium Channel Blockers (dihydropyridine and non-dihydropyridine) and Fixed-dose Combinations

Month/Year of Review: July 2015 **Date of Last Review:** January 2014

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

Research Questions:

- Is there new comparative evidence between dihydropyridine or non-dihydropyridine calcium channel blockers (CCBs) in the treatment of hypertension, morbidity outcomes, or mortality?
- Is there any new evidence of comparative safety between dihydropyridine or non-dihydropyridine CCBs?
- Are there any specific populations identified (e.g., based on age, race, co-morbid conditions, etc.) in which one dihydropyridine CCB or non-dihydropyridine CCB may be more effective or associated with more harms than another CCB?
- Is there evidence that fixed-dose combination products containing a CCB are associated with improved clinical outcomes relative to the respective drugs taken concomitantly as separate formulations for the treatment of hypertension?
- Is there comparative evidence for other fixed-dose antihypertensive combination products that have not been previously reviewed by the Oregon Pharmacy and Therapeutics committee?

Purpose for Class Update:
The Pharmacy and Therapeutics (P&T) Committee has not previously reviewed the evidence of fixed-dose combination products containing a CCB. In addition, fixed-dose combination products containing a beta-blocker have not been previously reviewed. This class update will evaluate new comparative evidence of CCBs since the class was reviewed in January 2014 and will also evaluate comparative evidence of fixed-dose drug combination products containing a CCB or a beta-blocker. Direct comparative evidence between fixed-dose combination products, or between a fixed-dose combination product and its respective drugs taken concomitantly as separate formulations, will be considered for Preferred Drug List (PDL) placement.

Conclusions:

- There is moderate to high quality of evidence CCBs, particularly amlodipine, have some benefits at reducing stroke when compared to angiotensin-2 blockers (ARB).[1] The CCB, when compared to ARB, was associated with a slightly lower reduction in stroke incidence (3.2% CCB vs 3.7% ARB; relative risk [RR] 0.87; 95% CI, 0.75-0.99; p=0.04; numbers needed to treat (NNT) = 200).[1] There is low to moderate quality evidence whether CCBs are associated with greater reduction in incidence of MI relative to ARBs.[1] A fixed-effect model showed statistically significant reduction in MI with CCBs compared to ARBs (3.3% CCB vs. 3.8% ARB; RR 0.86; 95% CI, 0.76-0.98; p=0.02, NNT = 200).[1] However, the random-effects model did not demonstrate a statistical significance between the two arms. There were no significant differences in all-cause death, heart failure (HF), and blood pressure (BP) between CCBs and ARBs.[1]

- There is insufficient evidence comparing relative efficacy and safety of CCBs with each other. Current guidelines continue to recommend CCBs as a first-line treatment option for hypertension.[2-4]
- There is insufficient evidence comparing a fixed-dose combination product containing a CCB with the respective drugs taken concomitantly as separate formulations for the treatment of hypertension.
- There is insufficient evidence comparing a fixed-dose combination product containing a beta-blocker with the respective drugs taken concomitantly as separate formulations for the treatment of hypertension. There is low quality evidence that fixed-dose combination products containing a beta-blocker with a diuretic may be inferior at lowering blood pressure than fixed-dose combination products containing a CCB with a diuretic.

Recommendations:
- Maintain at least 2 preferred dihydropyridine CCBs, including amlodipine, to allow for treatment options.
- Maintain at least 1 preferred extended-acting and immediate-release formulation of diltiazem and verapamil.
- Create a "Combination Antihypertensive" PDL class by incorporating the current "ACEI-HCTZ, ARB-HCTZ, & DRI-HCTZ" PDL class and including other fixed-dose antihypertensive combination products containing a CCB with another antihypertensive agent or beta-blocker with another antihypertensive agent. Fixed-dose combination products containing at least 2 preferred drugs may be considered for PDL placement based on cost effectiveness relative to the respective drugs taken concomitantly as separate formulations.
- At this time, fixed-dose combination products containing an antihypertensive drug with a non-antihypertensive drug (e.g., statin) will be incorporated into the "Combination Antihypertensive" PDL class to simplify management of these drugs.
- Review comparative drug costs in executive session for PDL placement.

Previous Conclusions and Recommendations:
There is no new significant comparative evidence for the efficacy or safety of CCBs; no further review or research needed.

