



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 25, 2013 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 | B. Origer (Chair) |
| b. Conflict of Interest Declaration | R. Citron (OSU) |
| c. Approval of Agenda and Minutes | B. Origer (Chair) |
| d. Department Update | T. Douglass (DMAP) |

II. DUR ACTIVITIES

- | | |
|---|-------------------|
| a. Quarterly Utilization Reports | R. Citron (OSU) |
| b. ProDUR Report | R. Holsapple (HP) |
| c. Updated RetroDUR Report Proposal | T. Williams (OSU) |
| d. CMS Annual Report | T. Williams (OSU) |
| e. Oregon State Drug Reviews | K. Sentena (OSU) |
| 1. Updates and Future Perspectives in Chronic Obstructive Pulmonary Disease | |

III. DUR OLD BUSINESS

- | | |
|--|----------------------|
| a. Juxtapid® (lomitapide) | M. Herink (OSU) |
| 1. Proposed PA Criteria | |
| 2. Public Comment | |
| 3. Discussion of Clinical Recommendations to OHA | |
| b. Kynamro® (mipomersen) | M. Herink (OSU) |
| 1. Proposed PA Criteria | |
| 2. Public Comment | |
| 3. Discussion of Clinical Recommendations to OHA | |
| c. Ampyra® (dalfampridine) | Sherri Argyres (OSU) |
| 1. Updated Drug Review | |
| 2. HCMB consideration | |
| 3. Public Comment | |
| 4. Discussion of Clinical Recommendations to OHA | |

IV. DUR NEW BUSINESS

- | | |
|--|----------------|
| a. Kuvan® (saproterin) | B. Liang (OSU) |
| 1. New Drug Evaluation | |
| 2. Public Comment | |
| 3. Discussion of Clinical recommendations to OHA | |

V. PREFERRED DRUG LIST

- | | |
|---|--|
| <ul style="list-style-type: none">a. Suboxone® and Opioid Addiction Therapies<ul style="list-style-type: none">1. Class Review2. Public Comment3. Discussion of Clinical Recommendations to OHA
b. Long Acting Opioids<ul style="list-style-type: none">1. Abbreviated Class Update<ul style="list-style-type: none">a. DERP Scanb. CDC Methadone Report2. Public Comment3. Discussion of Clinical Recommendations to OHA
c. Drug Class Scans<ul style="list-style-type: none">1. ADHD2. Controller Medications for Asthma3. Triptans4. Short Acting Opioids5. Public Comment6. Discussion of Clinical Recommendations to OHA | <p>B. Liang (OSU)</p> <p>K. Ketchum (OSU)</p> <p>M. Herink (OSU)</p> |
|---|--|

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. ADJOURN



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



Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, May 30, 2013 1:00-5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to coverage, PDL composition, or 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.

Members Present: David Pass, MD; Phillip Levine, PhD; Stacy Ramirez, PharmD; William Origer, MD; Zahia Esber MD

Members Present by Phone: James Slater, PharmD

Staff Present: Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD; Trevor Douglass, DC, MPH; Shannon Jasper

Staff Present by Phone: Kathy Sentena, PharmD

Audience: Karen Ward (Aegerion), Ann Nielson, Christopher DeSimane (Aegerion), Bruce Howard (Acorda); Gina Guinasso (Acorda); Michelle Bice (Gilead); Chris Haem (Gilead); Danielle Sobel (OMA); Patrick Moty; Kristina Hermach (BMS); Lou LaMarca National Patient Advocate Foundation; Jim Gardner (PhRMA); Bruce Smith; Venus Holder (Lilly); Mary Stumph (Lilly); Holly Batterman, MD ViiV Healthcare; Paul Nielsen (Med Immune); Lorren Sandt (CAP); Jim Hoover (Bayer); Kara Tyler (Amgen); Trish McDaid O'Neill (Astra Zeneca); Lisa Valaika (Genzyme); Nancy Martin (Genzyme); Deron Grothe (Teva); Mike Willett (Pfizer); Dianne Vanowski Smith (TMC); Barry Benson (Merck); Dr. Jill Kerrick Walker (Eisai); Paul Barham (NovoNordisk); BJ Cavnor (WWPEW); Carlene Halverson (Novartis)

I. CALL TO ORDER

- a. The meeting was called to order at approximately 1pm.
- b. Mr. Citron reported there are no new conflicts of interest to declare (Other than Dave Pass's Hawaiian shirt)
- c. The March 28th, 2013 meeting minutes were reviewed.
- d. Dr. Douglass introduced new staff: Shannon Jasper

ACTION: Approved as is.

II. DUR ACTIVITIES

- a. HCMB Process Discussion
 1. Draft Procedure and Timeline

ACTION: Approved with the establishment of a subcommittee to act as an advisory committee that includes representation from the P&T committee, as well as the HERC. Depending on the

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

topic, consider professional or lay experts, a general expert in such areas as statistics, and a patient advocate or patient advocate groups.

2. Public Comment and Testimony:

Lorren Sandt with Caring Ambassadors including written testimony

Jim Gardner with Gardner & Gardner Law Firm on behalf of PhRMA (written)

Lou LaMarca with National Patient Advocate Foundation

Danielle Sobel with OMA including written memorandum

Holly Batterman, MD with ViiV Healthcare

BJ Cavnor with NW Patient Education Network

b. Mr. Holsapple presented the ProDUR report.

c. Dr. Williams stated the RetroDUR report is still being worked on.

d. Mr. Citron presented the Quarterly Utilization Reports.

e. Dr. Sentena presented the Oregon State Drug Review

1. Management of Gout in the Presence of Chronic Kidney Disease

f. FDB Drug File Updates* - presented by Dr. Williams

III. NEW BUSINESS

a. Makena® (17 alpha-hydroxyprogesterone caproate)*

Dr. Fouts presented the drug use evaluation for 17 alpha-hydroxyprogesterone caproate recommending required PA criteria and apply quantity limits consistent with PA Criteria. Due to insufficient data to support the compounded product and additional inherent compounding risks, prefer the branded product over the compounded product.

*ACTION: All in favor.

b. Fycompa ® (Perampanel)*

Dr. Liang presented the drug evaluation for Perampanel for adjunctive therapy for treatment of partial-onset seizures with or without secondary generalized seizures in patients with epilepsy aged 12 years and older. Designate Perampanel a second line non-preferred oral anticonvulsant to ensure appropriate use as adjunct treatment when previous treatment with AEDs has not provided adequate response or has not been tolerated.

Testimony given by Dr. Jill Walker.

*ACTION: All in favor.

c. Aubagio ® (teriflunomide)*

Dr. Argyres presented the drug evaluation for teriflunomide and recommends non-preferred and limit use to confirmed patients with documentation of prior failed use of an interferon for MS or glatiramer acetate. Prior authorization required. Add proof of contraception for women of childbearing age to criteria.

*ACTION: All in favor.

d. Acthar Gel ® (Repository corticotropin injection)*

Dr. Herink presented the new drug evaluation for Acthar Gel ®. Recommendation is Prior Authorize to allow coverage for the treatment of infantile spasms in patients less than 2 years of age and restrict other use for those who cannot tolerate appropriate glucocorticoid therapy. Requires manual review of claims for patients > 2 years of age.

*ACTION: All in favor.

e. CF Vitamins Abbreviated Class Review (after executive session)*

Dr. Herink presented the evaluation for Cystic Fibrosis vitamins. Due to the consensus among CF practitioners of routine supplementation with fat-soluble vitamin preparations in patients with CF, compare and add appropriate formulations to the list of supplements that are included in the rebate exception policy. Make a broader recommendation to encourage CCO's to evaluate their CF vitamin utilization

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

and adopt similar coverage guidelines. Information will be shared through the medical and/or pharmacy director meetings.

*ACTION: After Executive Session, all in favor.

f. Juxtapid ® (lomitapide)*

Dr. Herink presented the new drug evaluation for Juxtapid ®. Recommendation to designate Juxtapid ® as non-preferred and prior authorize criteria to limit use to genetically confirmed HoFH only who have a medical contraindication to lipid lowering therapy and LDL apheresis and which is prescribed in consultation with a specialist. Requires manual review. Reach out to gather information and bring back to the committee on the reliability of genetic testing and more specific criteria that defines apheresis failure.

Testimony by Dr. Karen Ward from Aegerion.

*ACTION: After Executive Session, all in favor.

g. Kynamro ® (mipomersen)*

Dr. Herink presented new drug evaluation for Kynamro ®. Recommendation to designate Kynamro ® as non-preferred and prior authorize criteria to limit use to genetically confirmed HoFH only who have a medical contraindication to lipid lowering therapy and LDL apheresis and which is prescribed in consultation with a specialist. Requires manual review. Reach out to gather information and bring back to the committee on the reliability of genetic testing and more specific criteria that defines apheresis failure.

Testimony by Nancy Martin from Genzyme.

*ACTION: After Executive Session, all in favor.

h. Drug Class Scans*

1. Cough and Cold Products (after executive session)

Dr. Herink stated no further research or review is needed at this time. Evaluate comparative costs in executive session.

Recommendations to make this a PDL class. Preference only these lower cost GSN's Guaiifenesin liquid 100mg/5ml, guafenesin/dextromethorphan syrup, guafenesin/codeine phosphate liquid, psuedoephedrine HCL tablets 30mg and 60mg. Consider addition of benzoate capsules as a preferred alternative to Mucinex tablets.

*ACTION: After Executive Session, all in favor.

2. Topical Antibiotics (after executive session)

Dr. Herink stated no further research or review is needed at this time. Evaluate comparative costs in executive session.

Recommendations to designate double-antibiotic ointment as preferred and designate Centany AT Kits non-preferred.

*ACTION: After Executive Session, all in favor.

3. Oral Immunosuppressants (after executive session)

Dr. Herink stated no further research or review is needed at this time. Evaluate comparative costs in executive session.

Recommendations to designate Myfortic and Sandimmune solution as preferred to be consistent with previous recommendations.

*ACTION: After Executive Session, all in favor.

IV. The meeting was adjourned at approximately 4:30pm.

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*



OHP PPS Average Cost PMPM Top 40 Drugs (brand name) - Second Quarter 2013

previous year quarter is comparator (red = top 75th percentile of growth; yellow = top 50th percentile of growth)

Rank	Class Number	Brand Name	Cost PMPM			Rx Dispensed PMPM (x100)			Cost/Claim		
			2013	2012	%	2013	2012	%	2013	2012	%
1	7	ABILIFY	\$3.98	\$3.71	-7.3%	0.53	0.56	-5.8%	\$753	\$661	-13.9%
2	11	CYMBALTA	\$1.84	\$1.58	-16.3%	0.71	0.71	-0.9%	\$261	\$222	-17.3%
3	10	METHYLPHENIDATE ER	\$1.33	\$1.43	-7.0%	0.75	0.85	-12.3%	\$178	\$168	-6.0%
4	71	REMODULIN	\$0.85	\$1.71	-50.3%	0.00	0.01	-51.9%	\$24,327	\$23,448	-3.7%
5	15	PROAIR HFA	\$0.70	\$0.74	-5.4%	1.23	1.38	-11.2%	\$57	\$54	-5.3%
6	7	SEROQUEL XR	\$0.68	\$0.62	9.7%	0.13	0.14	-10.5%	\$533	\$433	-22.6%
7	58	LANTUS	\$0.61	\$0.67	-9.2%	0.25	0.31	-18.4%	\$241	\$217	-11.3%
8	11	INTUNIV	\$0.59	\$0.43	38.1%	0.27	0.23	18.1%	\$220	\$188	-17.1%
9	42	HUMIRA	\$0.58	\$0.72	-20.0%	0.02	0.03	-30.1%	\$2,447	\$2,143	-14.2%
10	11	STRATTERA	\$0.56	\$0.58	-3.0%	0.23	0.26	-12.6%	\$243.51	\$219.48	-11.0%
11	99	PULMOZYME	\$0.51	\$0.58	-11.7%	0.02	0.02	-14.5%	\$2,564.99	\$2,486.62	-3.2%
12	51	FLOVENT HFA	\$0.47	\$0.54	-11.8%	0.27	0.32	-15.8%	\$176.08	\$168.30	-4.6%
13	42	ENBREL	\$0.36	\$0.36	0.0%	0.02	0.02	0.0%	\$2,073.55	\$1,854.64	-11.8%
14	15	ADVAIR DISKUS	\$0.47	\$0.47	0.3%	0.17	0.18	-5.4%	\$280	\$262	-7.1%
15	7	INVEGA SUSTENNA	\$0.45	\$0.29	55.1%	0.04	0.03	43.9%	\$1,245	\$1,155	-7.8%
16	12	DEXTRAMPHETAMINE-AMPHETAMINE	\$0.44	\$0.53	-17.0%	0.28	0.30	-7.4%	\$157.85	\$176.15	-10.4%
17	12	VYVANSE	\$0.43	\$0.41	2.5%	0.24	0.25	-4.4%	\$179.70	\$167.59	-7.2%
18	33	TRUVEDA	\$0.41	\$0.81	-49.3%	0.04	0.08	-53.2%	\$1,149.48	\$1,061.30	-8.3%
19	23	TOBI	\$0.40	\$0.44	-8.4%	0.01	0.01	-14.4%	\$5,428.66	\$5,064.39	-7.2%
20	15	SPIRIVA	\$0.39	\$0.41	-4.2%	0.15	0.16	-9.0%	\$266.81	\$253.46	-5.3%
21	40	OXYCONTIN	\$0.38	\$0.85	-55.4%	0.08	0.17	-51.2%	\$466.44	\$510.82	-8.7%
22	48	VIMPAT	\$0.38	\$0.22	67.0%	0.06	0.04	-46.9%	\$623.36	\$544.78	-14.4%
23	58	HUMALOG	\$0.37	\$0.33	14.0%	0.14	0.14	-0.4%	\$276.04	\$240.96	-14.6%
24	40	HYDROCODONE-ACETAMINOPHEN	\$0.37	\$0.41	-10.1%	2.23	2.86	-22.4%	\$16.71	\$14.46	-15.5%
25	33	ATRIPLA	\$0.35	\$0.81	-56.8%	0.02	0.05	-59.4%	\$1,789.29	\$1,681.05	-6.4%
26	48	SABRIL	\$0.33	\$0.17	56.1%	0.00	0.00	55.6%	\$7,706.53	\$6,110.15	-26.1%
27	7	LATUDA	\$0.32	\$0.18	78.4%	0.05	0.04	43.9%	\$601.98	\$485.55	-24.0%
28	69	CREON	\$0.38	\$0.25	13.4%	0.03	0.03	-6.7%	\$1,044.37	\$862.77	-21.0%
29	7	ZIPRAZIDONE HCL	\$0.28	\$0.11	157.0%	0.15	0.05	204.0%	\$181.08	\$124.20	-35.5%
30	7	INVEGA	\$0.28	\$0.23	11.1%	0.04	0.04	-7.2%	\$7,757.61	\$6,333.13	-19.7%
31	58	NOVOLOG	\$0.26	\$0.28	-5.2%	0.11	0.13	-8.7%	\$230.88	\$222.70	-3.7%
32	33	INCIVEK	\$0.26	\$0.18	45.3%	0.00	0.00	26.5%	\$20,167.09	\$17,557.68	-14.9%
33	80	VITAMIN D	\$0.26	\$0.19	35.2%	2.87	2.07	38.5%	\$8,394	\$8,935	-6.2%
34	99	AVONEX PEN	\$0.25	\$0.03	619.6%	0.01	0.00	506.0%	\$3,926.41	\$5,306.80	-18.7%
35	1	OMEPRAZOLE	\$0.25	\$0.32	-21.7%	1.54	1.76	-12.6%	\$16.19	\$18.08	-10.5%
36	1	PREVACID	\$0.24	\$0.16	47.5%	0.08	0.07	18.4%	\$307.65	\$246.91	-24.6%
37	30	TEMODAR	\$0.24	\$0.29	-17.7%	0.01	0.01	-5.2%	\$3,239.45	\$3,829.21	-15.4%
38	11	MODAFINIL	\$0.24	\$0.21	11.8%	0.03	0.02	52.4%	\$817.68	\$1,114.88	-26.7%
39	51	OVAR	\$0.24	\$0.22	5.5%	0.18	0.19	3.2%	\$131.43	\$120.57	-9.0%
40	40	OXYCODONE HCL	\$0.22	\$0.28	-20.7%	0.93	1.11	-16.4%	\$23.81	\$25.12	-5.2%
			\$51.76	\$55.95	-7.5%	96.90	100.76	-3.8%	\$68	\$68	1.4%
					41.5%			27.5%			16.6%
					0.0%			-3.6%			3.5%

Last updated: July 23, 2013



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

College of Pharmacy

OHP FFS Average Cost PMPM Top 30 Drug Class – Second Quarter 2013

previous year quarter is comparator (red = top 75th percentile of growth; yellow = top 50th percentile of growth)