Background:
Hypertension is one of the most common and preventable conditions that contributes to stroke, myocardial infarction, chronic kidney disease, and premature death if left untreated.[2] In the United States, approximately 70 million adults are diagnosed with hypertension, but only 52% of patients have controlled hypertension.[5] The onset of hypertension occurs at age 20 to 50 years, usually with a higher prevalence with increasing age.[6] A normal blood pressure is defined as less than 120/80 mm Hg. Pre-hypertension is defined as a systolic blood pressure of 120 to 139 mm Hg or a diastolic blood pressure of 80 to 89 mm Hg. Diagnosis of hypertension requires two separate sphygmomanometer measurements by a health care professional of equal or greater than 140/90 mm Hg.[6]

The CCBs are one of the first-line antihypertensive agents for the management of non-complicated hypertension.[2] Additionally, CCBs are FDA approved for coronary artery disease (CAD) and certain arrhythmias.[6] There are two types of CCB based on their predominant physiologic effects, dihydropyridine CCBs (nifedipine, felodipine, isradipine, nicardipine, and amlodipine) and non-dihydropyridine CCBs (verapamil and diltiazem). Dihydropyridine CCBs are potent arterial vasodilators by acting on vascular smooth muscle causing reduction in peripheral vascular resistance and lowering blood pressure. Non-dihydropyridine CCBs are depressors of cardiac contractility through inhibition of calcium ion influx across membranes of myocardial cells, but have minor effects of vasodilation.[6]

The recommended target blood pressure is less than 140/90 mm Hg in most patients. In elder patients, greater than 60 years (JNC 8) or greater than 80 years (ESH/ESC, CHEP, NICE) depending on guideline, have a recommended systolic BP of less than 150 mm Hg. For diabetes and chronic kidney disease population, current guidelines recommend less than 140/90 (JNC 8, ADA) mm Hg, however, other guidelines suggest less than 130/80 mm Hg (CHEP, KDIGO).[6]

Blood pressure management often requires additional antihypertensive therapy to achieve hypertensive goals. Current guidelines recommend adding additional drugs from other classes recommended for first-line therapy (CCBs, angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker, thiazide-type diuretic). Fixed-dose combination antihypertensive agents were developed to reduce pill burden for patients. The first fixed-dose calcium channel blocker (FD CBB) combination, Lotrel (amlodipine and benazepril), was approved by the FDA in March 1995.[7] There are 11 FDA approved fixed-dose CCB combinations, dual and triple therapy, in the market.[7]

Methods:
A Medline literature search from October 2013 to present for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes between dihydropyridine CCBs, non-dihydropyridine CCBs, and fixed-dose combination products containing CCBs was conducted. A separate Medline literature search was conducted for fixed-dose antihypertensive combination products not previously reviewed by the Oregon P&T committee, which is limited to combinations containing a beta-blocker. The Medline search strategies used for this review are available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. Randomized controlled trials of fixed-dose combination products will only be included if the fixed-dose drug product is compared to both its individual components or another fixed-dose combination product.

Systematic Reviews:
Calcium channel blocker compared with angiotensin receptor blocker for patients with hypertension: a meta-analysis of randomized controlled trials[1]
A meta-analysis of RCTs comparing initial antihypertensive treatment of CCBs to angiotensin receptor blockers (ARBs) on major clinical outcomes was evaluated. Eight head-to-head RCTs were identified, which assessed all-cause mortality, stroke, myocardial infarction (MI), and heart failure (HF). All but one trial studied amlodipine as the CCB treatment arm. No statistically significant difference in mortality was observed in the two arms (8.5% CCB vs. 8.6% ARB; RR 0.99; 95% CI, 0.91-1.07; p=0.72). The CCBs were more effective at reducing incidence of stroke when compared with ARBs (3.2% CCB vs. 3.7% ARB; RR 0.87; 95% CI, 0.76-0.99; p=0.04). A fixed-effect model demonstrated CCBs were superior at reducing incidence of MI compared to ARBs (3.3% CCB vs. 3.8% ARB; RR 0.86; 95% CI, 0.76-0.98; p=0.02). However, no MI reduction was observed using a random-effects model (RR 0.87; 95% CI, 0.69-1.09; p=0.22). The conflict between the two models was potentially derived by the MOSES trial; when removed, it resulted in no statistical heterogeneity (RR 0.83; 95% CI, 0.72 – 0.95; I^2 = 0%). Lastly, the MOSES trial was a PROBE study which has higher risk of investigator and patient bias compared to the other double-blinded studies. There was no statistically significant differences in incidence of HF between the CCBs and ARBs (5% CCB vs. 3.9% ARB; RR 1.4; 95% CI, 0.99-1.98; p=0.06).

New Guidelines:

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)[2]

The Joint National Committee updated their 2003 JNC 7 guideline recommendations in 2014. The JNC 8 emphasizes evidence-based recommendations and targeted blood pressure control based on specific patient populations. The recommended target blood pressure in adult patients less than 60 years of age is less than 140/90 mm Hg. In patients 60 years of age or older, the recommended target blood pressure is less than 150/90 mm Hg, although there are limited data to support this recommendation. The JNC 8 based their targeted blood pressure goals in diabetes patients from evidence in the ACCORD-BP trial which showed no difference in clinical outcomes between a goal SBP <140 mm Hg compared to SBP <120 mm Hg. However, data are limited to be able to identify the optimum blood pressure goal for various populations. Additionally, patients under the age of 60 years of age with chronic kidney disease, with or without diabetes, have a targeted blood pressure goal of less than 140/90 mm Hg. First-line treatment options for non-complicated hypertension include CCBs, Angiotensin-Converting Enzyme Inhibitors (ACE-Is), ARBs, or thiazide diuretics.[3]

The 2015 Canadian Hypertension Education Program (CHEP)[3]

The Hypertension Canada organization updated their 2014 CHEP guideline in 2015. The CHEP 2015 hypertension guideline utilizes an algorithm that requires out-of-office measurements along with clinic visits for diagnosis of hypertension. The recommended blood pressure target in diabetes patients is less than 130/80 mm Hg. In patients less than 80 years old, including CKD patients, the recommended target blood pressure is less than 140/90 mm Hg. Elderly patients older than 80 years of age have a target systolic blood pressure goal of less than 150 mm Hg. CCBs, specifically long-acting DHP-CCBs, are a recommended first-line treatment option for hypertension as both a monotherapy and dual therapy.

Clinical Practice Guidelines for the Management of Hypertension in the Community: A Statement by the American Society of Hypertension and the International Society of Hypertension[4]

The American Society of Hypertension and International Society of Hypertension updated their 2013 guideline recommendations in 2014. Recommendations were based on evidence and expert opinion. Stage 1 hypertension is defined as SBP of 140 to 159 mm Hg and DBP of 90 to 99 mm Hg. The CCBs are the recommended first-line treatment option in African Americans, regardless of hypertension stage, and non-black patients over the age of 60 years with stage 1 hypertension. Stage 2 hypertension is defined as blood pressure greater than or equal to 160/100 mm Hg. The CCBs are recommended as a first-line therapy option in combination with either an ACE-I or ARB for patients with stage 2 hypertension.

New Safety Alerts:

None identified.

New Formulations or Indications:

None Identified.

Randomized Controlled Trials:

No clinical trials of a fixed-dose combination product containing a CCB compared to its respective drugs taken concomitantly as separate formulations were identified. Three potentially relevant clinical trials evaluating a CCB and assessing a clinically relevant outcome were evaluated from the literature search. After

further review, two trials were excluded. The remaining trial is briefly described in the table 1 below. The abstract is included in **Appendix 2**. In addition, abstracts of trials comparing a fixed-dose combination that included a beta-blocker are listed in **Appendix 2**.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Outcome	Results	Quality*
Reisin, et al.[8]	Chlorthalidone (C) vs. Amlodipine (A) vs. Lisinopril (L) Dosing: Titrate dose of blinded study drug and adding open-label step two (atenolol, clonidine, or reserpine) or step three (hydralazine) agents as necessary to obtain a BP goal of <140/90 mm Hg.	Age ≥55 yo, HTN men & women, Risk factor for CHD >1	Primary: Composite of fatal CHD or nonfatal MI Secondary: All-cause mortality, fatal and nonfatal stroke, combined CHD, and combined CVD	**Primary**: (A vs C) Fatal CHD or nonfatal MI - BMI <25: HR 1.04, 0.86 – 1.26 (p=0669) - BMI 25-29: HR 1.04, 0.91 – 1.19 (p=0.568) - BMI ≥30: HR 0.91, 0.79 – 1.05 (p=0.192) **Secondary**: (A vs C) All-cause mortality - BMI <25: HR 1.00, 0.88 – 1.14 - BMI 25-29: HR 0.98, 0.87 – 1.09 - BMI ≥30: HR 0.90, 0.81 – 1.01 *Combined CHD - BMI <25: HR 1.02, 0.87 – 1.18 (p=0.840) - BMI 25-29: HR 1.04, 0.94 – 1.15 (p=0.430) - BMI ≥30: HR 0.96, 0.87 – 1.06 (p=0.96) **Combined CVD - BMI <25: HR 1.07, 0.95 – 1.19 (p=0.264) - BMI 25-29: HR 1.02, 0.94 – 1.11 (p=0.606) - BMI ≥30: HR 1.03, 0.96 – 1.12 (p=0.417) Stroke - BMI <25: HR 0.97. 0.74 – 1.25 (p=0.792) - BMI 25-29: HR 0.89, 0.72 – 1.09 (p=0.256) - BMI ≥30: HR 0.95, 0.78 – 1.16 (p=0.95) Heart failure exacerbation - BMI <25: HR 1.34, 1.07 – 1.68 (p=0.012) - BMI 25-29: HR 1.23, 1.03 – 1.46 (p=0.019) - BMI ≥30: HR 1.48, 1.28 – 1.71 (p <0.001)	Poor