Rank	Class Number	Class Description	Cost PMPM			Rx Dispensed PMPM (x100)			Cost/Claim		
			2013	2012	%	2013	2012	%	2013	2012	%
1	7	Anaerotics, Tranquilizers	\$7.41	\$8.12	-8.7%	4.9	6.1	-20.2%	\$152	\$132	14.4%
2	11	Psychostimulants, Antidepressants	\$4.73	\$4.92	-3.8%	9.1	9.3	-1.7%	\$52	\$53	-2.2%
3	48	Anticonvulsants	\$3.11	\$2.63	18.3%	4.1	5.4	-23.5%	\$53	\$44	20.9%
4	99	Miscellaneous	\$3.05	\$3.19	-4.6%	1.5	1.5	0.9%	\$175	\$207	-15.6%
5	33	Antivirals	\$2.90	\$4.72	-38.6%	0.5	0.7	-31.9%	\$591	\$658	-10.2%
6	15	Bronchial Dilators	\$2.77	\$3.66	-24.2%	3.1	3.5	-13.0%	\$89	\$103	-13.2%
7	58	Diabetic Therapy	\$2.39	\$2.45	-2.3%	1.8	2.1	-13.9%	\$130	\$115	13.2%
8	10	CNS Stimulants	\$2.07	\$2.43	-14.8%	1.6	1.9	-15.9%	\$127	\$126	1.2%
9	71	Other Hypotensives	\$1.62	\$2.49	-35.0%	2.5	2.9	-13.7%	\$61	\$85	-28.9%
10	40	Narcotic Analgesics	\$1.58	\$2.52	-37.1%	5.4	7.1	-24.9%	\$29	\$35	-16.9%
11	42	Antiarthritis	\$1.37	\$1.43	-4.8%	1.9	2.2	-13.9%	\$72	\$65	10.5%
12	30	Antineoplastic	\$1.32	\$0.94	+40.5%	0.3	0.4	-30.4%	\$484	\$257	87.9%
13	51	Gluco Corticoids	\$1.28	\$1.29	-1.0%	1.7	2.0	-14.2%	\$73	\$63	15.2%
14	12	Amphetamine Preps	\$1.24	\$1.39	-11.0%	0.9	1.0	-11.0%	\$137	\$137	0.1%
15	63	Oral Contraceptives	\$1.20	\$1.13	6.4%	2.4	2.4	0.2%	\$49	\$46	6.3%
16	64	Other Hormones	\$1.15	\$0.78	47.1%	0.1	0.1	-0.3%	\$994	\$741	34.1%
17	1	Antacids	\$0.92	\$1.10	-16.0%	3.1	3.5	-12.3%	\$30	\$31	-3.3%
18	6	Laxatives	\$0.81	\$0.67	20.4%	6.7	5.4	22.9%	\$12	\$12	-2.2%
19	41	Non-narcotic Analgesics	\$0.80	\$0.76	5.1%	6.4	5.2	24.2%	\$12	\$15	-17.7%
20	27	Other Antibiotics	\$0.73	\$0.51	42.8%	0.7	0.7	-2.7%	\$89	\$59	49.6%
21	87	Electrolytes and Misc Nutr	\$0.73	\$0.61	19.3%	3.2	2.8	14.7%	\$23	\$22	5.1%
22	23	Streptomycins	\$0.63	\$0.57	10.8%	0.0	0.0	-19.1%	\$1,421	\$1,169	21.6%
23	65	Lipotropics	\$0.56	\$0.65	-13.9%	2.0	1.9	7.4%	\$28	\$35	-19.9%
24	80	Fat Soluble Vitamins	\$0.48	\$0.38	25.9%	4.9	3.8	28.9%	\$10	\$10	-2.4%
25	77	Anticoagulants	\$0.42	\$0.73	-42.6%	0.4	0.5	-8.4%	\$97	\$161	-40.0%
26	82	Multivitamins	\$0.41	\$0.35	17.0%	3.9	3.4	14.7%	\$10	\$10	1.5%
27	69	Enzymes	\$0.38	\$0.36	5.9%	0.0	0.0	-12.3%	\$903	\$735	22.9%
28	14	Antihistamines	\$0.32	\$0.34	-3.1%	2.7	2.9	-5.4%	\$12	\$12	2.3%
29	88	Hematinics with/without Iron	\$0.30	\$0.23	28.3%	1.8	1.4	23.9%	\$15	\$15	-1.5%
30	76	Other Cardiovascular Preps	\$0.28	\$0.33	-15.4%	1.7	1.9	-11.4%	\$17	\$17	-0.4%
		Aggregate	\$51.76	\$55.95	-7.5%	96.90	100.76	-3.8%	\$68	\$68	1.4%
		75th Percentile			27.2%			14.7%			19.3%
		50th Percentile (Median)			3.4%			-7.4%			5.1%

Last updated: July 23, 2013



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

College of Pharmacy

Pharmacy Utilization Summary Report: July 2012 - June 2013

	2012											2013											AVG/YTD		
	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE		
Eligibility																									
Total Members	618,940	619,527	621,079	619,870	618,962	621,328	621,239	624,167	625,033	624,596	625,809	625,937	622,291	622,291	622,291	622,291	622,291	622,291	622,291	622,291	622,291	622,291	622,291	622,291	
FFS Members	97,124	96,814	103,154	101,337	85,412	80,358	76,316	78,708	79,138	75,030	75,828	78,595	85,576	85,576	85,576	85,576	85,576	85,576	85,576	85,576	85,576	85,576	85,576	85,576	
Standard	5,694	5,626	6,046	6,171	4,095	3,466	2,980	3,134	3,078	2,969	2,931	3,120	4,111	4,111	4,111	4,111	4,111	4,111	4,111	4,111	4,111	4,111	4,111	4,111	
Plus	65,530	64,203	70,631	68,720	54,699	50,213	46,670	46,911	49,171	45,574	46,548	48,998	54,989	54,989	54,989	54,989	54,989	54,989	54,989	54,989	54,989	54,989	54,989	54,989	
Medicare Wrap	25,900	26,080	26,477	26,445	26,618	26,659	26,658	26,661	26,891	26,487	26,349	26,487	26,477	26,477	26,477	26,477	26,477	26,477	26,477	26,477	26,477	26,477	26,477		
Gross Figures																									
Total Cost	\$12,116,749	\$12,212,838	\$10,934,839	\$12,169,407	\$10,743,040	\$10,389,680	\$11,468,072	\$10,324,135	\$10,705,554	\$10,947,392	\$11,007,935	\$10,172,041	\$133,219,681	\$133,219,681	\$133,219,681	\$133,219,681	\$133,219,681	\$133,219,681	\$133,219,681	\$133,219,681	\$133,219,681	\$133,219,681	\$133,219,681	\$133,219,681	\$133,219,681
FFS Drugs	\$4,005,285	\$4,014,444	\$3,773,011	\$4,255,510	\$3,301,801	\$3,192,087	\$3,557,408	\$2,990,339	\$3,068,434	\$3,003,702	\$2,878,391	\$2,592,323	\$40,633,735	\$40,633,735	\$40,633,735	\$40,633,735	\$40,633,735	\$40,633,735	\$40,633,735	\$40,633,735	\$40,633,735	\$40,633,735	\$40,633,735	\$40,633,735	\$40,633,735
Mental Health Carveout Drugs	\$8,110,484	\$8,198,393	\$7,161,827	\$7,913,897	\$7,441,233	\$7,197,993	\$7,938,665	\$7,393,797	\$7,637,120	\$7,943,691	\$8,159,544	\$7,579,718	\$92,585,946	\$92,585,946	\$92,585,946	\$92,585,946	\$92,585,946	\$92,585,946	\$92,585,946	\$92,585,946	\$92,585,946	\$92,585,946	\$92,585,946	\$92,585,946	\$92,585,946
Total Rx	180,163	184,389	173,052	192,481	170,617	164,582	171,159	154,363	160,656	161,620	180,216	148,300	2,021,668	2,021,668	2,021,668	2,021,668	2,021,668	2,021,668	2,021,668	2,021,668	2,021,668	2,021,668	2,021,668	2,021,668	2,021,668
FFS Drugs	79,023	81,338	78,432	68,090	71,100	67,202	70,019	63,173	65,025	64,699	62,750	58,059	848,910	848,910	848,910	848,910	848,910	848,910	848,910	848,910	848,910	848,910	848,910	848,910	848,910
Mental Health Carveout Drugs	101,140	103,051	94,620	104,391	99,517	97,580	101,139	91,195	95,630	96,921	97,525	90,249	1,172,768	1,172,768	1,172,768	1,172,768	1,172,768	1,172,768	1,172,768	1,172,768	1,172,768	1,172,768	1,172,768	1,172,768	1,172,768
Cod/Rx	567,25	566,23	563,19	563,22	562,97	563,13	566,99	566,88	565,64	567,74	568,87	568,59	565,97	565,97	565,97	565,97	565,97	565,97	565,97	565,97	565,97	565,97	565,97	565,97	
FFS Drugs	\$50,70	\$49,35	\$48,11	\$48,31	\$46,44	\$47,50	\$50,81	\$47,34	\$47,19	\$48,43	\$45,87	\$44,65	\$47,72	\$47,72	\$47,72	\$47,72	\$47,72	\$47,72	\$47,72	\$47,72	\$47,72	\$47,72	\$47,72	\$47,72	
Mental Health Carveout Drugs	\$80,19	\$79,56	\$76,69	\$75,81	\$74,77	\$73,91	\$78,20	\$80,42	\$79,66	\$81,96	\$83,67	\$83,99	\$79,00	\$79,00	\$79,00	\$79,00	\$79,00	\$79,00	\$79,00	\$79,00	\$79,00	\$79,00	\$79,00	\$79,00	
Generic	\$29,16	\$28,21	\$25,87	\$25,80	\$24,40	\$23,64	\$23,64	\$23,89	\$24,05	\$24,19	\$23,63	\$23,63	\$25,03	\$25,03	\$25,03	\$25,03	\$25,03	\$25,03	\$25,03	\$25,03	\$25,03	\$25,03	\$25,03	\$25,03	
Brand	\$359,52	\$358,85	\$352,64	\$352,24	\$357,99	\$362,78	\$396,70	\$382,62	\$390,51	\$381,67	\$388,15	\$397,87	\$370,98	\$370,98	\$370,98	\$370,98	\$370,98	\$370,98	\$370,98	\$370,98	\$370,98	\$370,98	\$370,98	\$370,98	
PMPM Figures																									
Cost PMPM	\$54,43	\$55,09	\$48,11	\$54,76	\$50,68	\$51,31	\$59,34	\$49,74	\$50,97	\$52,75	\$51,00	\$45,09	\$51,93	\$51,93	\$51,93	\$51,93	\$51,93	\$51,93	\$51,93	\$51,93	\$51,93	\$51,93	\$51,93	\$51,93	
Standard	\$143,20	\$152,43	\$128,13	\$138,20	\$118,76	\$126,20	\$160,41	\$123,13	\$139,19	\$149,17	\$145,13	\$129,69	\$137,72	\$137,72	\$137,72	\$137,72	\$137,72	\$137,72	\$137,72	\$137,72	\$137,72	\$137,72	\$137,72	\$137,72	
Plus	\$55,55	\$56,35	\$49,09	\$56,82	\$56,81	\$57,64	\$58,27	\$56,47	\$56,72	\$61,03	\$59,73	\$51,68	\$57,35	\$57,35	\$57,35	\$57,35	\$57,35	\$57,35	\$57,35	\$57,35	\$57,35	\$57,35	\$57,35	\$57,35	
Medicare Wrap	\$18,04	\$17,18	\$15,79	\$17,84	\$13,48	\$18,18	\$15,73	\$14,65	\$12,16	\$12,13	\$11,34	\$10,66	\$14,45	\$14,45	\$14,45	\$14,45	\$14,45	\$14,45	\$14,45	\$14,45	\$14,45	\$14,45	\$14,45	\$14,45	
FFS Drugs	\$41,25	\$41,85	\$36,58	\$41,93	\$38,66	\$39,72	\$46,61	\$37,99	\$38,77	\$40,03	\$37,96	\$32,98	\$39,53	\$39,53	\$39,53	\$39,53	\$39,53	\$39,53	\$39,53	\$39,53	\$39,53	\$39,53	\$39,53	\$39,53	
Mental Health Carveout Drugs	\$13,10	\$13,23	\$11,53	\$12,77	\$12,02	\$11,58	\$12,73	\$11,75	\$12,20	\$12,72	\$13,04	\$12,11	\$12,40	\$12,40	\$12,40	\$12,40	\$12,40	\$12,40	\$12,40	\$12,40	\$12,40	\$12,40	\$12,40	\$12,40	
Rx PMPM	0.99	1.01	0.91	1.04	0.99	0.99	1.08	0.95	0.97	1.02	0.98	0.69	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98	
Standard	2.05	2.19	1.92	2.18	2.04	1.97	2.40	1.98	2.11	2.20	2.11	1.91	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	
Plus	0.83	0.86	0.77	0.89	0.86	0.86	0.99	0.86	0.87	0.92	0.88	0.77	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86	
Medicare Wrap	1.01	1.03	0.96	1.04	1.00	1.00	0.94	0.98	0.88	0.87	0.87	0.81	0.94	0.94	0.94	0.94	0.94	0.94	0.94	0.94	0.94	0.94	0.94	0.94	
FFS Drugs	0.81	0.85	0.76	0.87	0.83	0.84	0.92	0.80	0.82	0.66	0.63	0.74	0.83	0.83	0.83	0.83	0.83	0.83	0.83	0.83	0.83	0.83	0.83	0.83	
Mental Health Carveout Drugs	0.16	0.17	0.15	0.17	0.16	0.16	0.16	0.15	0.15	0.16	0.15	0.14	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	
POL %	93.9%	94.2%	94.2%	94.1%	93.9%	93.7%	92.4%	92.6%	92.2%	92.3%	91.1%	91.4%	93.0%	93.0%	93.0%	93.0%	93.0%	93.0%	93.0%	93.0%	93.0%	93.0%	93.0%	93.0%	93.0%

PMPM calculated as sum of physical health and mental health carve-outs

Data from OSSURs and DMHP FCHP first of month reports

Data are service dates

All eligibility groups included except for CAWEM, OS, QB

Drug Cost = Ant Paid + Copy + Other Insurance Paid

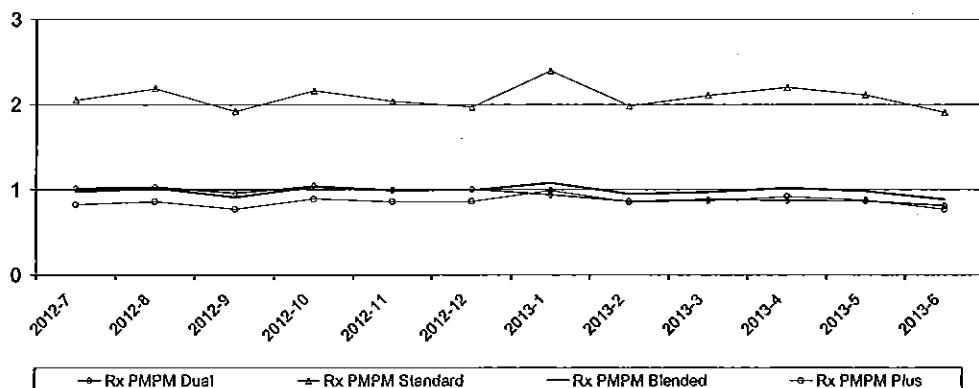
Last Updated: July 23, 2013



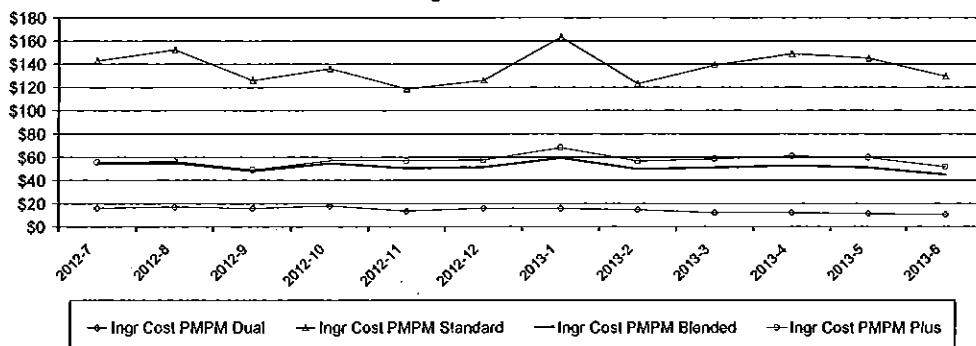
Drug Use Research & Management Program
DHS - Division of Medical Assistance Programs
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Pharmacy Utilization Summary Report: July 2012 - June 2013

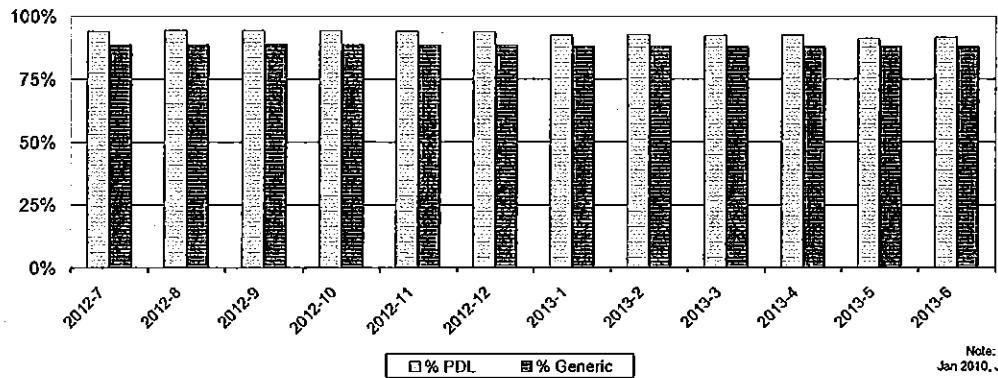
RX Dispensed PMPM



Ingredient Cost PMPM



Percent Generic and PDL



Note: PDL updated
Jan 2010, Jul 2010, Jan 2011

ProDUR Report for March 2013- April 2013
High Level Summary by DUR Alert

DUR Alert	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
ER (Early Refill)	35,315	6,869	58	28,381	67.00%
PG (Pregnancy/Drug Interaction)	1,804	1,195	4	604	3.40%
ID (Ingredient Duplication)	8,530	2,437	5	6,068	16.15%
TD (Therapeutic Duplication)	3,748	1,281	3	2,458	7.10%

ProDUR Report for March 2013-April 2013

Top Drugs in Early Refill- Requirement of Clarification Code began 1/13/2013

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	Claims	% Alerts/Total	% Alerts Overridden	% Change from Dec. to Jan/Feb
ER	Remeron (Mirtazapine)-Jan/Feb	491	83	408	3,737	13.1%	16.9%		
	Remeron (Mirtazapine)-March/April	497	97	400	3,535	14.1%	19.5%		15.5%
	Hydrocodone Bit/APAP-Jan/Feb	254	62	192	4,625	5.5%	24.4%		
	Hydrocodone Bit/APAP-March/April	210	33	177	3,951	5.3%	15.7%		-35.6%
	Oxycodone HCl-Jan/Feb	164	72	91	2,128	7.7%	43.9%		
	Oxycodone HCl-March/April	122	50	72	1,811	6.7%	41.0%		-6.6%
	Lorazepam-Jan/Feb	1,285	224	1,062	17,284	7.4%	17.4%		
Lorazepam-March/April									
	1,018	243	775	12,973	7.8%	23.9%			
	Alprazolam-Jan/Feb	980	162	816	11,977	8.2%	16.5%		
	Alprazolam-March/April	806	150	656	9,637	8.4%	18.6%		12.6%
	Diazepam-Jan/Feb	551	87	464	7,709	7.1%	15.8%		
	Diazepam-March/April	476	78	398	5,968	8.0%	16.4%		3.8%
	Buspar (Buspirone)-Jan/Feb	589	93	496	5,497	10.7%	15.8%		
	Buspar (Buspirone)-March/April	459	80	379	4,800	9.6%	17.4%		10.4%
	Lamictal (Lamotrigine)-Jan/Feb	1,401	283	1,117	11,856	11.8%	20.2%		
	Lamictal (Lamotrigine)-March/April	1,388	287	1,101	10,887	12.7%	20.7%		2.4%
	Depakote (Divalproex Sodium)-Jan/Feb	845	181	663	7,308	11.6%	21.4%		
	Depakote (Divalproex Sodium)-March/April	828	203	624	6,652	12.4%	24.5%		14.5%
	Clonazepam-Jan/Feb	264	47	217	2,859	9.2%	17.8%		
Clonazepam-March/April									
	156	44	112	1,666	9.4%	28.2%			
	Gabapentin-Jan/Feb	289	81	208	1,989	14.5%	28.0%		
	Gabapentin-March/April	218	65	153	1,626	13.4%	29.8%		6.4%
	Ability (Aripiprazole)-Jan/Feb	1,117	216	901	9,558	11.7%	19.3%		
	Ability (Aripiprazole)-March/April	1,122	215	906	8,256	13.6%	19.2%		-0.9%
	Seroquel (Quetiapine)-Jan/Feb	1,463	306	1,156	10,759	13.6%	20.9%		
	Seroquel (Quetiapine)-March/April	1,412	303	1,107	9,280	15.2%	21.5%		2.6%
	Risperidol (Risperidone)-Jan/Feb	1,261	227	1,033	9,872	12.8%	18.0%		
	Risperidol (Risperidone)-March/April	1,241	283	958	8,997	13.8%	22.8%		26.7%
	Zyprexa (Olanzapine)-Jan/Feb	748	150	598	5,774	13.0%	20.1%		
	Zyprexa (Olanzapine)-March/April	675	170	505	5,252	12.9%	25.2%		25.6%
	Geodon (Ziprasidone)-Jan/Feb	361	70	289	2,925	12.3%	19.4%		
	Geodon (Ziprasidone)-March/April	342	66	276	2,638	13.0%	19.3%		-0.5%
	Albuterol-Jan/Feb	254	50	203	4,608	5.5%	19.7%		
	Albuterol-March/April	237	38	199	3,457	6.9%	16.0%		-18.5%
	Lithium Carbonate-Jan/Feb	513	113	400	4,145	12.4%	22.0%		
	Lithium Carbonate-March/April	484	95	389	3,663	13.2%	19.6%		-10.9%
	Wellbutrin (Buproprion)-Jan/Feb	1,305	182	1,123	13,938	9.4%	13.9%		
	Wellbutrin (Buproprion)-March/April	1,317	164	1,153	12,654	10.4%	12.5%		-10.7%
	Prilosec (omeprazole)-Jan/Feb	326	78	248	3,543	9.2%	23.9%		
	Prilosec (omeprazole)-March/April	273	49	224	3,088	8.9%	17.9%		-25.0%
	Zoloft (Sertraline)-Jan/Feb	1,904	317	1,587	17,581	10.8%	16.6%		
	Zoloft (Sertraline)-March/April	1,768	302	1,466	15,853	11.2%	17.1%		2.6%
	Celebrex (Citalopram)-Jan/Feb	1,581	224	1,356	15,870	10.0%	14.2%		
	Celebrex (Citalopram)-March/April	1,399	192	1,205	14,486	9.7%	13.7%		-3.1%

ProDUR Report for March 2013-April 2013

Top Drugs in Early Refill- Requirement of Clarification Code began 1/13/2013

DUR Alert	Drug Name	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-13 Emergency	CC-14 LTC Leave of Absence	CC-Other
ER	Remeron (Mirtazapine)-March/April	2	11	20	1	38	0	1	1
	Hydrocodone Bit/ APAP-March/April	1	1	17	0	5	0	0	1
	Oxycodone HCl-March/April	2	1	14	1	16	0	0	2
	Cetirizine HCl-March/April	12	7	98	2	75	0	0	2
	Desipramine HCl-March/April	6	11	54	0	38	0	0	0
	Alprazolam-March/April								
	Diazepam-March/April	2	8	20	2	34	0	0	1
	Buspar (Buspirone)-March/April	4	7	28	3	16	0	0	0
	Lamictal (Lamotrigine)-March/April	8	17	120	2	64	0	1	2
	Depakote (Divalproex Sodium)-March/April	0	6	56	1	86	0	1	4
	Clobazam-March/April	3	1	13	0	17	0	0	2
	Gabapentin-March/April	1	3	29	1	13	0	0	0
	Abilify (Aripiprazole)-March/April	7	12	65	8	85	0	0	1
	Seroquel (Quetiapine)-March/April	6	12	81	2	106	0	1	4
	Risperdal (Risperidone)-March/April	4	8	85	5	121	0	0	1
	Zyprexa (Olanzapine)-March/April	3	12	45	3	54	0	0	0
	Geodon (Ziprasidone)-March/April	0	5	21	0	21	0	0	0
	Albuterol-March/April	1	2	13	1	15	0	0	0
	Lithium Carbonate- March/April	3	1	20	0	32	0	0	0
	Wellbutrin (Bupropion)-March/April	5	13	48	0	51	0	0	4
	Prilosec (Omeprazole)-March/April	0	2	12	0	21	0	1	2
	Zoloft (Sertraline)-March/April	6	12	127	4	96	0	1	1
	Celexa (Citalopram)-March/April	8	11	57	4	74	0	0	1
	Prozac (Fluoxetine)-March/April	9	19	87	2	47	0	0	3
	Lexapro (Escitalopram)-March/April	6	5	30	2	31	0	0	0
	Paxil (Paroxetine)-March/April	3	6	15	0	16	0	0	0
	Trazodone-March/April	11	15	127	10	120	0	0	2
	Cymbalta (Duloxetine)-March/April	6	9	31	2	51	0	0	1
	Effexor (Venlafaxine)-March/April	6	5	24	0	34	0	0	1
	Amitriptyline-March/April	2	6	54	2	41	0	0	1
	Strattera (Atomoxetine)-March/April	0	2	10	0	15	0	0	0
	TOTALS	127	230	1422	58	1433	0	6	37

Retro-DUR Intervention History by Quarter FFY 2013-2014

Program	Initiative	Metric	Quarter 1 - Oct - Dec				Quarter 2 - Jan - Mar		Quarter 3 - Jul - Sep		Quarter 4 - Jul - Sep		Year-to-Date
			Quarter 1 - Oct - Dec	Jan	Quarter 2 - Jan - Mar	Jul - Sep	Quarter 3 - Jul - Sep	Jul - Sep	Quarter 4 - Jul - Sep	Jul - Sep	Quarter 4 - Jul - Sep	Jul - Sep	
General	Pharmacy Management Program (aka Lock In)	Cases Reviewed Members Enrollment Anticipated Cost Savings											
	Polypharmacy Reviews	Cases Reviewed Provider Letters Sent Provider Responses											
	Annual Foster Care Psychotropic Reviews	Cases Reviewed & Forwarded to Child Welfare Member Profiles Sent											
	Antipsychotic Metabolic Monitoring	Member With Responses Members With New Scheduled Monitoring											
		New Onset Diabetes											
		Response Rate Providers Contacted Provider Response Response Rate Provider Agree With Follow-up											
Pediatric Psychotropics		Provider Agree With Follow-up											
		Reviewed # Cases reviewed											
		Value Providers Contacted # Value Providers Contacted											
		Agree With Recommendation # Members Agreed											
		Follow up Within 30 Days # Members Followed Up Within 30 Days*											
Incentive Measures & Digital Dashboard	ADHD New Start Follow Up	Reviewed within 30 days											
		Case Review # Cases reviewed											
		Value Providers Contacted # Value Providers Contacted											
Academic Detailing	Improving the Use of Antipsychotics	Agree With Recommendation # Members Agreed											
		Follow up Within 30 Days # Members Followed Up Within 30 Days*											
		Academic Detailing Meetings Scheduled Academic Detailing Meetings Conducted Other data points TBD											

Notes:

* Medical claims are typically delayed 3-6 months which delays outcome measurements

Month	19 Scans	30 Class Reviews	26 New Drugs	31 Policy/Practice Approvals
Nov-11	Antiplatelet Drugs	Prasugrel Ticagrelor	P&T Policies & Procedures clinical PA on prasugrel & ticagrelor	New Drug Policy Clinical PA on Pradaxa (dabigatran) and Xarelto (rivaroxaban)
Jan-12	HSV Antivirals Influenza Antivirals Beta Blockers Calcium Channel Blocker	Oral Anticoagulants Hep C Agents ACE-Is/ARBs/DRIs	Methadone / LAO Drug Use Evaluation Xarelto (rivaroxaban) Incivek (telaprevir) Vichetis (boceprevir) Ecarbi (azilsartan)	Clinical PA on Incivek (telaprevir) and Vichetis (boceprevir)
Feb-12	Parkinsons' Drugs NSAIDs Gout Drugs Alzheimers' Drugs	Hepatitis B Neuropathic Pain COPD medications	Rofumilast inacaterol	Clinical PA on Hep B drugs Update ESA clinical PA Update PPI clinical PA Update topiramate clinical PA Update Androgen clinical PA Update PAH clinical PA Update early refill threshold to 80% Clinical PA on new COPD drugs
Mar-12	Sedatives Skeletal Muscle Relaxants Triptans	MS Drugs Atypical Antipsychotics Statins ADHD Drugs	Dalfampridine Iurasidone pitavastatin Icatibant	SAO DUE SAO Dose Limits Dalfampridine clinical PA Simvastatin 80mg Dose Limit
Apr-12	Pulmonary Arterial Hypertension Oral Hypoglycemics	Amylin Analogs, Incretin Enhancers and Incretin Mimetics Drugs for C. Diff	Kalydeco® (ivacaftor) Egrifta® (tesamorelin)	Clinical PA on Kalydeco® (ivacaftor) Clinical PA on Egrifta® (tesamorelin) Updated Amylin Analogs, Incretin Enhancers and Incretin Mimetics Clinical PA
TZDs Insulins	Second Gen. Antidepressants Smoking Cessation	Diffid® (fidaxomicin) vilazodone	ICS/LABA Policy Evaluation Synagis Drug Use Evaluation	Update ICS/LABA Clinical PA Eliminate Ondansetron quantity limit Updated Synagis Clinical PA Comment on HERC Low Back Pain coverage guidance
May-12	Asthma Controllers Anticonvulsants Topical Antiparasite Other Lipid Lowering Agents	clobazam ezogabine Spinosad ivermectin		
Jun-12	ESA Class Nitrates class TMs	pEGINesatide (Omnitrope®) deferiprone (Ferrirprox®)		
Aug-12	Antipsoratics Inhaled drugs for CF Diuretic Agents	Fingolimod (Gilenya®) Ranolazine (Ranexa®)	Update Clinical PA on Rivaroxaban (Xarelto®) Clinical PA on non-preferred TMs Update on Clinical PA for Antipsoratics Clinical PA on Fingolimod (Gilenya®) Update on ESA Clinical PA	Update Clinical PA on Rivaroxaban (Xarelto®) Clinical PA on non-preferred TMs Update on Clinical PA for Antipsoratics Clinical PA on Fingolimod (Gilenya®) Update on ESA Clinical PA Clinical PA on Intravenous/sub-Q Pulmonary Arterial Hypertension (PAH) Evaluated SSDC SR bids for 2013 placement
Sep-12	Growth Hormones Ulcerative Colitis Drugs	Bone Metabolism Drugs CSFs intravenous/Sub-Q Pulmonary Arterial Hypertension (PAH)		
	Ophthalmic antibiotics Phosphate Binders			

FFY 2012 Medicaid Drug Utilization Review Annual Report

Page 1

Thank you for taking our survey. Your response is very important to us.

OMB approved # 0938-0659

MEDICAID DRUG UTILIZATION REVIEW ANNUAL REPORT
FEDERAL FISCAL YEAR 2012

Section 1927(g)(3)(D) of the Social Security Act requires each State to submit an annual report on the operation of its Medicaid Drug Utilization Review (DUR) program. Such reports are to include: descriptions of the nature and scope of the prospective and retrospective DUR programs; a summary of the interventions used in retrospective DUR and an assessment of the education program; a description of DUR Board activities; and an assessment of the DUR program's impact on quality of care as well as any cost savings generated by the program.

This report is to cover the period October 1, 2011 to September 30, 2012 and is due for submission to CMS by no later than June 28, 2013. Answering the attached questions and returning the requested materials as attachments to the report will constitute full compliance with the above-mentioned statutory requirement.

If you have any questions regarding the DUR annual report, please contact CMS at : DURPolicy@cms.hhs.gov

According to the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number. The valid OMB control number for this information collection is 0938-0659. The time required to complete this information collection is estimated to average 30 hours per response, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection. If you have comments concerning the accuracy of the time estimate(s) or suggestions for improving this form, please write to: CMS, 7500 Security Boulevard, Attn: PRA Reports Clearance Officer, Mail Stop C4-26-05, Baltimore, Maryland 21244-1850.

DUR ANNUAL REPORT

Nomenclature Format for Attachments and Tables

States: Please use the standardized format for naming attachments and tables beginning with the 2012 reporting period.

State Abbrev-FFY-ATT.#-Abbreviated Report name (NO SPACES!)

Example for Arizona: (each state should insert their State code)

Attachments:

AZ-2012-ATT.1-PRS	(Produr Review Summary)
AZ-2012-ATT.2-PPCR	(Produr Pharmacy Compliance Report)
AZ-2012-ATT.3-RSIS	(Retrodur Screening & Invention Summary)
AZ-2012-ATT.4-SDBA	(Summary of DUR BD Activities)
AZ-2012-ATT.5-GDSP	(Generic Drug Substitution Policies)
AZ-2012-ATT.6-CSE	(Cost Savings Estimate)
AZ-2012-ATT.7-PDMP	(Prescription Drug Monitoring Program)
AZ-2012-ATT.8-IPN	(Innovative Practices Narrative)
AZ-2012-ATT.9-EAS	(E-Prescribing Activity Summary)

CMS-R-153 (03/2011)

Next

95%

FFY 2012 Medicaid Drug Utilization Review Annual Report

Page 2

1. I. STATE**I-1. STATE NAME ABBREVIATION ***OR **2. II. MEDICAID AGENCY INFORMATION****II-1. Identify State person responsible for DUR Annual Report preparation.****Name ***First Name Last Name **3. Address ***Address City **4. State ***OR **5. Zip Code *****6. Email *****7. Phone (number only, no hyphen, example 4107860000) *****8. II-2. Identify pharmacy POS vendor – (Contractor, State-operated, Other). *** Contractor **9. Please enter the vendor name or explain: ***

Hewlett Packard Enterprise Services operates the POS claims system and Prospective DUR services.
Oregon Health Sciences University (OHSU) College of Pharmacy is subcontracted to operate the Retrospective DUR services.

10. II-3. If not State-operated, is the POS vendor also the MMIS Fiscal agent? *

Yes No

CMS-R-153 (03/2011)

Please print a copy of this section for your records before clicking "NEXT" button.

95%

[Survey Software powered by SurveyGizmo](#)

 [SurveyGizmo Under the Hood](#)

FFY 2012 Medicaid Drug Utilization Review Annual Report

Page 3

11. III. PROSPECTIVE DUR**III-1. Identify prospective DUR criteria source.***

First Data Bank

**12. III-2. Are new prospective DUR criteria approved by the DUR Board? ***

No

**13. If answer to III-2 above is "No," please explain ***

DUR criteria are updated by FDB.
There is ability to modify how the alerts
are responded to (override required,
informational), but not to change the
criteria itself.

**14. III-3. When the pharmacist receives prospective DUR messages that deny the claim,
does your system: ***

c) a) and/or b) above - depending on the situation

**15. If answer to III-3 above is "c)," please explain ***

A pharmacist can override an early
refill and/or pregnancy/drug interaction
with correct conflict intervention and
outcome codes. A high dose alert
requires a prior authorization.

**16. III-4. Early Refill:****III-4. a) At what percent threshold do you set your system to edit? ***

	Percentage
Non-controlled drugs: *	80%
Controlled drugs: *	80%

17. III-4. b) When an early refill message occurs, does the State require prior authorization for non-controlled drugs?

*

No

**18. If answer to III-4 (b) above is 'No', can the pharmacist override at the point of service? ***

Yes

**19. III-4. c) When an early refill message occurs, does the State require prior authorization for controlled drugs? ***

No



20. If answer to III-4 (c) above is 'No', can the pharmacist override at the point of service? *

Yes

21. III-5. Therapeutic Duplication:

III-5. a) When there is therapeutic duplication, does the State require prior authorization for non-controlled drugs?

Sometimes

22. If answer to III-5 (a) above is "Sometimes," please explain *

Therapeutic duplication involving CNS sedatives such as benzodiazepines, zolpidem, or zaleplon require a prior authorization.

23. III-5. b) When there is therapeutic duplication, does the State require prior authorization for controlled drugs? *

Sometimes

24. If answer to III-5 (b) above is "Sometimes," please explain *

Prior authorization is required when a patient is taking more than one long acting opioid.

CMS-R-153 (03/2011)

Please print a copy of this section for your records before clicking "NEXT" button.

Back Next

95%

Survey Software powered by SurveyGizmo

<http://s-fa7f6a-i.sgizmo.com/s3>

FFY 2012 Medicaid Drug Utilization Review Annual Report

Page 4

OMB approved#: 0938-0659

25. III-6. State Is providing DUR criteria data requested on Table 1- Prospective DUR Criteria Reviewed by DUR Board, indicating by problem type those criteria with the most significant severity levels that were reviewed In-depth by the DUR Board in this reporting period. *

Yes

26. TABLE 1 – PROSPECTIVE DUR CRITERIA REVIEWED BY DUR BOARD

Indicate by problem type those criteria with the most significant severity levels that were reviewed In-depth by DUR Board.

FOR EACH PROBLEM TYPE BELOW IN THE FIRST COLUMN LIST THE DRUGS/ DRUG CATEGORY/ DISEASE COMBINATIONS FOR WHICH DUR BOARD CONDUCTED IN-DEPTH REVIEWS.