Abbreviations: BMI = body mass index; CHD = coronary heart disease; CVD = cardiovascular disease; HR = hazard ratio; HTN = hypertension; MI = myocardial infarction; p = p-value

*Combined CHD is defined as the primary outcome, coronary revascularization, or hospitalized angina.

**Combined CVD is defined as combined CHD, stroke, treated angina, heart failure (fatal, hospitalized, or not hospitalized), or peripheral artery disease.

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

References:

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2. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507-20.
3. Daskalopoulou SS, Rabi DM, Zarnke KB, et al. The 2015 Canadian hypertension education program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol*. 2015;31(5):549-68.
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5. High blood pressure facts. CDC. 2015. Available at: http://www.cdc.gov/bloodpressure/facts.htm. Accessed April 14, 2015.
6. Hypertension. Dynamed, 2015. Available at: http://web.b.ebscohost.com/dynamed/detail?vid=3&sid=f0818303-8861-46f0-8d7a-af69a2bcefe3%40sessionmgr113&hid=128&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=115345&anchor=Treatment. Accessed June 2, 2015.
7. FDA Approved Drug Products. FDA. 2015. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfol. Accessed June 2, 2015.
8. Reisin E, Graves JW, Yamal JM, et al. Blood pressure control and cardiovascular outcomes in normal-weight, overweight, and obese hypertensive patients treated with three different antihypertensives in ALLHAT. *J Hypertension*. 2014;32(7):1503-13.

Appendix 1: Current Preferred Drug List

Calcium Channel Blockers, Dihydropyridine

Formulation	Brand	Generic	PDL
TABLET	AMLODIPINE BESYLATE	AMLODIPINE BESYLATE	Y
TABLET	NORVASC	AMLODIPINE BESYLATE	Y
CAPSULE	NICARDIPINE HCL	NICARDIPINE HCL	Y
TABLET ER	ADALAT CC	NIFEDIPINE	Y
TABLET ER	AFEDITAB CR	NIFEDIPINE	Y
TABLET ER	NIFEDIPINE	NIFEDIPINE	Y
TABLET ER	NIFEDIPINE ER	NIFEDIPINE	Y
TABLET ER	ADALAT CC	NIFEDIPINE	Y
TABLET ER	AFEDITAB CR	NIFEDIPINE	Y
TAB ER 24	NIFEDICAL XL	NIFEDIPINE	Y
TAB ER 24	NIFEDIPINE ER	NIFEDIPINE	Y
TAB ER 24	NIFEDIPINE XL	NIFEDIPINE	Y
TAB ER 24	PROCARDIA XL	NIFEDIPINE	Y
TAB ER 24H	FELODIPINE ER	FELODIPINE	N
CAPSULE	DYNACIRC	ISRADIPINE	N
CAPSULE	ISRADIPINE	ISRADIPINE	N
CAPSULE ER	CARDENE SR	NICARDIPINE HCL	N
CAPSULE	NIFEDIPINE	NIFEDIPINE	N
CAPSULE	PROCARDIA	NIFEDIPINE	N
TAB ER 24H	NISOLDIPINE	NISOLDIPINE	N
TAB ER 24H	SULAR	NISOLDIPINE	N