PROBLEM TYPE KEY:

INAPPROPRIATE - IA; THERAPEUTIC - TC; DRUG DRUG - D/D; DRUG ALLERGY - D/A; DRUG DISEASE - D/Ds;

	AHFS TC (Level 2)	AHFS TC (Level 4)	
IA DOSE1	Central Nervous System Agents <input checked="" type="checkbox"/>	Analgesics and Antipyretics <input checked="" type="checkbox"/>	Opiat
IA DOSE2	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
IA DOSE3	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
TC DUPLICATION1	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
TC DUPLICATION2	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
TC DUPLICATION3	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
D/A INTERACTION1	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
D/A INTERACTION2	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
D/A INTERACTION3	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
IA DURATION1	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
IA DURATION2	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
IA DURATION3	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
D/D INTERACTIONS1	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
D/D INTERACTIONS2	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
D/D INTERACTIONS3	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
D/Dis CONTRAINDICTION1	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
D/Dis CONTRAINDICTION2	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
D/Dis CONTRAINDICTION3	-- Please Select -- <input type="checkbox"/>	-- Please Select -- <input type="checkbox"/>	-- Ple
OTHER (specify)1	Gastrointestinal Drugs <input type="checkbox"/>	Antivirals <input type="checkbox"/>	Antire
OTHER (specify)2	Gastrointestinal Drugs <input type="checkbox"/>	Antivirals <input type="checkbox"/>	Antire

	AHFS TC (Level 2)	AHFS TC (Level 4)	
OTHER (specify)3	Cardiovascular Drugs <input checked="" type="checkbox"/>	Antithrombotic Agents <input checked="" type="checkbox"/>	Thrombotic Agents <input type="checkbox"/>
OTHER (specify)4	Cardiovascular Drugs <input checked="" type="checkbox"/>	Antithrombotic Agents <input checked="" type="checkbox"/>	Platelet Aggregates <input type="checkbox"/>
OTHER (specify)5	Anti-infective Agents <input checked="" type="checkbox"/>	Antivirals <input checked="" type="checkbox"/>	Antiviral Agents <input type="checkbox"/>
OTHER (specify)6	Hormones and Synthetic Substitutes <input checked="" type="checkbox"/>	Hematopoietic Agents <input checked="" type="checkbox"/>	– Platelet <input type="checkbox"/>
OTHER (specify)7	Respiratory Tract Agents <input checked="" type="checkbox"/>	Mucolytic Agents <input checked="" type="checkbox"/>	– Pleural <input type="checkbox"/>
OTHER (specify)8	Respiratory Tract Agents <input checked="" type="checkbox"/>	– Please Select – <input checked="" type="checkbox"/>	– Pleural <input type="checkbox"/>
OTHER (specify)9	Gastrointestinal Drugs <input checked="" type="checkbox"/>	Diabetes Mellitus <input checked="" type="checkbox"/>	Incretin Agents <input type="checkbox"/>

27. III-7. State has included Attachment 1 – Prospective DUR Review Summary *

Yes

28. ATTACHMENT 1 - PRODUR REVIEW SUMMARY

This attachment is a year-end summary report on prospective DUR screening. It should be limited to the Top 20 type/drug combinations which generate the largest number of messages. For each problem type/drug combination included, a denominator must be reported. The denominator is the total number of prescription claims adjudicated (during a given time period) for the drug compared to the number of messages generated for the problem type/drug (incorrect dosage/drug) during the same time period. Denominators permit comparison in percentage terms of the relative frequency of different problem type/drug combinations. For problem type/drug combinations involving more than one drug (e.g., drug/drug interactions), the denominator is the number of prescription claims for the drug submitted for adjudication.

Include for the Top 20 problem type/drug alerts with a severity of Level 1:

- * The number of messages generated by the system and a denominator. The number of messages must relate to problem type/drug combinations (incorrect dosage/drug). Report levels of messages by problem type only, incorrect dosage or drug only are not acceptable.
- * The number of messages overridden (i.e., adjudication process carried through to completion even though a message was generated).
- * The number of reversals/cancellations/denials (i.e., adjudication not carried through to completion) and data on types of interventions by pharmacists and the outcomes of such interventions using applicable NCPDP standards (e.g. Standard Format Version 5.1).
- * The number of refill too soon messages, duplicate prescription messages transmitted and, where applicable, claims denials.

State Abbrev-FFY-ATT.#-Abbreviated Report name (NO SPACES!) Example for Arizona: (each state should insert their State code) AZ-2012-ATT.1-PRS

Attachment 1 File Name *

OR-2012-ATT.1-PRS

29. Attachment 1 *

File. OR-2012-ATT.1-PRS.xlsx

30. III-8. State has included Attachment 2- Prospective DUR Pharmacy Compliance Report, a report on State efforts to monitor pharmacy compliance with the oral counseling requirement *

Yes

31. ATTACHMENT 2 - PROSPECTIVE DUR PHARMACY COMPLIANCE REPORT

This attachment reports the monitoring of pharmacy compliance with all prospective DUR requirements performed by the State Medicaid agency, the State Board of Pharmacy, or other entity responsible for monitoring pharmacy activities. If the State Medicaid agency itself monitors compliance with these requirements, it may provide a survey of a random sample of pharmacies with regard to compliance with the OBRA 1990 prospective DUR requirement. This report details State efforts to monitor pharmacy compliance

with the oral counseling requirement. This attachment should describe in detail the monitoring efforts that were performed and how effective these efforts were in the fiscal year reported.

State Abbrev-FFY-ATT.#-Abbreviated Report name (NO SPACES!) Example for Arizona: (each state should insert their State code) AZ-2012-ATT.2-PPCR

Attachment 2 File Name *

OR-2012-ATT.2-PPCR

32. Attachment 2 *

File: OR-2012-ATT.2-PPCR.doc

CMS-R-153 (03/2011)

Please print a copy of this section for your records before clicking "NEXT" button. Please note that when printing Table 1, the entire table will not print out on a single screenshot. You may need to adjust the size and/or printing two screenshots.

Back

Next

95%

Survey Software powered by SurveyGizmo

[SurveyGizmo](#)

FFY 2012 Medicaid Drug Utilization Review Annual Report

Page 5

OMB approved#: 0938-0659

33. IV. RETROSPECTIVE DUR**IV-1. Identify the vendor that performed your retrospective DUR activities during the time period covered by this report. (company, academic institution or other organization) *** Academic institution **34. Organization Name *** OSU College of Pharmacy**35. IV-1. a) Is the retrospective DUR vendor also the Medicaid fiscal agent? *** No **36. IV-1. b) Is this retrospective DUR vendor also the developer/supplier of your retrospective DUR Criteria? *** Yes **37. IV-2. Does the DUR Board approve the retrospective DUR criteria supplied by the criteria source? *** Yes **Please print a copy of this section for your records before clicking "NEXT" button.** Back Next

95%

Survey Software powered by SurveyGizmo

<http://s-fa7f6a-i.sgzmo.com/s3>

FFY 2012 Medicaid Drug Utilization Review Annual Report

Page 6

38. IV-3. State has provided the DUR Board approved criteria data requested on Table 2 – Retrospective DUR Approved Criteria

Yes

39. TABLE 2 – RETROSPECTIVE DUR BOARD APPROVED CRITERIA

Therapeutic categories reviewed by the DUR Board (Check All Relevant Boxes)

On the vertical axis, list the therapeutic categories number reviewed by the DUR Board and on the horizontal axis list the therapeutic categories (AHFS level 2 and level 4) and the problem types that may be associated with a therapeutic category. If the retrospective DUR program has approved criteria for drugs in a given therapeutic category, check boxes for the relevant problem types for which criteria have been established.

DRUG PROBLEM TYPE KEY

ID = Insufficient Dose; DDI = Drug/ Drug Interaction; IDU = Incorrect Duration; DDC = Drug/ Disease Contradiction; OU = Over Utilization; TD = Therapeutic Duplication; UU = Under Utilization; AG = Appropriate Use of Generics;

THERAPEUTIC CATEGORY - TC

THERAPEUTIC CATEGORY	AHFS TC (Level 2)		AHFS TC (Level 4)		ID	IDU	OU
	Category	Description	Category	Description			
THERAPEUTIC CATEGORY 1	Central Nervous System Agents	<input checked="" type="checkbox"/>	Analgesics and Antipyretics	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 2	Anti-infective Agents	<input checked="" type="checkbox"/>	Antivirals	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 3	Cardiovascular Drugs	<input checked="" type="checkbox"/>	Antidiabetic Agents	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 4	Cardiovascular Drugs	<input type="checkbox"/>	Antithrombotic Agents	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 5	Anti-infective Agents	<input checked="" type="checkbox"/>	Antivirals	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 6	Cardiovascular Drugs	<input type="checkbox"/>	Antithrombotic Agents	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 7	Anti-infective Agents	<input checked="" type="checkbox"/>	Antivirals	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 8	Anti-infective Agents	<input checked="" type="checkbox"/>	Antivirals	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 9	Hormones and Synthetic Substitutes	<input checked="" type="checkbox"/>	Hematopoietic Agents	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 10	Respiratory Tract Agents	<input checked="" type="checkbox"/>	Mucolytic Agents	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 11	Respiratory Tract Agents	<input checked="" type="checkbox"/>	Other Miscellaneous Therapeutic Agents	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 12	Gastrointestinal Drugs	<input checked="" type="checkbox"/>	Diabetes Mellitus	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 13	– Please Select --	<input checked="" type="checkbox"/>	– Please Select --	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 14	– Please Select --	<input checked="" type="checkbox"/>	– Please Select --	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 15	– Please Select --	<input checked="" type="checkbox"/>	– Please Select --	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 16	– Please Select --	<input checked="" type="checkbox"/>	– Please Select --	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THERAPEUTIC CATEGORY 17	– Please Select --	<input checked="" type="checkbox"/>	– Please Select --	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	AHFS TC (Level 2)	AHFS TC (Level 4)	ID	IOU	O
THERAPEUTIC CATEGORY 18	<input type="button" value="... Please Select ..."/>	<input type="button" value="... Please Select ..."/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
THERAPEUTIC CATEGORY 19	<input type="button" value="... Please Select ..."/>	<input type="button" value="... Please Select ..."/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
THERAPEUTIC CATEGORY 20	<input type="button" value="... Please Select ..."/>	<input type="button" value="... Please Select ..."/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

40. IV-4. State has included Attachment 3 - Retrospective DUR Screening and Intervention Summary Report *

Yes	<input type="checkbox"/>
-----	--------------------------

41. ATTACHMENT 3 – RETROSPECTIVE DUR SCREENING AND INTERVENTION SUMMARY REPORT

This is a year-end summary report on retrospective DUR screening and interventions. Separate reports on the results of retrospective DUR screening and on interventions are acceptable at the option of the State. The report(s) should:

- * Report the level of criteria exceptions by drug class (or drugs within the class) and problem type. (An exception is an instance where a prescription submitted for adjudication does not meet the DUR Board-approved criteria for one or more problem types within a drug class.)

NOTE:

- a) Reporting levels of criteria exceptions by only drug class (drug) or problem type is not acceptable.
- b) Year end summary reports should be limited to the Top20 problem types with the largest number of exceptions.

* Include a denominator for each drug class/problem type for which criteria exceptions are reported. A denominator is the number of prescription claims adjudicated for a drug class (or individual drugs in the class) during a given time period compared to the number of criteria exceptions for the drug class (or individual drugs in the class) during that time period.

* Also report, for each drug class/drug and problem type included in this summary report, the number of interventions (letters, face-to-face visits, etc.) undertaken during the reporting period.

* States which engage in physician, pharmacy profile analysis (i.e., review prescribing or dispensing of multiple prescriptions for multiple patients involving a particular problem type or diagnosis) or engage in patient profiling should report the number of each type of profile (physician, pharmacy, patient) reviewed and identify the subject(s) (diagnosis, problem type, etc.) involved.

State Abbrev-FFY-ATT.#-Abbreviated Report name (NO SPACES!) Example for Arizona: (each state should insert their State code) AZ-2012-ATT.3-RSIS

Attachment 3 File Name *

OR-2012-ATT.3-RSIS	<input type="checkbox"/>
--------------------	--------------------------

42. Attachment 3 *

File: OR-2012-ATT.3-RSIS.docx

CMS-R-153 (03/2011)

Please print a copy of this section for your records before clicking "NEXT" button. Please note that when printing Table 2, the entire table will not print out on a single screenshot. You may need to adjust the size and/or printing two screenshots.

Back	Next
------	------

95%

FFY 2012 Medicaid Drug Utilization Review Annual Report

Page 7

OMB approved#: 0938-0659

43. V. PHYSICIAN ADMINISTERED DRUGS

The Deficit Reduction Act requires collection of NDC numbers for covered outpatient physician administered drugs. These drugs are paid through the physician and hospital programs. Has your MMIS been designed to incorporate this data into your DUR criteria for both Prospective DUR and Retrospective DUR? *

Yes No

44. Comment for V

CMS-R-153 (03/2011)

Please print a copy of this section for your records before clicking "NEXT" button.

Back Next

95%

Survey Software powered by SurveyGizmo

www.surveygizmo.com

FFY 2012 Medicaid Drug Utilization Review Annual Report

Page 8

OMB approved#: 0938-0659

45. VI. DUR BOARD ACTIVITY

VI-1. State is Including a summary report of DUR Board activities and meeting minutes during the time period covered by this report as Attachment 4 - Summary of DUR Board Activities *

 Yes **46. ATTACHMENT 4 - SUMMARY OF DUR BOARD ACTIVITES**

This summary should be a brief descriptive report on DUR Board activities during the fiscal year reported.

- * Indicate the number of DUR Board meetings held.
- * List additions/deletions to DUR Board approved criteria.

- a. For prospective DUR, list problem type/drug combinations added or deleted.
- b. For retrospective DUR, list therapeutic categories added or deleted.

* Describe Board policies that establish whether and how results of prospective DUR screening are used to adjust retrospective DUR screens. Also, describe policies that establish whether and how results of retrospective DUR screening are used to adjust prospective DUR screens.

* Describe DUR Board Involvement in the DUR education program. (e.g., newsletters, continuing education, etc.) Also, describe policies adopted to determine mix of patient or provider specific Intervention types (e.g., letters, face to face visits, increased monitoring).

State Abbrev-FFY-ATT.#-Abbreviated Report name (NO SPACES!) Example for Arizona: (each state should insert their State code) AZ-2012-ATT.4-SDBA

Attachment 4 File Name *

 OR-2012-ATT.4-SDBA **47. Attachment 4 ***

File: OR-2012-ATT.4SDBA.docx

48. VI-2. Does your State have a Disease Management Program? * Yes **49. If answer to VI-2 above is 'Yes', Is your DUR Board involved with this program? *** Yes **50. VI-3. Does your State have a Medication Therapy Management Program? *** Yes **51. If answer to VI-3 above is 'Yes', Is your DUR Board involved with this program? *** Yes

CMS-R-153 (03/2011)

Please print a copy of this section for your records before clicking "NEXT" button.

95%

Survey Software powered by SurveyGizmo



FFY 2012 Medicaid Drug Utilization Review Annual Report

Page 9

OMB approved#: 0938-0659

52. VII. GENERIC POLICY AND UTILIZATION DATA

VII-1. State is including a description of new policies used to encourage the use of therapeutically equivalent generic drugs as Attachment 5 - Generic Drug Substitution Policies *

 Yes

53. ATTACHMENT 5 – GENERIC DRUG SUBSTITUTION POLICIES

Describe any policies used to encourage the use of generic drugs such as State maximum/minimum allowable cost (pricing, higher dispensing fee for generic and/or lower co-pay for generics). Include relevant documentation.

State Abbrev-FFY-ATT.#-Abbreviated Report name (NO SPACES!) Example for Arizona: (each state should insert their State code) AZ-2012-ATT.5.GDSP

Attachment 5 File Name *

 OR-2012-ATT.5-GDSP

54. Attachment 5 *

File: OR-2012-ATT.5-GDSP.dccx

55. Answer to question VII-2 and VII-3 below use TABLE 3 – GENERIC UTILIZATION DATA

Please provide the following utilization data for this DUR reporting period for all covered outpatient drugs paid. Exclude Third Party Liability.

Computation Instructions:

1. Generic Utilization Percentage: To determine the generic utilization percentage of all covered outpatient drugs paid during this reporting period, use the following formula:

$$N + (S + N + I) \times 100 = \text{Generic Utilization Percentage}$$

2. Generic Expenditures Percentage of Total Drug Expenditures: To determine the generic expenditure percentage (rounded to the nearest \$1000) for all covered outpatient drugs for this reporting period use the following formula:

$$N + (S + N + I) \times 100 = \text{Generic Expenditure Percentage}$$

CMS has developed an extract file from the Medicaid Drug Rebate Program Drug Product Data File identifying each NDC along with sourcing status of each drug: S, N, or I (see Key below), which can be found at <http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Drug-Utilization-Review.html> (Click on the link "an NDC and Drug Category file [ZIP]," then open the Medicaid Drug Product File 4th Qtr 2012 Excel file). This file will be made available from CMS to facilitate consistent reporting across States with this data request.

KEY:

Single-Source (S) - Drugs that have an FDA New Drug Application (NDA) approval for which there are no generic alternatives available on the market.

Non-Innovator Multiple-Source (N) - Drugs that have an FDA Abbreviated New Drug Application (ANDA) approval and for which there exists generic alternatives on the market. **Innovator Multiple-Source (I)** - Drugs which have an NDA and no longer have patent exclusivity. *

	Total Number of Claims	Total Reimbursement Amount Less Co-Pay
Single-Source (S) Drugs *	253657	82326565
Non-Innovator (N) Drugs *	1648290	29750626
Innovator Multi-Source (I) Drugs *	174462	32281648

56. VII-2. Indicate the generic utilization percentage for all covered outpatient drugs paid during this reporting period, using the computation instructions in Table 3 - Generic Drug Utilization Data.

Number of Generic Claims *

1648290

57. Total Number of claims *

29750626

58. Generic Utilization Percentage *

79.38%

59. VII-3. Indicate the percentage dollars paid for generic covered outpatient drugs in relation to all covered outpatient drug claims paid during this reporting period using the computation instructions in Table 3 – Generic Drug Utilization Data.

Generic Dollars *

29750626

60. Total Dollars *

144358839

61. Generic Expenditure Percentage *

20.61%

CMS-R-153 (03/2011)

Please print a copy of this section for your records before clicking "NEXT" button.

95%

FFY 2012 Medicaid Drug Utilization Review Annual Report

Page 10

OMB approved#: 0938-0659

62. VIII. PROGRAM EVALUATION/COST SAVINGS**VIII-1. Did your State conduct a DUR program evaluation/cost savings estimate? *** Yes**63. VIII-2. Who conducted your program evaluation/cost savings estimate? (company, academic institution , other institution) *** Company**64. Organization Name to VIII-2 *** HP Enterprise Services**65. VIII-3. State is providing the Medicaid program evaluations/cost savings estimates as Attachment 6 – Cost Savings Estimate *** Yes**66. ATTACHMENT 6 - COST SAVINGS ESTIMATE**

Include copies of program evaluations/cost savings estimates prepared by State or its contractor noting the methodology used.