Calcium Channel Blockers, non-Dihydropyridine

Formulation	Brand	Generic	PDL
TABLET	CALAN	VERAPAMIL HCL	Y
TABLET	VERAPAMIL HCL	VERAPAMIL HCL	Y
TABLET ER	CALAN SR	VERAPAMIL HCL	Y
TABLET ER	VERAPAMIL ER	VERAPAMIL HCL	Y
TABLET ER	ISOPTIN S.R.	VERAPAMIL HCL	Y
CAP24H PEL	VERAPAMIL ER	VERAPAMIL HCL	Y
CAP24H PEL	VERAPAMIL SR	VERAPAMIL HCL	Y
CAP24H PEL	VERELAN	VERAPAMIL HCL	Y
TABLET ER	CALAN SR	VERAPAMIL HCL	Y
TABLET ER	ISOPTIN S.R.	VERAPAMIL HCL	Y
TABLET ER	VERAPAMIL ER	VERAPAMIL HCL	Y
CAP24H PEL	VERAPAMIL HCL	VERAPAMIL HCL	Y
CAP ER 12H	CARDIZEM SR	DILTIAZEM HCL	Y
CAP ER 12H	DILTIAZEM 12HR ER	DILTIAZEM HCL	Y
CAP ER 12H	DILTIAZEM HCL	DILTIAZEM HCL	Y
TABLET	CARDIZEM	DILTIAZEM HCL	Y
TABLET	DILTIAZEM HCL	DILTIAZEM HCL	Y
CAP ER 24H	CARDIZEM CD	DILTIAZEM HCL	Y
CAP ER 24H	CARTIA XT	DILTIAZEM HCL	Y
CAP ER 24H	DILTIAZEM 24HR CD	DILTIAZEM HCL	Y
CAP ER 24H	DILTIAZEM 24HR ER	DILTIAZEM HCL	Y
CAP ER 24H	DILTIAZEM HCL	DILTIAZEM HCL	Y
CAP ER DEG	DILTIAZEM ER	DILTIAZEM HCL	Y
CAP ER DEG	DILT-XR	DILTIAZEM HCL	Y
CAP ER DEG	DILACOR XR	DILTIAZEM HCL	Y

CAPSULE ER	DILTIAZEM ER	DILTIAZEM HCL	Y
CAPSULE ER	TAZTIA XT	DILTIAZEM HCL	Y
CAPSULE ER	TIAZAC	DILTIAZEM HCL	Y
CAPSULE ER	TAZTIA XT	DILTIAZEM HCL	Y
CAP24H PCT	VERAPAMIL ER PM	VERAPAMIL HCL	N
CAP24H PCT	VERELAN PM	VERAPAMIL HCL	N
TAB ER 24H	CARDIZEM LA	DILTIAZEM HCL	N
TAB ER 24H	DILTIAZEM ER	DILTIAZEM HCL	N
TAB ER 24H	MATZIM LA	DILTIAZEM HCL	N

Calcium Channel Blocker Fixed-dose Combination Products
Amlodipine/aliskiren (TEKAMLO)
Amlodipine/atorvastatin (CADUET)
Amlodipine/benazepril (LOTREL, generic)
Amlodipine/olmesartan (AZOR)
Amlodipine/perindopril (PRESTALIA)
Amlodipine/telmisartan (TWYNSTA)
Amlodipine/valsartan (EXFORGE, generic)
Amlodipine/aliskiren/hydrochlorothiazide (AMTURNIDE)
Amlodipine/olmesartan/hydrochlorothiazide (TRIBENZOR)
Amlodipine/valsartan/hydrochlorothiazide (EXFORGE HCT)
Verapamil/trandolapril (TARKA)

Appendix 2: Abstracts of Clinical Trials

Reisin E, Graves JW, Yamal JM, et al. Blood pressure control and cardiovascular outcomes in normal-weight, overweight, and obese hypertensive patients treated with three different antihypertensives in ALLHAT. J Hypertens. 2014;32(7):1503-13.

Objective: Epidemiologically, there is a strong relationship between BMI and blood pressure (BP) levels. We prospectively examined randomization to first-step chlorthalidone, a thiazide-type diuretic; amlodipine, a calcium-channel blocker; and lisinopril, an angiotensin-converting enzyme inhibitor, on BP control and cardiovascular outcomes in a hypertensive cohort stratified by baseline BMI (kg/m^2) [normal weight (BMI <25), overweight (BMI = 25-29.9), and obese (BMI >30)]. Methods: In a randomized, double-blind, practice-based Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, 33,357 hypertensive participants, aged at least 55 years, were followed for an average of 4.9 years, for a primary outcome of fatal coronary heart disease or nonfatal myocardial infarction, and secondary outcomes of stroke, heart failure, combined cardiovascular disease, mortality, and renal failure. Results: Of participants, 37.9% were overweight and 42.1% were obese at randomization. For each medication, BP control (<140/90 mmHg) was equivalent in each BMI stratum. At the fifth year, 66.1, 66.5, and 65.1% of normal-weight, overweight, and obese participants, respectively, were controlled. Those randomized to chlorthalidone had highest BP control (67.2, 68.3, and 68.4%, respectively) and to lisinopril the lowest (60.4, 63.2, and 59.6%, respectively) in each BMI stratum. A significant interaction (P = 0.004) suggests a lower coronary heart disease risk in the obese for lisinopril versus chlorthalidone (hazard ratio 0.85, 95% confidence interval 0.74-0.98) and a significant interaction (P = 0.011) suggests a higher risk of end-stage renal disease for amlodipine versus chlorthalidone in obese participants (hazard ratio 1.49, 95% confidence interval 1.06-2.08). However, these results were not consistent among other outcomes. Conclusion: BMI status does not modify the effects of antihypertensive medications on BP control or cardiovascular disease outcomes.

Beta-blocker Combinations

Radchenko GD, Sirenko YM, Kushnir SM, et al. Comparative effectiveness of a fixed-dose combination of losartan+HCTZ versus bisoprolol+HCTZ in patients with moderate-to-severe hypertension: results of the 6-month ELIZA trial. *Vascular Health and Risk Management*. 2013;9:535–549.

Background: The aim of this study was to compare the antihypertensive efficacy of losartan 100 mg + hydrochlorothiazide (HCTZ) 25 mg versus bisoprolol 10 mg + HCTZ 25 mg and their influence on arterial stiffness and central blood pressure (BP). Methods: Of 60 patients with a mean BP of 173.3 ± 1.7/98.4 ± 1.2 mmHg, 59 were randomized to losartan + HCTZ (n = 32) or bisoprolol + HCTZ (n = 27). Amlodipine was added if target BP was not achieved at 1 month, and doxazosin was added if target BP was not achieved after 3 months. Body mass index, office and 24-hour ambulatory BP, pulse wave velocity (carotid-femoral [PWVE] and radial [PWVM]), noninvasive central systolic BP, augmentation index (AIx), laboratory investigations, and electrocardiography were done at baseline and after 6 months of treatment. Results: Losartan + HCTZ was as effective as bisoprolol + HCTZ, with target office BP achieved in 96.9% and 92.6% of patients and target 24-hour BP in 75% and 66.7% of patients, respectively, after 6 months. Effective treatment of BP led to significant lowering of central systolic BP, but this was decreased to a significantly ($p<0.05$) greater extent by losartan + HCTZ (−23.0 ± 2.3 mmHg) than by bisoprolol + HCTZ (−15.4 ± 2.9 mmHg) despite equal lowering of brachial BP. Factors correlated with central systolic BP and its lowering differed between the treatment groups. Losartan + HCTZ did not alter arterial stiffness patterns significantly, but bisoprolol + HCTZ significantly increased AIx. We noted differences in ΔPWVE, ΔPWVM, and ΔAIx between the groups in favor of losartan + HCTZ. Decreased heart rate was associated with higher central systolic BP and AIx in the bisoprolol + HCTZ group, but was not associated with increased AIx in the losartan + HCTZ group. Conclusion: Although both treatments decreased both office and 24-hour BP, losartan + HCTZ significantly decreased central systolic BP and had a more positive influence on pulse wave velocity, with a less negative effect of decreased heart rate on AIx and central systolic BP.

Scholze J, Grimm E, Herrmann D, et al. Optimal treatment of obesity-related hypertension: the Hypertension-Obesity-Sibutramine (HOS) Study. *Circulation*. 2007;115:1991-98.

Background: Current guidelines for the treatment of hypertension do not provide specific recommendations for obese hypertensive patients. To identify an optimal treatment regimen for obese hypertensive patients, we studied the interactions between a drug-based weight loss approach by sibutramine and different antihypertensive drug regimens. Methods and Results: This was a prospective, 16-week double-blind placebo-controlled randomized multicenter study in 171 obese hypertensive patients. After a 2-week run-in period, patients receiving 1 of the 3 antihypertensive combination therapies (felodipine 5 mg/ramipril 5 mg [n=57], verapamil 180 mg/trandolapril 2 mg [n=55], or metoprolol succinate 95 mg/hydrochlorothiazide 12.5 mg [metoprolol/hydrochlorothiazide; n=59]) were assigned randomly to sibutramine (15 mg) or placebo. Sibutramine treatment resulted in a significantly greater decrease in body weight, body mass index, and waist circumference and a significant increase in diastolic blood pressure during 24-hour blood pressure monitoring compared with placebo treatment. Sibutramine-induced weight loss and reduction of visceral obesity were markedly attenuated in the metoprolol/hydrochlorothiazide group compared with the other groups. Consistently, improvement in glucose tolerance and hypertriglyceridemia by sibutramine was abrogated in the cohort treated with metoprolol/hydrochlorothiazide compared with the other groups. Conclusions: The present study demonstrates for the first time that an antihypertensive combination therapy regimen with angiotensin-converting enzyme inhibitors and calcium channel blockers is more advantageous than a beta-blocker/diuretic–based regimen in supporting the weight-reducing actions and concomitant metabolic changes induced by sibutramine in obese hypertensive patients. These data may help to develop future comprehensive treatment strategies and guidelines for this high-risk patient population.