State Abbrev-FFY-ATT.#-Abbreviated Report name (NO SPACES!) Example for Arizona: (each state should insert their State code) AZ -2012-ATT.6-CSE

Attachment 6 File Name * OR-2012-ATT.6-CSE**67. Attachment 6 *** File: OR-2012-ATT.6-CSE.doc**68. VIII-4. Please state the Estimated net savings amount. \$ *** 113338**69. VIII-5. Please provide the estimated percent impact of your state's cost savings program compared to total drug expenditures for covered outpatient drugs. Divide the estimated net savings amount provided in Section VIII, Question 4 above by the total dollar amount provided in Section VII, Question 3. Then multiply this number by 100.****Estimated Net Savings Amount / Total Dollar Amount * 100 = *** 1%

CMS-R-153 (03/2011)

FFY 2012 Medicaid Drug Utilization Review Annual Report

Page 11

OMB approved#: 0938-0659

70. IX. FRAUD, WASTE AND ABUSE DETECTION**IX-1. Do you have a process in place that identifies potential fraud or abuse of controlled drugs by recipients ? *** Yes **71. If 'Yes' to IX-1 above, what action(s) do you initiate? Check all that apply. ***

- a. Deny claim, and require pre-authorization
- b. Refer recipient to lock-in program
- c. Refer to Medicaid Fraud Control Unit (MFCU) or Program Integrity
- d. Other

72. IX-2. Do you have a process in place that identifies possible fraud or abuse of controlled drugs by prescribers ? * No **73. IX-3. Do you have a process in place that identifies potential fraud or abuse of controlled drugs by pharmacy providers ? *** No **74. IX-4. Does your State have a Prescription Drug Monitoring Program (PDMP)? See Attachment 7 – Prescription Drug Monitoring Program for a description of this program. *** Yes **75. ATTACHMENT 7 – PRESCRIPTION DRUG MONITORING PROGRAM**

In FY 2002, Congress appropriated funding to the U.S. Department of Justice to support Prescription Drug Monitoring Programs (PDMPs). These programs help prevent and detect the diversion and abuse of pharmaceutical controlled substances, particularly at the retail level where no other automated information collections system exists. States that have implemented PDMPs have the capability to collect and analyze data on filled and paid prescriptions more efficiently than those without such programs, where the collection of prescription information can require a time-consuming manual review of pharmacy files. If used properly, PDMPs are an effective way to identify and prevent diversion of the drugs by health care providers, pharmacies, and patients.

Please attach the file which describe your PDMP and explain how the State applies this information to control fraud and abuse.

State Abbrev-FFY-ATT.#-Abbreviated Report name (NO SPACES!) Example for Arizona: (each state should insert their State code) AZ-2012-ATT.7-PDMP

Attachment 7 File Name *

 76. Attachment 7 *

FFY 2012 Medicaid Drug Utilization Review Annual Report

Page 12

OMB approved#: 0938-0659

77. X. INNOVATIVE PRACTICES

X-1. Have you developed any innovative practices during the past year which you have included in Attachment 8 – Innovative Practices.*

No	<input checked="" type="checkbox"/>
----	-------------------------------------

CMS-R-153 (03/2011)

Please print a copy of this section for your records before clicking "NEXT" button.

95%

Survey Software powered by SurveyGizmo



FFY 2012 Medicaid Drug Utilization Review Annual Report

Page 13

OMB approved#: 0938-0659

78. XI. E-PRESCRIBING**XI-1. Has your State implemented e-prescribing? ***

Yes	<input type="checkbox"/>
-----	--------------------------

79. If 'Yes', please respond to questions XI-2 and XI-3 below.**80. XI-2. Does your system use the NCPDP Origin Code that indicates the prescription source? ***

Yes	<input checked="" type="checkbox"/>
-----	-------------------------------------

81. XI-3. Does your program system (MMIS or pharmacy vendor) have the capability to electronically provide a prescriber, upon inquiry, patient drug history data and pharmacy coverage limitations prior to prescribing? *

No	<input type="checkbox"/>
----	--------------------------

82. c) If 'No', are you planning to develop this capability? *

No	<input type="checkbox"/>
----	--------------------------

CMS-R-153 (03/2011)

Please print a copy of this section for your records before clicking "NEXT" button.

Back	Next
------	------

95%

Survey Software powered by SurveyGizmo



FFY 2012 Medicaid Drug Utilization Review Annual Report

Page 14

OMB approved#: 0938-0659

83. XII. EXECUTIVE SUMMARY

Drug Use Review (DUR) within the Division of Medical Assistance Programs is a program designed to measure and assess the proper utilization, quality, therapy, medical appropriateness, appropriate selection and cost of prescribed medication through evaluation of claims data. This is done on both a retrospective and prospective basis. This program includes, but is not limited to, education in relation to over-utilization, under-utilization, therapeutic duplication, drug-to-disease and drug-to-drug interactions, incorrect drug dosage, duration of treatment and clinical abuse or misuse. The DUR Board's priorities focused on prior authorization criteria, drug use evaluations, etc.

CMS-R-153 (03/2011)

Please review report for accuracy and print a copy of report for your records before clicking "SUBMIT" button.

FFY 2012 Medicaid Drug Utilization Review Annual Report

Thank you for completing this survey.

This is your confirmation that your survey has been successfully submitted.

Please print a copy of this page and keep it with a copy of your report.

100%

Survey Software, powered by SurveyGizmo



THE OREGON STATE DRUG REVIEW®

AN EVIDENCE BASED DRUG THERAPY RESOURCE

http://pharmacy.oregonstate.edu/drug_policy/newsletter

July 2013 Volume 3, Issue 2

© Copyright 2013 Oregon State University. All Rights Reserved

Updates and Future Perspectives in the Management of Stable Chronic Obstructive Pulmonary Disease

By Amy Higginson and Kathy Nguyen, PharmD Candidates 2013, Megan Henrik, Pharm.D. and Harleen Singh, Pharm.D., BCPS, all from Oregon State University College of Pharmacy

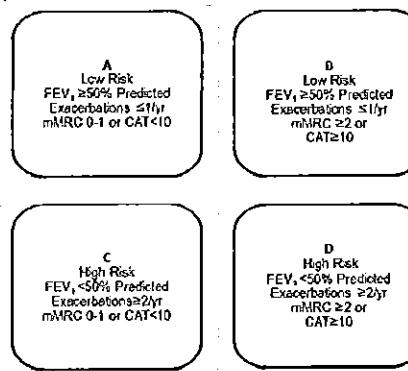
Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by loss of lung function over time. The World Health Organization estimates that by 2030, COPD will be the third leading cause of death worldwide.¹ Cigarette smoking is the major risk factor for COPD; other risk factors include genetic, air pollution and occupational exposures.

Bronchodilators such as beta agonists and long acting anticholinergic agents constitute the mainstay of therapy. Inhaled corticosteroids are used in combination with bronchodilators depending on the frequency of exacerbations and severity of COPD. New evidence and development of novel agents have resulted in significant changes in the management of COPD. As a result, The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines were revised in late 2011 and updated in 2013.^{2,3} This review will highlight pertinent GOLD guideline revisions and evaluate the evidence behind the addition of new treatment options.

2011 Revision-2103 Updates

The definition of COPD is no longer limited to chronic bronchitis or emphysema; it is a mixture of airflow obstruction, alveolar destruction and chronic inflammation. Previous GOLD guidelines categorized COPD severity by post-bronchodilator FEV₁ alone.

Figure 1: Combined assessment of COPD based on FEV₁, symptom scores, and exacerbation history



Adapted from the Global strategy for the diagnosis, management, and prevention of COPD.¹ mMRC score = modified Medical Research Council symptom score. CAT = COPD assessment test.

Recently, an epidemiological study compared the 2007 staging classification¹⁻⁴ versus the 2011 staging classification A-D in predicting exacerbations, morbidity and mortality among patients with COPD.⁴ The new COPD stratification was able to identify a higher percentage of patients at risk of exacerbations. Another finding was that patients presenting with dyspnea in the group B category (low risk and more symptoms) had higher 3-year mortality rates than patients in group C (high risk and less symptoms) despite minimally reduced FEV₁ (10.6% vs. 8.2%, respectively; P=0.02). Patients in subgroups B and C also had a higher prevalence of cardiovascular (CV) disease and cancer, with reduced survival. Since dyspnea is commonly reported by patients with CV disease as well as patients with COPD, screening for comorbidities is essential in the assessment and treatment of COPD.⁴ Short-acting beta agonists (SABA) and short acting anticholinergics are recommended as first-line as-needed therapy, followed by long-acting drugs for more ongoing control.³ These are followed by recommendations for combination drugs. Inhaled corticosteroids with a long-acting beta agonist (LABA) is more effective than the individual components alone in reducing exacerbations, improving lung function, and enhancing health status (Evidence A in severe COPD; Evidence B in moderate COPD). There is evidence to support that long acting anticholinergics are superior to LABAs, however; the guidelines note that the difference is small and give each agent the same level of evidence.^{2,5}

New Therapeutic Options

Appropriate medical management of stable COPD can reduce symptoms, reduce the frequency of exacerbations, and improve overall health status of the patient. Despite recent improvements, existing medications have not been shown to consistently modify the long-term decline in lung function.

Indacaterol (Arcapta®) was the first new bronchodilator approved and added to the 2011 update of the GOLD guidelines.^{2,7} Indacaterol is a once daily LABA therapy with a faster onset of action than salmeterol. It has shown to reduce days of poor control and need for rescue medication, reduce symptoms and exacerbations and improve health status.^{2,8} While the FDA approved the 75 mcg dose, the two dose strengths (150 and 300 mcg) that were most commonly studied in the original efficacy studies were not FDA approved due to a lack of evidence of increased efficacy with dose escalation. The most recent guidelines state that the bronchodilator effect of indacaterol is significantly greater than that of formoterol and salmeterol, and similar to tiotropium (Evidence A).³ A meta-analysis evaluated the efficacy of indacaterol, tiotropium, salmeterol, and formoterol in COPD.⁸ A total of 22 publications were included in the analysis and found that indacaterol resulted in a comparable FEV₁ at 12 weeks to tiotropium and salmeterol, and higher FEV₁ versus formoterol (0.05 L difference; 95% CI 0.01-0.09).⁸ Indacaterol has an acceptable safety profile, however; cough occurring after inhalation of indacaterol has been observed in up to 24% of patients.³ Similar to other LABA's, indacaterol contains a black box warning of an increase in the risk of asthma-related death and is contraindicated in patients with asthma without the use of a long-term asthma control medication.⁷

Acidinium bromide (Tudorza Pressair®) is a new inhaled long-acting anticholinergic drug that is administered twice daily.⁹ Until recently, tiotropium was the only available long acting inhaled anticholinergic. The ATTAIR and ACCORD COPD I studies were phase III trials evaluating the approved 400 mcg twice daily dose of acidinium versus placebo.⁹ Both found that treatment of moderate to severe COPD patients with twice-daily acidinium was associated with significant improvements in bronchodilation, health status, and COPD symptoms. A minimum clinically important difference for FEV₁ has not been defined in COPD, although improvement of around 100 to 140ml has been suggested as a benchmark.¹⁰ The treatment effect of acidinium 400 ug ranged from 61 ml to 124 ml across the studies at week 12. In comparison, tiotropium has been shown to increase FEV₁ by around 140ml compared to placebo. There remains insufficient evidence to determine acidinium's effects on mortality and other patient-centered outcomes, including exacerbations.⁹ In clinical trials, serious adverse event rates were low with acidinium. However, the CV risks are not well defined and need to be studied in larger clinical trials. Although acidinium was added to the 2013 GOLD guidelines as a therapeutic option, tiotropium has level A evidence to support its use in reducing exacerbations, reducing hospitalizations, and improving symptoms and health status.³

Agents have also been developed that target specific inflammatory processes, including inhibition of phosphodiesterase-4 (PDE4). However, theophylline is a nonselective phosphodiesterase inhibitor and is associated with potentially life-threatening and difficult to treat adverse effects.¹³ Roflumilast (Daliresp®) is the first oral selective PDE4 inhibitor approved as 500 mcg daily to reduce the risk of exacerbations in patients with severe COPD (FEV₁ <50% predicted) associated with chronic bronchitis and a history of exacerbations.¹⁴ Roflumilast is supported in the 2011 and 2013 GOLD guidelines with level A evidence for its proven efficacy in reducing moderate and severe exacerbations requiring treatment with corticosteroids by 15-20% in patients with severe COPD.^{2,3} It is recommended based on level B evidence in appropriate patients who are not adequately controlled

with long-acting bronchodilators; it should always be used in combination with bronchodilator therapy. The most frequent adverse effects being nausea, reduced appetite, abdominal pain, diarrhea, sleep disturbance, and headache. Psychiatric adverse events are also a concern with the use of roflumilast.

Recently, the combination of fluticasone furoate, an inhaled corticosteroid, and vilanterol inhalation powder (Breo Ellipta®), a LABA, was approved for the long-term, once-daily, maintenance treatment in patients with COPD, as well as for reducing exacerbations in patients with a history of exacerbations.¹⁵ This is the first approval of vilanterol for any indication and is a once daily alternative to Advair (fluticasone/salmeterol) and Symbicort (budesonide/formoterol), which are both dosed twice daily. This therapy was approved in May of 2013 and has not yet been evaluated for inclusion in treatment guidelines. Clinical trials showed improved lung function compared to placebo with an improved FEV1 of 173ml and 209 ml compared to placebo.^{15,16} In the exacerbation trials, treatment with fluticasone/vilanterol demonstrated a statistically significant 31% reduction in moderate and severe exacerbations in one trial, and a non-significant 15% reduction in a second trial.¹⁷ An increase in the incidence of pneumonia was observed in subjects receiving fluticasone/vilanterol in clinical trials (6%), including pneumonias resulting in hospitalizations.^{15,16} Treatment with inhaled corticosteroids or combination therapy is associated with a further increased risk of pneumonia in patients with COPD. In patients who develop repeated episodes of pneumonia, the guidelines recommend that inhaled corticosteroids be discontinued and evaluated as a causative factor, however, they take no stance on which agents are implicated more frequently in the development of pneumonia. A Cochrane systematic review found an increased rate of pneumonia in patients on ICS therapy versus placebo (11% vs. 7.6% respectively, OR 1.56; 95% CI 1.30-1.86).¹⁸

New Delivery Devices

In addition to novel COPD treatments, new devices and formulation strategies are being developed to improve drug delivery. Inhaled medications are delivered by MDI, dry-powder inhaler (DPI), or nebulizer. A new delivery option is the soft mist inhaler (SMI). Combivent® is the ipratropium and albuterol combination previously available as a metered dose inhaler (MDI), which has recently been replaced by a SMI formulation called Combivent Respimat®, the only SMI available for clinical use. The ipratropium/albuterol MDI is being phased out because of government restrictions on the use of chlorofluorocarbons (CFCs), which were contained within the inhaler. The ipratropium/albuterol Respimat will be the only formulation available after January 1, 2014. Main differences between the products include its general appearance, dosing, and the Respimat inhaler does not contain soy lecithin and therefore is not contraindicated in patients with soybean or peanut allergy.¹⁹ The ipratropium/albuterol Respimat dose is one puff four times daily compared to the previous inhaler, which is two puffs four times daily.¹⁹ A systematic review was conducted to evaluate the effectiveness of the Respimat inhaler and demonstrated no difference in risk of exacerbations (RR 1.20, 95% CI 0.95 to 1.51; p=0.12).¹⁹ Currently, no evidence suggests that the Respimat inhaler device provides any additional clinical benefit to that provided by other devices. Because of differences between the delivery devices, patients will require education on use when converting to the new product. The 2013 GOLD guideline update discourages the use of tiotropium delivered via the Respimat SMI until additional studies comparing delivery devices and doses are completed.³ A systematic review and meta-analysis of randomized controlled trials found tiotropium delivered via the Respimat soft mist inhaler to be associated with a significant increase in mortality (RR 1.52; 95% CI 1.06 to 2.5; p=0.02) compared to placebo substantiating safety concerns regarding the use of this agent.²⁰

Conclusion

The new GOLD guidelines classification is an important update, because it highlights the importance of both symptom severity and exacerbations in better understanding the disease course and tailoring therapy. Furthermore, when symptoms improvement is minimal, it prompts to search for comorbidities that could potentially mimic COPD symptoms.

Peer Reviewed By: Tom D. Yan, MD, Northwest Permanente, Pulmonary Critical Care and Jonathan White, Pharm D, BCPS, Clinical Pharmacy Specialist, Primary Care, Providence Medical Group.

References

- World Health Organization: Chronic obstructive pulmonary disease burden of disease. Available from: <http://www.who.int/respiratory/copd/burden/en/index.htm>
- Barbera JA, Buist AS, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Updated 2011. Available from: www.goldcopd.org.
- Barbera JA, Buist AS, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Updated 2013. Available from: www.goldcopd.org
- Lange P, Louis Marot J, Vestbo J, et al. Prediction of the Clinical Course of Chronic Obstructive Pulmonary Disease, Using the New GOLD Classification. A study of the General Population. *Am J Respir Crit Care Med* 2012;186(10):975-981.
- Chong J, Kerner C, Poole P, et al. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012 Sep 12;9:CD009157.doi:10.1002/14651858.CD009157.pub2.
- Ngkelo A, Adcock I. New treatments for COPD. *Current Opinion in Pharmacology* 2013;13:1-8.
- Indacaterol FDA Center for Drug Evaluation and Research: Summary review. Available at: www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202450Orig1s000SumR.pdf. Accessed 5/7/2013.
- Cope S, Zhang J, Williams J, et al. Efficacy of once-daily indacaterol 75 µg relative to alternative bronchodilators in COPD: A study level and a patient-level network meta-analysis. *BMC Pulmonary Medicine* 2012;12(29):2-15.
- Acidinium bromide New Drug Evaluation. OSU Drug Use Research and Management Program. 2013. Available at: http://pharmacy.oregonstate.edu/drug_policy/evaluations
- Acidinium FDA Summary Review.pdf. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202450Orig1s000SumR.pdf.
- Buhl R, Banerji D. Profile of glycopyrronium for once-daily treatment of moderate-to-severe COPD. *International Journal of COPD*. 2012;7:729-741.
- National Institute for Health and Clinical Excellence (NICE). Evidence summary: Chronic obstructive pulmonary disease: glycopyrronium bromide. 2013. Available at: <http://publications.nice.org.uk/esnm9-chronic-obstructive-pulmonary-disease-glycopyrronium-bromide-esnm9>
- Field S. Roflumilast, a Novel Phosphodiesterase 4 Inhibitor, for COPD Patients with a History of Exacerbations. *Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine*. 2011;5:57-70.
- Roflumilast New Drug Evaluation.pdf. OSU Drug Use Research and Management Program. Available at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/reviews/articles/DUR_Review_2012_02_23_Roflumilast.pdf
- FDA News Release. FDA approves Breo Ellipta to treat chronic obstructive pulmonary disease. May 10, 2013. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm351664.htm>
- Martinez FJ, Boscia J, Feldman G, Scott-Wilson C, et al. Fluticasone furoate/vilanterol (100/25; 200/25 ug) improves lung function in COPD: a randomized trial. *Respir Med*. 2013;107(4):550-559.
- FDA Center for Drug Evaluation and Research. Summary review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204275Orig1s000TOC.cfm
- Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012 11:7.
- Combivent Respimat New Drug Evaluation.pdf. OSU Drug Use Research and Management Program. 2013. Available at: http://pharmacy.oregonstate.edu/drug_policy/evaluations
- Singh S, Loke YK, Enright PL, et al. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomized controlled trials. *BMJ* 2011; 342: 3215-3223.