Breithaupt-Grogler K, Gerhardt G, Lehmann G, et al. Blood pressure and aortic elastic properties--verapamil SR/trandolapril compared to a metoprolol/hydrochlorothiazide combination therapy. *International Journal of Clinical Pharmacology & Therapeutics*. 1998;36(8):425-31.

The effects of 2 fixed antihypertensive combination drugs on blood pressure and aortic elastic properties were compared in 2 parallel groups. Twenty-six patients for 6 months received a calcium antagonist plus ACE inhibitor (verapamil SR 180 mg/trandolapril 1 mg (Vera/Tran)) and 25 patients a beta-adrenoceptor antagonist plus diuretic (metoprolol 100 mg/hydrochlorothiazide 12.5 mg (Meto/HCTZ)). In addition to blood pressure (SBP, DBP), carotidofemoral pulse wave velocity (PWV) was assessed non-invasively. Total peripheral resistance (TPR) was determined from cardiac output derived by electrical impedance cardiography. Sitting DBP decreased for -14.4 mmHg following Vera/Tran compared with -9.2 mmHg following Meto/HCTZ (p = 0.02 for difference between treatments). Blood pressure was normalized (i.e. DBP < 90 mmHg) in 69% of patients with Vera/Tran and in 52% with Meto/HCTZ. PWV was lowered with Vera/Tran to a higher extent than with Meto/HCTZ (differences between group means -0.46 to -0.98 m/sec, statistically not significant). Vera/Tran induced a decrease in TPR of about 15% of baseline values, whereas Meto/HCTZ showed no influence. Treatment-related adverse events following Meto/HCTZ were bradycardia and associated symptoms; following Vera/Tran these were cough and edema in 1 case each. In the Meto/HCTZ group, there were more withdrawals/drop-outs (9/25) than in the Vera/Tran group (2/26). The somewhat more intense reduction in PWV with Vera/Tran is indicative of an increase in aortic elastic properties associated with the more potent decrease in BP. In the present study, the combination of calcium antagonist plus ACE inhibitor was found to be an effective and well tolerated antihypertensive regimen and in these respects appears to have some advantages compared with a combination of beta-blocker plus diuretic.

Stimpel M, Koch B. Antihypertensive treatment with moexipril plus HCTZ vs metoprolol plus HCTZ in patients with mild-to-moderate hypertension. *Journal of Human Hypertension*. 1997;11(2):133-7.

Combination therapy with the new ACE inhibitor moexipril plus hydrochlorothiazide (HCTZ) results in significant blood pressure (BP) reductions. This study compares the efficacy and safety of moexipril plus HCTZ to that of a standard combination treatment in patients with mild-to-moderate hypertension. After a 1 month placebo run-in period, 140 hypertensive patients whose sitting diastolic BP (DBP) averaged 95-114 mm Hg were randomized to receive either once daily moexipril 7.5 mg/HCTZ 12.5 mg or metoprolol 100 mg/HCTZ 12.5 mg for the following 12-week double-blind treatment period. At biweekly visits BP was controlled sphygmomanometrically and the occurrence of adverse events (AE) was documented. At study endpoint adjusted mean reductions in sitting systolic/diastolic BP seen with both combinations were -17.6 mm Hg/-12.8 mm Hg and -17.2 mm Hg/-13.9 mm Hg in the moexipril/HCTZ and metoprolol/HCTZ groups, respectively. The response rate to both kinds of combinations were very similar, 69% and 74% in the moexipril/HCTZ and metoprolol/HCTZ groups, respectively. The percentage of patients which experienced one or more AEs were 46% in the moexipril/HCTZ and 61% in the metoprolol/HCTZ group. Headache and cough which are the most frequently reported AEs after treatment with ACE inhibitors were seen in 9% and 10% of the patients in the moexipril/HCTZ group compared to 10% and 4% in the metoprolol/HCTZ group. The study indicates that the combination of moexipril 7.5 mg plus HCTZ 12.5 mg is as efficacious and safe as metoprolol 100 mg plus HCTZ 12.5 mg in the treatment of mild-to-moderate hypertension.

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de Leeuw PW, Notter T, Zilles P. Comparison of different fixed antihypertensive combination drugs: a double-blind, placebo-controlled parallel group study. *Journal of Hypertension*. 1997;15(1):87-91.