New Drug Evaluation: lomitapide**Month/Year of Review:** May 2013**Generic Name:** lomitapide**PDL Class:** Non-Statin Lipid Lowering Agents**Food and Drug Administration (FDA) Approved Indication:**

“Juxtapid™ is a microsomal triglyceride transfer protein inhibitor (MTP) indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol(LDL-C), total cholesterol(TC), apolipoprotein B(apo B), and non-high density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia(HoFH).”¹ There is a Black Box Warning and a Risk Evaluation and Mitigation Strategy is required to determine if the potential benefits of lomitapide outweigh the potential risk of liver injury.¹

Potential Off-Label Indications:

- Heterozygous familial hypercholesterolemia (HeFH)
- Drug resistant hypercholesterolemia

Research Questions:

- Is lomitapide more effective than statins, statin combination therapy or other recommended therapies to prevent coronary heart disease (CHD) events in patients with hypercholesterolemia?
- Is lomitapide safer than statins, statin combination therapy or other recommended therapies in patients with hypercholesterolemia?
- Are there sub-populations of patients with hypercholesterolemia where lomitapide is more or less effective or safe?

Conclusions:

- There is insufficient evidence from a single uncontrolled, open-label trial of 29 HoFH patients to evaluate lomitapide effectiveness to prevent CHD events.
- The safety database is very small, but there are potential risks of serious acute and/or chronic liver injury. It is teratogenic in animals. There are serious GI effects and known malabsorptions of essential fatty acids and vitamins. There are many drug interactions.
- HoFH patients have limited therapeutic options and lomitapide may be a viable third-line alternative to reduced LDL-C levels.

Recommendations:

- Prior authorize lomitapide to limit use to confirmed adult HoFH patients that have failed or are unable to tolerate maximum lipid-lowering therapy and LDL-C apheresis.

NDE: lomitapide

Background: Hypercholesterolemia and specifically high levels of low-density lipoprotein cholesterol (LDL-C) are risk factors for CHD.² Currently, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are the first line treatment to reduce LDL-C because they are proven to reduce CHD morbidity and mortality with a relatively low incidence of serious adverse events.² Primary prevention recommendations are a minimum 30-40% LDL-C reduction to achieve CHD benefit and secondary prevention recommendations are a minimum of 50% LDL-C reduction.² Statins are not tolerated (myalgia or myositis) or not effective in all patients (e.g. antiretroviral associated dyslipidemia). Some patients with HoFH and HeFH can be refractory to statin therapy because they are genetically lacking LDL-C receptor activity (absent entirely or significantly reduced). Lomitapide has a new mechanism of action and reduces LDL-C levels by inhibiting MTP.¹ This prevents the assembly of apo B and subsequent synthesis of LDL-C.

Familial hypercholesterolemia (FH) has a worldwide prevalence of 0.2% which is mostly comprised of HeFH.³ FH is characterized by a high LDL-C level from birth, a propensity to tendon xanthomata, and early onset CHD.⁴ HeFH is a partial deficiency of the LDL receptor and is associated with total cholesterol levels >300mg/dL and high risk of coronary artery disease by age 30-40 years.³ HoFH is most often a total LDL receptor deficiency but may also be caused by mutations of apo B or subtilisin/keping type 9 genes.³ It is extremely rare but myocardial infarction by age 10 and death by age 20 is common. HoFH is associated with total cholesterol levels > 600-1000mg/dL.³ HoFH statin LDL-C response is < 10-25% decrease at maximum doses.⁵ Cholesterol absorption inhibitors provide additional LDL-C lowering or <10%.⁵ LDL-C apheresis is currently the standard of care for HoFH patients resistant to statin therapy and can lower LDL-C by as much as 30-40%.^{5,6} However, apheresis needs to be performed on a chronic repetitive basis (i.e. every 1-2 weeks), is associated with LDL-C rebound and is currently performed at only 35 centers in the United States.⁵ Liver transplantation is a last resort.⁵ HoFH is an FDA orphan indication due to the lack of good therapeutic options.

Clinical Efficacy: The dossier identified 15 Phase I, 6 Phase II and 1 Phase III with safety extension. ClinicalTrials.gov identified nine lomitapide trials: 1 Phase I,⁶ Phase II and 2 Phase III of which only 1 was completed and published. Cuchel et al.⁷ was a poor quality, non-controlled, open label trial investigating the efficacy and safety of lomitapide in 29 HoFH patients. The study did not evaluate CHD events. The primary endpoint was LDL-C change from baseline to 26 weeks and patients were followed an additional 52 weeks to assess safety. Concomitant lipid-lowering therapies were stable during the efficacy phase but could change during the safety phase. Apheresis was allowed and LDL-C response allowed it to be stopped in 3 patients and the interval extended in another 3. There was a 50% decrease in LDL-C at 26 weeks ($p < 0.0001$) to a median level of 169 mg/dL.⁵ Eight patients achieved LDL-C levels <100mg/dL with 4 of these concomitantly receiving apheresis.⁵

Clinical Safety: The safety database is very limited and per the FDA reviewer "can only provide assurance that the true incidence of an ADE is no greater than 10% when the outcome is not observed in the trial."⁵ Two patients experienced serious adverse events likely related to drug-drug interactions with CYP3A4 inhibitors.⁵ One patient had severe hepatotoxicity and the other experienced over-anticoagulation while concurrently on warfarin.⁵ Thirty-eight percent of patients experienced at least one ALT $\geq 3x$ ULN in the combined efficacy and safety trial but these were not accompanied by other tests of liver dysfunction.⁵ The risk of serious liver injury remains undefined due to the small safety database.⁵ Diarrhea, nausea, vomiting, dyspepsia or abdominal pain were nearly universal (>90% of patients) and should be managed with a diet where <20% of energy is derived from fat.⁵ Lomitapide interferes with dietary fat absorption via its mechanism of action but this can be overcome with dietary supplementation. It is teratogenic in rats and ferrets and carries a FDA pregnancy category X.

NDE: lomitapide

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

- 1) CHD events
- 2) Withdrawals due to ADEs

3) Serious ADEs

Ref./Study Design	Drug Regimens / Duration	Patient Population	N	Outcomes/Efficacy Results (CI, P-values)		ARR/NNT (CI, P-values)	ARI/NNH	Quality Rating: Internal Validity Risk of Bias/External Validity Concerns
				Total withdrawals due to AEs	%Δ in LDL-C @ baseline to 26 weeks.			
Cuchel et al. ⁷	L: Lomitapide @ 5mg/day x 2 wks; increased to 10, 20, 40, + 60mg a day at 4-week intervals until an individually determined maximum dose was achieved on the basis of safety and tolerability.	Patients with HoFH already on lipid-lowering treatment.	ITT: L: 29	Primary Outcome: %Δ in LDL-C @ baseline to 26 weeks. Total Attrition: L: 6 (20.7%)	N=23 L: -50% (-62%, -39%) to 168mg/dL	NA / SAE: L: 3 (10.3%) 1 ACS, 1-elective hysterectomy for menorrhagia, 1-angina	17% / NA	Quality Rating: POOR Internal Validity: RoB Selection: HIGH = No randomization and no control arm. Performance: HIGH = No blinding Detection: MOD-No blinding Attrition: HIGH External Validity: Recruitment: Highly selective with long run-in; 12 week screening then 6 week run-in to establish stable lipid-lowering therapies. Apheresis was allowed. Patient Characteristics: Study results apply to HoFH patients only Setting: Lipid clinics Outcomes: LDL-C surrogate, short duration Low Power: 90% to detect 25% difference (n=20)

AMI = acute myocardial infarction;
 CA = cancer;
 CAD = coronary artery disease;
 CHD = cardiac heart disease;
 CHF = congestive heart failure;
 CVA = cardiovascular accident;
 DB = Double-Blind;
 DM = diabetes mellitus;
 flu = Follow-up;
 fx = fracture;
 Hx = history of;
 HTN = hypertension;
 L = Lomitapide group
 LDL-C = low-density lipoprotein cholesterol;
 MC = Multi-Center;
 NA = not available or applicable;

P=placebo group;
 PC = Placebo Controlled;
 PE = pulmonary embolism;

RCT = Randomized Controlled Trial;
 SCR = serum creatinine
 SC = subcutaneous;
 SVT = supraventricular tachycardia;

References:

1. Aegerion Pharmaceuticals, Inc. Juxtapid Label - Reference ID: 3236196. 2012. Available at: http://www.accessdata.fda.gov/drugsatfa_docs/label/203858s000lbl.pdf. Accessed April 3, 2013.
2. NIH NHLBI. ATP 3 Cholesterol Guidelines, NHLBI. 2004. Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>. Accessed March 18, 2013.
3. DynaMed. DynaMed: Familial hypercholesterolemia. 2013. Available at: <http://web.ebscohost.com.liboff.ohsu.edu/dynamed/detail?vid=3&sid=b25a0568-afdd-45e4-ab58-90387124a828%40sessionmgr111&hid=124&bdata=JnNpdGU9ZHLuyW1|ZC1saXZlJnNjb3BIPXNpdGU%3d#db=dme&AN=115368>. Accessed April 1, 2013.
4. Rosenson RS, de Ferranti SD, Durrington P. Primary disorders of LDL-cholesterol metabolism. 2012. Available at: <http://www-uptodate.com.liboff.ohsu.edu/contents/primary-disorders-of-ldl-cholesterol-metabolism?source=preview&anchor=H1&selectedTitle=1~67#H1>. Accessed April 1, 2013.
5. FDA. Lomitapide Summary Review - Reference ID 3236195. 2012. Available at: http://www.accessdata.fda.gov/drugsatfa_docs/nda/2012/203858Orig1s000SumR.pdf. Accessed April 3, 2013.
6. Ito MK, McGowan MP, Moriarty PM. Management of Familial Hypercholesterolemias in adult patients: Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *Journal of Clinical Lipidology*. 2011;5(3):S38–S45. doi:10.1016/j.jacl.2011.04.001.
7. Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolemia: a single-arm, open-label, phase 3 study. *The Lancet*. 2013;381(9860):40–46. doi:10.1016/S0140-6736(12)61731-0.

Appendix 1: Specific Drug Information**CLINICAL PHARMACOLOGY**

Lomitapide binds and inhibits MTP which prevents the assembly of apo B and subsequently inhibits the synthesis of LDL-C.¹

PHARMACOKINETICS¹

Parameter	Result
Oral Bioavailability	7%
Protein Binding	> 99.8%
Elimination	< 59.5% recovered in the urine and 33.4% in feces
Half-Life	39.7 hours
Metabolism	Extensively liver metabolized primarily by CYP3A4 and to a small extent by CYP1A2, SB6 2C8 AND 2C19.

DOSE & AVAILABILITY¹

STRENGTH	ROUTE	FREQUENCY	RENAL ADJ.	HEPATIC ADJ.	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
5mg 10mg 20mg	PO	Take capsules once daily, whole, with water and without food, at least 2 hours after evening meal	Patients with end stage renal disease or dialysis or with baseline mild hepatic impairment should not exceed 40 mg daily	Contraindicated in patients with moderate to severe hepatic impairment or active liver disease.	Safety and effectiveness not established	NA (not studied in sufficient numbers to determine if adjustments are needed)	Initiate at 5mg daily and titrate dose based on acceptable tolerability to 10mg daily at 2 weeks and then at a minimum of 4 week intervals to a maximum of 60mg daily. Before treatment, measure ALT, AST, alkaline phosphatase, and total bilirubin; Obtain a negative pregnancy test in females of reproductive potential

DRUG SAFETY¹

Serious (REMS, Black Box Warnings, Contraindications):

Black Box Warning for risk of hepatotoxicity. Lomitapide is only available through a restricted REMS program for certified clinicians (1-855-898-27430

It is contraindicated in pregnancy.

It is contraindicated in patients taking strong or moderate CYP3A4 inhibitors.

Warnings and Precautions:

“Gastrointestinal adverse reactions occur in 93% of patients and could affect absorption of concomitant oral medications.”¹

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

Loperamide

Lodoxamide

Loratadine

Appendix 2: Suggested PA Criteria**Lomitapide (Jumrapid®)****Goal(s):**

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

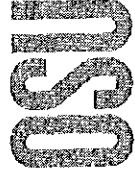
Length of Authorization: 6 months

	Approval Criteria	Record ICD-9 code
1. What is the diagnosis?		
2. Is the client ≥ 18 years of age AND have a diagnosis of homozygous familial hypercholesterolemia?	Yes: Go to #3. No: Pass to RPH; Deny (medical appropriateness)	
a) Genetically confirmed OR b) Untreated LDL-C $>500\text{mg/dl}$ + xanthoma before 10 yrs. OR c) Both parental heterozygous FH		
3. Has the patient failed or are they intolerant to maximum statin and combination therapy?	Yes: Go to #4. No: Pass to RPH; Deny (medical appropriateness)	
4. Has the patient failed or are they not appropriate for LDL-C apheresis?	Yes: Go to #5. No: Pass to RPH; Deny (medical appropriateness)	
5. Is the patient currently on any moderate or strong CYP3A4 inhibitors (e.g. boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibepradil, nefazodone, neflavavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, amrenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil)?	Yes: Pass to RPH; Deny (medical appropriateness) No: Go to #6.	
6. Is the patient male OR female not of child bearing age or confirmed not pregnant?	Yes: Approve x 6 months No: Pass to RPH; Deny (medical appropriateness)	

Limitations of Use:

Lomitapide is approved only for HoFH, a rare but serious disorder associated with premature cardiovascular morbidity and mortality with few effective treatment options. It is proven effective in reducing LDL-C levels, but there is uncertainty about whether this equates to reduced cardiovascular morbidity and mortality. It is not feasible to do an outcomes study due to the low prevalence of the disease. However, the current safety data does not support the use of lomitapide in patients with lower CHD risk.¹

1. FDA. Lomitapide Summary Review - Reference ID 3236195. 2012. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203858Orig1s000SumR.pdf. Accessed April 3, 2013.



© Copyright 2012 Oregon State University. All Rights Reserved

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

College of Pharmacy

Health

Month/Year of Review: May 2013

Generic Name: mipomersen

PDL Class: Non-Statin Lipid Lowering Agents

New Drug Evaluation: mipomersen

End date of literature search: Week 3, March 2013 (MedLine/Scopus); 2/11/2013 (ClinicalTrials.gov)

Brand Name (Manufacturer): Kynamro™ (Genzyme)

Dossier Received: requested March 1, 2013; Received 4/30/2013

Food and Drug Administration (FDA) Approved Indication:

"KYNAMRO™ is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), total cholesterol (TC), and non-high density lipoprotein-cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH)."¹ There is a Black Box Warning and a Risk Evaluation and Mitigation Strategy is required to determine if the potential benefits of mipomersen outweigh the potential risk of liver injury.¹

Potential Off-Label Indications:

- Heterozygous familial hypercholesterolemia (HeFH)
- Drug resistant hypercholesterolemia

Research Questions:

- Is mipomersen more effective than statins, statin combination therapy or other recommended therapies to prevent coronary heart disease (CHD) events in patients with hypercholesterolemia?
- Is mipomersen safer than statins, statin combination therapy or other recommended therapies in patients with hypercholesterolemia?
- Are there sub-populations of patients with hypercholesterolemia where mipomersen is more or less effective or safe?

Conclusions:

- The three randomized placebo-controlled phase III trials were only 28 weeks long and did not evaluate CHD outcomes. LDL-C goal was achieved only in the HeFH study. There is insufficient evidence to determine if mipomersen lowers the incidence of CHD events in patients with HoFH, HeFH or drug resistant hypercholesterolemia.
- The potential for liver injury secondary to chronic fat accumulation is the primary concern. However, 100% of mipomersen patients experienced adverse events (ADEs) including injection-site reactions, flu-like symptoms and proteinuria. Longer-term exposure in more patients is needed to adequately define the risks.
- There are few treatment options for HoFH. Mipomersen is a viable third-line alternative behind LDL-C apheresis.

Recommendations:

- Prior authorize mipomersen to limit use to confirmed HoFH patients that have failed or are unable to tolerate maximum lipid-lowering therapy and LDL-C apheresis.

NDE: mipomersen

Background: Hypercholesterolemia and specifically high levels of low-density lipoprotein cholesterol (LDL-C) are risk factors for CHD.² Currently, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are the first line treatment to reduce LDL-C because they are proven to reduce CHD morbidity and mortality with a relatively low incidence of serious adverse events.² Primary prevention recommendations are a minimum 30-40% LDL-C reduction to achieve CHD benefit and secondary prevention recommendations are a minimum of 50% LDL-C reduction.² Statins are not tolerated (myalgia or myositis) or not effective in all patients (e.g. antiretroviral associated dyslipidemia). Some patients with HoFH and HeFH can be refractory to statin therapy because they are genetically lacking LDL-C receptor activity (absent entirely or significantly reduced). Mipomersen has a new mechanism of action and reduces LDL-C levels by reducing the production of apolipoprotein B-100 (apo B-100).¹ Apo B-100 is a precursor to synthesis of LDL-C.

Familial hypercholesterolemia (FH) has a worldwide prevalence of 0.2% which is mostly comprised of HeFH.³ FH is characterized by a high LDL-C level from birth, a propensity to tendon xanthomata, and early onset CHD.⁴ HeFH is a partial deficiency of the LDL receptor and is associated with total cholesterol levels >300mg/dL and high risk of coronary artery disease by age 30-40 years.³ HoFH is a total LDL receptor deficiency. It is very rare (estimated prevalence of 1 per 3 million people) but myocardial infarction by age 10 and death by age 20 is common. HoFH is associated with total cholesterol levels > 600-1000mg/dL.³ LDL-C apheresis is currently the standard of care for HoFH patients resistant to statin therapy.⁵ However, apheresis needs to be performed on a chronic repetitive basis (i.e. every 1-2 weeks) and is currently performed at only 35 centers in the United States. Liver transplantation is a last resort. HoFH is an orphan indication due to the lack of good therapeutic options.

Clinical Efficacy: ClinicalTrials.gov identified 18 mipomersen randomized controlled trials. Five were Phase I trials, seven were Phase II and seven were Phase III of which four were completed and three were published.^{6,7,8} Raal et al.⁶ studied mipomersen in HoFH patients. Stein et al.⁷ evaluated it in HeFH patients and McGowan et al.⁸ in patients with drug resistant hypercholesterolemia.

Mipomersen was approved based upon a single phase III trial of 51 genetically or clinically confirmed HoFH patients.⁶ Raal et al.⁶ was a fair quality trial that randomized 34 patients to 200mg of subcutaneous mipomersen per week and 17 patients to a matching volume of placebo subcutaneously per week. All patients were allowed to be on maximum tolerated lipid-lowering therapy as long as the doses were stable 12 weeks. LDL-C apheresis was not allowed. Randomization and allocation concealment were well done and described. The groups were only slightly different at baseline with more children and more significant CHD history in the mipomersen group but more metabolic syndrome in the placebo group. There was no loss to follow-up but total attrition was high and uneven in the mipomersen patients experienced ADEs, primarily injection site reactions. This threatened the blinding and increases the risk of performance bias. CHD outcomes were not assessed it is not likely they will be in the future given the low prevalence of HoFH. The primary outcome was percent change in LDL-C from baseline. The mean treatment time was 25 weeks and follow-up was two weeks after the last dose. There was a mean difference of 21% reduction between groups, favoring mipomersen ($p < 0.0003$) which had a 25% reduction in LDL-C. However, the LDL-C at the end of the study remained very high in both groups: mipomersen 324 mg/dL versus placebo 390mg/dL.

Stein et al.⁷ was a fair quality trial that randomized 83 patients to self-administered subcutaneous mipomersen 200mg and 41 patients to an un-described, but self-administered placebo. Both were given weekly for 26 weeks. All patients were genetically or clinically confirmed with HeFH on a stable, maximally tolerated lipid-lowering drug regimen for 12 weeks. LDL-C apheresis was not allowed. There was slightly more patients with cardiovascular history and who smoked in the mipomersen group. Risks for selection, performance and attrition biases were identified. There was inadequate description of randomization, allocation concealment and blinding. Three mipomersen patients withdrew due to ADEs. Again CHD

NDE: mipomersen

outcomes were not assessed and the percent change from baseline to 28 weeks in LDL-C was the primary outcome. The mean difference in LDL-C between groups was a decrease of 33% favoring mipomersen ($p < 0.001$) to final LDL-C levels of: mipomersen 104 mg/dL and placebo 143 mg/dL.

McGowan et al.⁸ was a good quality trial that randomized 39 patients to self-administered mipomersen 200mg subcutaneously per week to and 19 patients to a self-administered similarly appearing placebo for 26 weeks. It included adults with severe hypercholesterolemia on maximum lipid-lowering therapy and excluded from apheresis. There was a good description of randomization, allocation concealment and blinding. The groups differed in that there was more alcohol use and metabolic syndrome in the mipomersen group but more tobacco use in the placebo group. The mipomersen group experienced more loss to follow-up (13%) and total attrition (36%) than the placebo group (5% and 16% respectively). Blinding may have been broken due to all mipomersen patients experiencing an ADE, most of which were injection site reactions. CHD outcomes were not assessed. The mean difference in the primary outcome, percent change in LDL-C at 28 weeks, was 48% favoring mipomersen (0.001). The final LDL-C for both groups remained high: mipomersen 174mg/dL versus placebo 263mg/dL.

Another trial⁹ was identified in the dossier but was not available for review except in abstract form.¹⁰

Clinical Safety:

According to the FDA Summary Review¹¹ the primary safety concern with mipomersen is the potential liver injury secondary to chronic fat accumulation. Other safety issues include injection-site reactions, flu-like symptoms and proteinuria. The FDA safety assessment was derived from four phase III trials involving 390 patients that were randomized to mipomersen 2: placebo 1 for 6 months.⁹ Table 1 summarizes the FDA Summary Review data.⁹

Table 1. Summary of FDA Summary Review Safety Data

Endpoint	Placebo Percent of Patients	Mipomersen Percent of Patients
Percent fat content change from baseline $\geq 5\%$	8.3%	61.8%
ALT $> 3\times$ Upper Limits of Normal (ULN)	1.0%	16.0%
AST $\geq 3\times$ ULN	0.0%	4.2%
Injection-site reactions	33.0%	84.0%
Flu-like symptoms	16.0%	30.0%
Antibody Response at Week 50	0.0%	33.0%
Proteinuria	0.8%	2.3%
Cardiovascular Events reported as ADE	6.0%	9.0%
Neoplasms	0.5%	1.2%
Withdrawals due to ADE	2.3%	18.0%

NDE: mipomersen

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

- 1) CHD events
- 2) Withdrawals due to ADEs
- 3) Serious ADEs

Primary Study Endpoints:

- 1) Percent change in LDL-C from baseline to 28 weeks
- 2) Withdrawals due to ADEs
- 3) Serious ADEs

Ref./Study Design	Drug Regimens / Duration	Patient Population	N	Outcomes/ Efficacy Results [CI, p-values]	ARR Safety Results (CI, p-values)	ARR/ NNH	Quality Rating/ Internal Validity Bias/ External Validity Concerns	
							Primary Outcome: % Δ in LDL-C @ baseline to 2 weeks after last dose.	Total withdrawals due to AE: M: 5 (14.7%) P: 0 (0.0%) RR: NA 95% CI NA p-value NA
Raal et al. ⁶	M: Mipomersen 200mg/week SQ; mean treatment period 159 days. P: Matching SQ placebo 1 week mean treatment period 176 days. flu 28 weeks	Patients with HoFH already on lipid-lowering treatment. <u>Demographics:</u> Mean age: 31.3 years SD 12.4; 7 patients <18 Female: M: 56%, P:59%	IT: M:34 P:17	Total attrition: M: 6 (17.6%) P: 0 (0.0%) Loss to flu: M: 5 (14.7%) P: 0 (0.0%) <u>Group comparison at baseline:</u> Group differences include: more children and significant CV history in control; more metabolic syndrome in mipomersen.	M: 24.7% (-31.6%, 17.7%) to 324mg/dL P: 3.3% (-12.1%, 5.5%) to 390mg/dL MD: -21.3% 95% CI (-32.9%, -3.8%) P <0.0003	SAE: M: 2 (7.1%) [ACS, ankle fx] NA / P: 1 (5.9%) [nephrolithiasis] RR: 1.21 95% CI (0.12, 12.40) p-value NA	1.3% / 79	Internal Validity: ROB Selection: LOW - Adequate description of randomization and allocation concealment. Stratified by weight (<50kg, ≥50kg). Though baseline group comparison of prognostic factors has small differences. No effect. Performance: MOD- Good description of blinding of patients, caregivers, investigators and outcomes assessors, but all mipomersen patients experienced ADE. Possible bias away from null. Detection: LOW - Good description of blinding of patients, caregivers, investigators and outcomes assessors, but all mipomersen patients experienced ADE. Objective outcome likely not affected. Attrition: HIGH - small sample size, >10% difference between groups in total attrition and loss to follow-up. Possible bias towards the null. External Validity: Recruitment: Un-described Patient Characteristics: Study results apply to HoFH patients only

NDE: mipomersen

		Quality Rating: FAIR	
Stein et al. ⁷	<p>Patients with HeFH and CAD on maximally tolerated lipid-lowering therapies.</p> <p>Demographics: Mean Age: M-56.2, P-55.9 Female: M-39.8%, P-31.7% White: M-97.6%, P-92.7%</p> <p>Baseline: More in CV history and smoking in mipomersen group generally</p> <p>Interventions: M: mipomersen 200mg / week self-administered SQ x 26 weeks P: placebo undisclosed self-administered SQ x 26 weeks</p> <p>Outcomes: Primary outcome: % Δ LDL-C from baseline to 2 weeks after the last dose M: -28.0% (-34, -22.1) P: 5.2% (-0.5, 10.9) Loss to follow-up: M: 3 (4%) P: 0 (0%) Only 1 loss to f/u was excluded from analysis.</p> <p>Inclusion: ≥ 18 years old HeFH (genetic confirmation) OR HeFH defined as untreated LDL-C >2.9mmol/L [180mg/dL] + Simon Broome Register criteria for HeFH + documented stable CAD LDL-C ≥ 100mg/dL ; TG <2.26 200mg/dL Stable max tolerated dose of lipid-lowering therapy x 12 wks.</p> <p>Exclusion: LDL apheresis within 8 wks. Unstable angina CHF – Class II or IV DM Condition causing 2° hyperlipidemia ALT >1.5x upper limit of normal (ULN) CK ≥ 3x ULN Significant renal or hepatic disease</p>	<p>Primary outcome: % Δ LDL-C from baseline to 2 weeks after the last dose M: -28.0% (-34, -22.1) P: 5.2% (-0.5, 10.9) Loss to follow-up: M: 3 (4%) P: 0 (0%) Only 1 loss to f/u was excluded from analysis.</p> <p>Inclusion: ≥ 18 years old HeFH (genetic confirmation) OR HeFH defined as untreated LDL-C >2.9mmol/L [180mg/dL] + Simon Broome Register criteria for HeFH + documented stable CAD LDL-C ≥ 100mg/dL ; TG <2.26 200mg/dL Stable max tolerated dose of lipid-lowering therapy x 12 wks.</p> <p>Exclusion: LDL apheresis within 8 wks. Unstable angina CHF – Class II or IV DM Condition causing 2° hyperlipidemia ALT >1.5x upper limit of normal (ULN) CK ≥ 3x ULN Significant renal or hepatic disease</p>	<p>Total withdrawals due to AE: M: 9 (10.8%) P: 0 (0%) RR: NA 95% CI: NA p-value: NA</p> <p>SAE: M: 6 (7.2%) [baseline CA, angina, AML, PE, non-cardiac chest pain]</p> <p>Detrition: LOW - No description of placebo only the assurance that "Patients and study personnel were blinded to treatment assignment and to lipid data." In addition, the hepatic fat assessor was said to be blinded to allocation. Objective outcomes at lower risk from lack of blinding.</p> <p>Attrition: HIGH – small sample size, >10% difference between groups in total attrition. Possible bias towards the null.</p> <p>External Validity: <u>Recruitment:</u> Un-described <u>Patient Characteristics:</u> Study results apply to HeFH patients only <u>Setting:</u> Lipid clinics <u>Outcomes:</u> LDL-C surrogate, short duration but mipomersen group did get close to LDL-C goal in primary. <u>Low Power:</u> 90% power to detect 20% difference.</p>
RCT PC DB MC	<p>ITT: M: 83 P: 41</p> <p>Total Attrition: M: 10 (12%) P: 0 (0%)</p> <p>Loss to follow-up: M: 3 (4%) P: 0 (0%) Only 1 loss to f/u was excluded from analysis.</p>	<p>Primary outcome: % Δ LDL-C from baseline to 2 weeks after the last dose M: -28.0% (-34, -22.1) P: 5.2% (-0.5, 10.9) Loss to follow-up: M: 3 (4%) P: 0 (0%) Only 1 loss to f/u was excluded from analysis.</p> <p>Inclusion: ≥ 18 years old HeFH (genetic confirmation) OR HeFH defined as untreated LDL-C >2.9mmol/L [180mg/dL] + Simon Broome Register criteria for HeFH + documented stable CAD LDL-C ≥ 100mg/dL ; TG <2.26 200mg/dL Stable max tolerated dose of lipid-lowering therapy x 12 wks.</p> <p>Exclusion: LDL apheresis within 8 wks. Unstable angina CHF – Class II or IV DM Condition causing 2° hyperlipidemia ALT >1.5x upper limit of normal (ULN) CK ≥ 3x ULN Significant renal or hepatic disease</p>	<p>Total withdrawals due to AE: M: 9 (10.8%) P: 0 (0%) RR: NA 95% CI: NA p-value: NA</p> <p>SAE: M: 6 (7.2%) [baseline CA, angina, AML, PE, non-cardiac chest pain]</p> <p>Detrition: LOW - No description of placebo only the assurance that "Patients and study personnel were blinded to treatment assignment and to lipid data." In addition, the hepatic fat assessor was said to be blinded to allocation. Objective outcomes at lower risk from lack of blinding.</p> <p>Attrition: HIGH – small sample size, >10% difference between groups in total attrition. Possible bias towards the null.</p> <p>External Validity: <u>Recruitment:</u> Un-described <u>Patient Characteristics:</u> Study results apply to HeFH patients only <u>Setting:</u> Lipid clinics <u>Outcomes:</u> LDL-C surrogate, short duration but mipomersen group did get close to LDL-C goal in primary. <u>Low Power:</u> 90% power to detect 20% difference.</p>

NDE: mipomersen

McGowan et al. ⁸	Nt. Mipomersen 200mg / week P: Placebo = 9mg NaCl + 0.0004mg riboflavin / week	Primary Outcome:		Quality Rating: GOOD	
		ITT: M: 39 P: 19	% Δ in LDL-C @ baseline to 2 weeks after last dose. M: -35.9% 95% CI (-51.3, -15.3) to 174mg/dL	Withdrawals due to ADE: M: 8 (20.5%) C: 1 (5.3%) RR 3.90 95% CI (0.52, 28.95) p-value NA SAE: M: 5 (20.0%) [Irr-toxicity, CVA] P: 1 (6.3%) [MI] RR 3.20 95% CI (0.41, 24.94) p-value NA	Internal Validity: RoB Selection: LOW – Good description of adequate randomization & allocation concealment though baseline group comparison of prognostic factors is uneven. No effect.
		Baseline comparison: Both are 1 ml self-administered SQ injections, similar in appearance and administration. flu 28 weeks.	Loss to FU: M: 5 ([26.8%]) P: 1 (5.3%) MD: 48.4% 95% CI NA p-value < 0.001	Exclusion: There were significant differences between groups in protocol deviations: M: 16 (41%) P: 2 (11%) Inclusion: ≥ 18 years old LDL-C ≥ 26.1 mg/dL + CHD, OR LDL-C ≥ 30.1 mg/dL with no CHD Stable low-fat diet with stable weight Maximum tolerated lipid lowering therapy Met LDL-apheresis criteria but was prohibited	External Validity: Recruitment: Un-described Attrition: HIGH – small sample size, >10% difference between groups in total attrition. Possible bias towards the null.

AMI = acute myocardial infarction;
 CA = cancer;
 CAD = coronary artery disease;
 CHD = cardiac heart disease;
 CHF = congestive heart failure;
 CVA = cardiovascular accident;
 DB = Double-Blind;
 DM = diabetes mellitus;

flu = Follow-up;
 fx = fracture;
 Hx = history of;
 HTN = hypertension;
 LDL-C = low-density lipoprotein cholesterol;
 M=mipomersen group;
 MC = Multi-Center;
 NA = not available or applicable;

P=placebo group;
 PC = Placebo Controlled;
 PE = pulmonary embolism;
 RCT = Randomized Controlled Trial;
 SCr = serum creatinine
 SQ = subcutaneous;
 SVT = supraventricular tachycardia;

References:

1. Genzyme Corporation. KYNAMRO Label - Reference ID: 3252315. 2013 Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203568s000lbl.pdf. Accessed April 1, 2013.
2. NIH NHLBI. ATP 3 Cholesterol Guidelines, NHLBI. 2004. Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>. Accessed March 18, 2013.
3. DynaMed. DynaMed: Familial hypercholesterolemia. 2013. Available at: <http://web.ebscohost.com.liboff.ohsu.edu/dynamed/detail?vid=3&sid=b25a0568-afdd-45e4-ab58-90387124a828%40sessionmgr111&hid=124&bdata=JnNpdGU9ZHZlJnNjb3B1PXNpdGU%3d#db=dme&AN=115368>. Accessed April 1, 2013.
4. Robert S Rosenson, Sarah D de Ferranti, Paul Durrington. Primary disorders of LDL-cholesterol metabolism. 2012. Available at: <http://www-upToDate-com.liboff.ohsu.edu/contents/primary-disorders-of-ldl-cholesterol-metabolism?source=preview&anchor=H1&selectedTitle=1~67#H1>. Accessed April 1, 2013.
5. Ito MK, McGowan MP, Moriarty PM. Management of Familial Hypercholesterolemias in adult patients: Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *Journal of Clinical Lipidology*. 2011;5(3):S38–S45. doi:10.1016/j.jacl.2011.04.001.
6. Raaij FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolemia: a randomised, double-blind, placebo-controlled trial. *The Lancet*. 2010;375(9719):998–1006. Accessed April 1, 2013.
7. Stein EA, Dufour R, Gagne C, et al. Apolipoprotein B Synthesis Inhibition With Mipomersen in Heterozygous Familial Hypercholesterolemia: Clinical Perspective Results of a Randomized, Double-Blind, Placebo-Controlled Trial to Assess Efficacy and Safety as Add-On Therapy in Patients With Coronary Artery Disease. *Circulation*. 2012;126(19):2283–2292. doi:10.1161/CIRCULATIONAHA.112.104125.
8. McGowan MP, Tardif J-C, Ceska R, et al. Randomized, Placebo-Controlled Trial of Mipomersen in Patients with Severe Hypercholesterolemia Receiving Maximally Tolerated Lipid-Lowering Therapy. *PLoS ONE*. 2012;7(11):e49006. doi:10.1371/journal.pone.0049006.
9. Cromwell W, Thomas G, Boltje I, Chin W, Davidson M. Safety and Efficacy of Mipomersen Administered as Add-on Therapy in Patients with Hypercholesterolemia and High Cardiovascular Risk. *J Clin Lipidol*. 2012;6(3):291–292.

NDE: mipomersen

10. Cromwell WC, Thomas GS, Boltje I, Chin W, Davidson M. SAFETY AND EFFICACY OF MIPOMERSEN ADMINISTERED AS ADD-ON THERAPY IN PATIENTS WITH HYPERCHOLESTEROLEMIA AND HIGH CARDIOVASCULAR RISK. *J Am Coll Cardiol.* 2011;57(14s1):E504-E504. doi:10.1016/S0735-1097(11)60504-4.

11. FDA Summary Review. Reference ID 3252189. 2013. Available at:
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203568Orig1s000SumR.pdf. Accessed April 1, 2013.

NDE: mipomersen

Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

Mipomersen is an antisense oligonucleotide that reduces the genetic production of apo-B 100 which is the principle apolipoprotein of LDL. Thus, LDL is not produced.¹

PHARMACOKINETICS¹

Parameter	Result
SQ Bioavailability	54 – 78%
Protein Binding	≥ 90%
Elimination	< 4% recovered in the urine
Half-Life	1 – 2 months
Metabolism	Metabolized in tissues by endonucleases

INTERACTIONS¹

Drug interactions are not anticipated via the cytochrome P450 enzymes or via the P-glycoprotein transporter mechanism.