To compare the effects of fixed-dose preparations containing 180 mg sustained-release verapamil and 2 mg trandolapril, 100/25 mg atenolol/chlorthalidone, 20/12.5 mg lisinopril/hydrochlorothiazide and placebo in patients with essential hypertension. DESIGN: A 4-week placebo run-in period followed by a double-blind, placebo-controlled parallel group study lasting 8 weeks. SETTING: Office practices (21 centres). PATIENTS: Patients with essential hypertension (World Health Organization grades I or II); supine diastolic blood pressure 101-114 mmHg in week 4 of the run-in period; 215 patients were enrolled, of whom 205 were assigned randomly to double-blind therapy. MAIN OUTCOME MEASURES: Reduction in supine and standing blood pressures. RESULTS: All three active treatments with a single daily dose were significantly more effective than was placebo in reducing the blood pressure of seated subjects (P=0.0001). The reductions in sitting diastolic blood pressure (DBP) from baseline to the last visit with each active treatment were

comparable: 13 mmHg [95% confidence interval (CI) 16-9] with sustained-release verapamil/trandolapril, 13 mmHg (16-9) with atenolol/chlorthalidone and 12 mmHg (15-8) with lisinopril/hydrochlorothiazide. Normalization of blood pressure (DBP < 90 mmHg) was observed in 48% of patients with sustained-release verapamil/trandolapril, in 46% with atenolol/chlorthalidone and in 40% with lisinopril/hydrochlorothiazide. Response rates (normalization of DBP or a reduction in DBP by > 10 mmHg) with each active treatment were 72% for sustained-release verapamil/trandolapril, 76% for atenolol/chlorthalidone and 69% for lisinopril/hydrochlorothiazide. All three active treatments were tolerated well. CONCLUSION: This study demonstrates that the low-dose combination sustained-release verapamil/trandolapril may be a suitable alternative for combinations containing a thiazide diuretic or a beta-blocker for longer term management of hypertensive patients for whom combination therapy is indicated.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2015, [Database Field Guide] Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 22, 2015

1 exp Calcium Channel Blockers/ 33458
2 exp Amlodipine/ 2657
3 exp Nifedipine/ 5173
4 exp Nicardipine/ 922
5 exp Isradipine/ 401
6 exp Felodipine/ 494
7 exp Nisoldipine/ 217
8 exp Diltiazem/ 2147
9 exp Verapamil/ 5395
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 33458
11 limit 10 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or pragmatic clinical trial or randomized controlled trial) 7832
12 limit 11 to (english language and yr="2013 -Current") 431

11

Ovid MEDLINE(R) without Revisions 1996 to January Week 3 2015, [Database Field Guide] Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 22, 2015

1 exp Calcium Channel Blockers/ 33132
2 exp Amlodipine/ 2609
3 exp Nifedipine/ 5149
4 exp Nicardipine/ 912
5 exp Isradipine/ 399
6 exp Felodipine/ 488
7 exp Nisoldipine/ 216
8 exp Diltiazem/ 2132
9 exp Verapamil/ 5352
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 33132
11 limit 10 to (meta analysis or systematic reviews) 633
12 limit 11 to (english language and yr="2013 -Current") 73

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2015, [Database Field Guide] Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 22, 2015

1 exp Verapamil/ 5395
2 trandolapril.mp./ 561
3 combination.mp./ 508676
4 1 and 2 and 3/ 110
5 exp Amlodipine/ 2657

6 atrovastatin.mp./ 6780
7 3 and 5 and 6/ 94
8 olmesartan.mp./ 1181
9 3 and 5 and 8/ 111
10 aliskiren.mp./ 960
11. 3 and 5 and 10/ 42
12 benazepril/ 550
13 3 and 5 and 12/ 83
14 exp perindopril/ 1150
15 3 and 5 and 14/ 54
16 telmisartan.mp./ 1765
17 3 and 5 and 16/ 60
18 valsartan.mp./ 2518
19 3 and 5 and 18/ 149
20 exp felodipine/ 494
21 exp enalapril/ 3117
22 3 and 20 and 21/ 11
23 4 or 7 or 9 or 11 or 13 or 15 or 17 or 19 or 22/ 669
24 limit 23 to (English language and (clinical trial, phase III or clinical trial, phase IV or comparative study or controlled clinical trial or pragmatic clinical trial or randomized controlled trial))/ 383

1 exp Atenolol/ 4890
2 exp Bisoprolol/ 863
3 exp Metoprolol/ 4902
4 exp Propranolol/ 31093
5 exp Chlorthalidone/ 1365
6 exp Hydrochlorothiazide/ 6060
7 1 and 5 138
8 2 and 6 47
9 3 and 6 101
10 4 and 6 235
11 7 or 8 or 9 or 10 508
12 combination.mp. or exp Drug Therapy, Combination/ 729776
13 11 and 12 273
14 limit 13 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or pragmatic clinical trial or randomized controlled trial) 192