DOSE & AVAILABILITY¹

STRENGTH	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	PEDIATRIC DOSE	ELDERLY DOSE	OTHER DOSING CONSIDERATIONS
200 mg / 1 mL	SQ	Weekly	NA	Withhold dose x 1 week if ALT or AST is ≥ 3 ULN. Resume when ≤ 3 ULN and monitor weekly.	NA (only 7 patient < 18 were included in the trials)	NA (only 22.6% of patients in trial were ≥ 65 years old)	May cause fetal harm; Pregnancy category B

NDE: mipomersen

DRUG SAFETY¹

Serious (REMS, Black Box Warnings, Contraindications):

Black Box Warning for risk of hepatotoxicity. Mipomersen is only available through a restricted REMS program. Only certified providers may prescribe and pharmacies may distribute it. Further information is available at www.KynamtoREMS.com or by telephone at 1-877-KYNAMRO (1-877-596-2676).¹

Warnings and Precautions:

"Injection site reactions occur in 84% of patients and typically consist of one or more of the following: erythema, pain, tenderness, pruritus and local swelling. Flu-like symptoms, which typically occur within 2 days after an injection, occur in 30% of patients and include one or more of the following: influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise or fatigue."¹

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

Misoprostil
Miconazole
Kalydeco

Appendix 2: Suggested PA Criteria**Mipomersen (Kytril®)****Goal(s):**

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

Length of Authorization: 6 months

		Approval Criteria	
			Record ICD-9 code
1.	What is the diagnosis?		
2.	Is the client ≥12 years of age AND have a diagnosis of homozygous familial hypercholesterolemia?	Yes: Go to #3. a) Genetically confirmed OR b) Untreated LDL-C >500mg/dl + xanthoma before 10 yrs. OR c) Both parental heterozygous FH	No: Pass to RPH; Deny (medical appropriateness)
3.	Has the patient failed or are they intolerant to maximum statin and combination therapy?	Yes: Go to #4.	No: Pass to RPH; Deny (medical appropriateness)
4.	Has the patient failed or are they not appropriate for LDL-C apheresis?	Yes: Approve for 6 months. a) Genetic confirmation of homozygous FH b) Xanthomas before age 10 yrs. c) Untreated LDL-C >500 mg/dl d) Failed statin therapy e) Intolerant to statin therapy f) Cannot tolerate statin therapy due to side effects g) Statin contraindication h) Statin non-compliance i) Statin contraindication j) Statin non-compliance	No: Pass to RPH; Deny (medical appropriateness)

Limitations of Use:

Mipomersen is approved only for HoFH, a rare but serious disorder associated with premature cardiovascular morbidity and mortality with few effective treatment options. It is proven effective in reducing LDL-C levels, but there is uncertainty about whether this equates to reduced cardiovascular morbidity and mortality. It is not feasible to do an outcomes study due to the low prevalence of the disease. However, the current safety data does not support the use of mipomersen in patients with lower CHD risk.¹

1. FDA Summary Review. Reference ID 3252189. 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203568Orig1s000SumR.pdf. Accessed April 1, 2013.



Oregon State Drug Use Research & Management Program

UNIVERSITY Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079

College of Pharmacy Phone 503-945-5220 | Fax 503-947-1119

Month/Year of Review: July 2013

Generic Name: Dalfampridine

Brand Name: (Manufacturer): Ampyra™

Class: Potassium Channel Blocker for MS symptoms

FDA Approved Indications:¹

Dalfampridine extended release tablets are indicated for the improvement of walking in patients with multiple sclerosis (MS), as demonstrated by increased walking speed.

Conclusions:

1. Does FAM produce changes in disability or impairment scales assessing motor function?

The differences between FAM-treated and placebo-treated patients for change in walking speed and MSWS-12 were small and achieved inconsistent statistical significance. In the phase 2 trial, there was no statistically significant difference between FAM-treated and placebo-treated patients for mean percent change in walking speed as assessed by the T25FW. Therefore, post-hoc data analysis was performed to identify a new endpoint—response to treatment—that would achieve statistical significance in the phase 3 trials. Statistical significance was indeed achieved for the primary endpoint in the two phase 3 clinical trials. However, FDA analysis shows the absolute difference in walking speed between responders and non-responder is about 2 seconds over 25 feet. No published information is available for distances beyond 25 feet. A post approval subgroup analysis assessed the effect in distances longer than 25 feet which showed a significant improvement; however this analysis has not been published. Other limitations of the studies include lack of long-term data and lack of clarity on how one would determine in practice who could potentially respond to FAM. Three unpublished extension studies have been completed that address the long-term efficacy and safety of FAM; however, no studies have been published addressing quality of life or activities of daily living. MS has no cure; therefore, the mainstays of treatment are disease-modifying agents that slow the progression of the disease and symptomatic and supportive therapies. FAM is a potassium channel inhibitor that may act by increasing action potential conduction in demyelinated axons, thereby improving walking speed

2. Does FAM change disease progression, hospitalization rates, improve the performance of activities of daily living, or reduce resources used for home care?

FAM is not a disease-modifying agent and, therefore, does not reduce relapse rates or slow disease progression. No studies have been performed addressing whether the use of FAM decreases hospitalization rates, reduces resources used for home care, or improves the performance of activities of daily living.

3. Does FAM improve quality of life?

Quality of life was not measured in the phase 3 studies. The phase 2 study reported the MSQLI was used as a secondary efficacy measure but did not report the results, thus there is no evidence FAM improves quality of life.

4. How does FAM compare with non-pharmacologic therapies, such as exercise therapy?

No head-to-head comparisons have been performed between FAM and exercise therapy or any other therapy. While exercise is recommended for those with MS, there is little consistent data concerning its efficacy in improving walking in MS.²

5. Is FAM safe?

The most concerning adverse event for FAM-treated patients is the risk of seizures. Doses exceeding 10 mg twice daily have been associated with increased seizure risk. Also, seizure risk has not been truly evaluated in studies of FAM, because patients with a history of seizure and evidence of epileptiform activity on EEG have been excluded and safety evaluations have been performed in just 807 MS patients taking FAM SR. A postmarketing analysis demonstrated that during the first year, a total of 85 cases of seizure were reported (5.4 cases per 1000 patient-years).³

Ampyra does have a Risk Evaluation and Mitigation Strategy (REMS), including a medication guide and annual letters to prescribers and pharmacists with warnings about the potential risk of seizure. Extension trials that may shed more light on safety have yet to be published.

Other noteworthy adverse events are the rate of UTIs (NNH 25) and the rates of dizziness (NNH 33), asthenia (NNH 33), weakness (NNH 33), and balance disorder (NNH 25) in patients who are having difficulty with mobility. Nevertheless, the overall discontinuation rate due to adverse events for FAM-treated patients was just 4% compared with 2% for placebo-treated patients.

No evidence of mutagenicity, carcinogenicity, or impaired fertility has been observed in animals given doses well above the MRHD. However, decreased offspring viability and growth has been observed in animals given doses similar to the MRHD. Therefore, managing the risks and benefits of using FAM in pregnancy is real, especially given that MS is a chronic disease that disproportionately affects women.

6. Is the benefit of FAM commensurate with the cost?

Because FAM is the only approved drug for the indication improvement in walking in MS patients, one cannot compare its cost to other drugs. One could ask whether the improvement in walking leads to direct or indirect healthcare cost savings, but no pharmacoeconomic studies have been performed for FAM.

Recommendations:

- Consider adding to the recommendation that physician reassessment after a 12-week trial includes demonstration of a ≥20% improvement in walking speed as assessed by the T25FW.
- Recommend revising PA criteria to allow for use in patients with moderate ambulatory dysfunction who do not require a walking aid.
- Recommend to consider dalafampridine for the high cost marginal benefit policy.

BACKGROUND/CURRENT LANDSCAPE

FAM is the first drug approved for the improvement of walking in MS patients, and the measure of efficacy used in the two pivotal FAM phase 3 trials on which FAM's approval has been based is a novel one. Because MS has no cure, disease modifying agents and symptomatic therapies are the mainstay for managing the disease.

MS is a chronic, progressive, immune-mediated disorder characterized by inflammation of the white and gray matter of the central nervous system and destruction of axonal myelin sheaths, resulting in neurodegeneration and gliotic sclerosis. MS affects about 350,000 people in the US and more than 1 million worldwide. MS occurs 2 to 2.5 times more frequently in women than in men.^{4,5}

Symptoms of MS typically present between the ages of 18 and 45 and include combinations of the following: fatigue; heat sensitivity; weakness; depression; bladder, bowel, or sexual dysfunction; or impaired vision, sensation, coordination or balance.^{3,4} Nearly 50 percent of those with MS will require the use of a walking aid within 15 to 25 years of diagnosis.⁶

The three major subtypes of MS are relapsing remitting, secondary progressive, and primary progressive. About 85 to 90 percent of patients present with relapsing remitting MS, which is marked by episodes of worsening or new neurological symptoms followed by periods of inactivity. Most patients with relapsing remitting MS develop secondary progressive MS within twenty to forty years, which is characterized by steady neurological decline with few or no clinically recognized relapses. About 10 to 15 percent of patients present with primary progressive MS, which is characterized by steady neurologic decline from onset for at least a year without distinct relapses.^{3,4,5}

The course of MS is highly unpredictable and varies from person to person. About 10 percent of patients have a relatively benign course and do well for more than 20 years, while about 70 percent develop secondary progression. Life expectancy may be slightly shorter for those with MS. In rare cases, patients with fulminant MS die within months of disease onset.⁷

The total mean annual cost of MS in 2004, which is after the introduction of disease modifying agents, has been estimated to be about \$47,000 per patient.⁸ Both direct and indirect costs rise continuously with each stepwise increase in disability as measured by the Expanded Disability Status Scale (EDSS).⁹

MS is managed by disease-modifying agents and symptomatic and supportive therapies. First-line disease-modifying agents for slowing the progression of MS and reducing the associated disability include interferon (IFN)- β 1a (Betaseron), IFN- β 1a (Avonex), glatiramer acetate (Copaxone), natalizumab (Tysabri), and mitoxantrone (Novantrone).^{4,5} Many agents are used to treat the symptoms of MS, such as baclofen or tizanidine for spasticity and gabapentin or amitriptyline for neuropathy. Non-pharmacologic therapies for MS symptoms include physical therapy for spasticity, gait dysfunction, and imbalance as well as exercise for osteoporosis and walking mobility.^{5,7} Now FAM has been approved for the improvement of walking.

In clinical trials of disease modifying agents, the most often used primary efficacy endpoint has been relapse rate, while disease progression as measured by change in Expanded Disability Status Scale (EDSS) score has been more often used as a secondary efficacy endpoint. The EDSS is based on the results of a neurological examination and the patient's ability to walk and is scored from 0, no neurological abnormality, to 10, death from multiple sclerosis.¹⁰⁻¹² An EDSS of 4.0 and 6.0 typically would correspond to limited walking ability and to the need for unilateral support for walking.¹³

In most clinical trials of disease modifying agents, progression has been defined as a sustained 3- or 6-month increase in EDSS of at least one point recorded in a period when the patient had no exacerbation. From the pooled data of three trials, the calculated relative risk of progression at 2 years for MS patients taking beta-interferon versus placebo was 0.70 (0.55–0.88, p=0.002).¹⁰

The measure of efficacy used in the two pivotal FAM phase 3 trials is a novel one that appears to have been created for the purpose of achieving clinical significance. The primary efficacy measure, called response to treatment, is defined as a consistent improvement in walking speed as measured by the Timed 25-Foot Walk (T25FW). The T25FW is a timed test of walking that measures patients' ability to safely and quickly walk 25 feet in his or her usual manner.¹⁴ Four feet per second is normal walking speed.¹⁵ A 20% change from baseline has been previously suggested to be a minimally important difference.¹⁶

The T25FW is a component of the MS Functional Composite (MSFC), which was developed in the mid-1990s by the Clinical Outcomes Assessment Task Force of the National MS Society to overcome the limitations of the EDSS.^{11,15,17} The MSFC, which was a secondary efficacy measure in a pivotal phase 2 FAM trial, is a composite measure of impairment and disability and, in addition to the T25FW, measures two other clinical dimensions: (1) the 9-Hole Peg Test (9HPT), which tests arm function and (2) the Paced Auditory Serial-Addition Task (PASAT), a cognitive function test.¹⁷

In FAM phase 3 trials, the 12-item MS walking scale (MSWS-12) was used to validate the clinical significance of the primary efficacy endpoint.^{4,3} The MSWS-12 assesses MS patients' perspectives on their ambulatory disability. Patients rate the degree of limitation they've experienced in walking due to MS in the previous 2 weeks for each of 12 walking-related items. The ratings are summed and turned into a scale of 0 to 100, with higher scores indicating greater limitation on walking abilities.¹⁹

Efficacy:

Sustained-release FAM was approved by the FDA for improvement of walking in patient with MS based on two pivotal phase 3 clinical trials: MS-F203 and MS-F204.^{13,21} Both have been published. The phase 2 trial, MS-F202, also provides evidence concerning the efficacy of FAM and the origins of the primary endpoint used in the phase 3 trials. (See Clinical Efficacy Evidence Table)

Low level evidence from two phase 3 studies and one phase 2 study show dalfampridine (FAM) statistically increases walking speed in a subset of patients with MS called timed-walk responders (TWRs). However, FDA analysis of the absolute difference in walking speed over 25 feet between responders and non-responders is small.

The phase 2 study MS-F202 was negative and compared three doses of sustained-release FAM with placebo in MS patients. The primary endpoint was mean percent change in walking speed during treatment using the Timed 25-Foot Walk (T25FW), which measures patients' ability to safely and quickly walk 25 feet and has been validated in MS.

Though statistical significance for the endpoint was not achieved, researchers performed a post-hoc analysis that found a greater percentage of FAM-treated patients had a “consistent” improvement in walking speed. This newly created, as-yet-to-be-validated endpoint was called “response to treatment,” and responders were defined as those whose walking speed for at least three visits during the double-blind treatment period of the trial was faster than the maximum speed in five non-treatment visits, four before and one after treatment.¹³ The response rate for patients treated with FAM 10, 15, and 20 mg was 35.3%, 36.0%, and 38.6% and for placebo 8.5% (p value not given), giving an NNT of 3.55 (95% CI 2.16–4.94). Therefore, response to treatment was used as the primary endpoint for the phase 3 trials.

Published phase 3 study MS-F203 randomized 301 patients 3:1 to receive FAM 10 mg bid or placebo, respectively, during a 14-week, double-blind treatment period. Enrolled in the study were patients 18–70 years old with clinically defined MS who were able to complete two trials of the T25FW in an average time of 8–45 s at screening. The study population had an average EDSS of 5.8.¹³ The range for the placebo population was 1.5–7.0 in one study; however, the mean ± SD was 5.6 ± 1.2 for the placebo group and the mean ± SD and range for the treatment groups, overall, were 5.8 ± 2.0 (2.5–6.5).¹⁴ Similarly, in the second study, they were 5.8 ± 1.1 (2.5–6.5) for placebo and 5.0 ± 1.0 (2.5–7.0) for the treatment groups combined. Patients with EDSS scores between 4.5 and 6.5 have moderate ambulatory dysfunction. The cutoff 4.5 distinguishes patients with moderate dysfunction from patients with mild dysfunction. EDSS ≤ 6.5 are patients who have preservation of some ambulatory function.²¹

Patients who were unable to complete the T25FW within 45 s were excluded from the trial, implying that FAM lacks benefit in more severely disabled patients. This was corroborated by the FDA report in which reviewers said “the sponsor, in 2005 alluded to the lack of reliability of the data in more disabled subjects when walking speed exceeded 45 seconds.”¹⁴

Study MS-F203 found that, for a group of MS patients able to complete the T25FW within 45 s, the percentage of time walked responders (TWR) in the FAM group was 35% compared with 8% in the placebo group (p<0.001, OR 4.75; 95% CI 2.08–10.86), giving an NNT of 4.¹³

The phase 3 study MS-F204 was similar to that of MS-F203, except the double-blind treatment period was 9 weeks long. The investigators did not reveal why the lengths of the treatment phases of the two studies were different. The study found that the percentage of responders in the FAM group was 43% compared with 9% in the placebo (p<0.001), giving an NNT of 3.¹⁹

Though the phase 3 studies showed statistical significance for their primary endpoint, questions about the clinical significance of the endpoint remained, given that the endpoint has not yet been shown to be a valid one for assessing FAM or any other MS drug. The studies addressed this by asking patients to complete the MSWS-12 (a validated patient-based measure of the impact of MS on walking) and calculating the average change from baseline in the score. Researchers found a statistically significant decrease in MSWS-12 score for responders compared to non-responders, independent of treatment group: −6.84 (−9.65 to −4.02) versus 0.05 (−1.48 to 1.57), respectively, (p=0.002) for study MS-F203 and −6.04 (−9.75 to −2.52) versus 0.85 (−0.72 to 2.43).^{13,19}

The positive findings for the change in MSWS-12 are questionable. The MSWS-12 may be an inappropriate instrument to use to validate the results of the T25FW. Also, the analysis using the MSWS-12 should have been performed on the intent-to-treat population rather than responders versus non-responders. Therefore, the achieved change in MSWS-12 may not truly represent clinical significance.¹⁴

Investigators also performed an assessment of average change from baseline in walking speed for the responders versus placebo group. The changes in walking speed for FAM responders compared with total placebo group in study MS-F203 were 0.51 feet/s (0.41 to 0.61) and 0.1 feet/s (0.03 to 0.17), respectively.¹³ FDA analysis of MS-F203 showed that this translated to a 1.75 s difference in walking speed between total non-responders and responders, a 1.99 s difference between placebo-treated responders and non-responders, and a 1.6 s difference between FAM-treated responders and non-responders.¹⁴ The changes in walking speed for FAM responders versus total placebo group in study MS-F204 were 0.51 ft/s (0.43 to 0.59) versus 0.17 ft/s (0.10 to 0.23) for placebo group.¹⁹ FDA analysis of MS-F204 showed that this translated to a 1.71 s difference in walking speed over 25 feet between total non-responders and responders, a 1.54 s difference between placebo-treated responders and non-responders, and a 2.15 s difference between FAM-treated responders and non-responders.¹⁴

Before FAM should be considered an option for improving the lives of MS patients, longer-term studies should be performed with more clinically relevant outcomes that include the impact FAM would have on the quality of life of MS patients or their activities of daily living, health, or healthcare requirements. The phase 2 study included the Multiple Sclerosis Quality of Life Inventory (MSQLI) as a secondary efficacy measure but the scores were not reported.¹⁸ Extension studies (MS-F202 EXT, MS-F203 EXT, MS-F204 EXT), which have been completed but not yet published, may shed light on the long-term efficacy of FAM, but primarily in terms of walking speed.

Finally, assuming FAM allows patients to achieve clinically meaningful changes in mobility, it is unclear how one would use FAM in practice given that only a subset of patients are responders and no method is available to identify which patients would potentially respond. Patients should discontinue treatment after a 4 to 6 week trial of the drug if they are not responding.

FAM may have negligible benefit relative to its annual cost and its associated safety risks. Should criteria be developed to restrict FAM's use, the following should be included: FAM should be limited to those who (1) have moderate ambulatory dysfunction who do not require a walking aid or those that require the use of a walking aid, (2) be able to complete the T25FW in 8–45 s, and (3) do not have moderate or severe renal impairment or a history of seizure disorder or epileptiform activity on EEG. Physician reassessment by T25FW should be required after a 12-week trial and could include demonstration of a >20% improvement in walking speed as assessed by the T25W based on the suggested minimally clinically important difference.

Safety: In clinical trials, the most common serious adverse events occurring in FAM-treated patients were urinary tract infections (NNH 25) and multiple sclerosis relapse (NNH 100). However, seizure risk has been the focus of concern because of past experience with immediate release fampiridine and higher doses of sustained-release FAM. Patients with a history of seizure and evidence of epileptiform activity on EEG were excluded from the trials, so it has been impossible to quantify the actual risk to patients taking FAM 10 mg BID. Accordingly, patients with history of seizure disorder have been contraindicated from taking FAM, and patients should be cautioned to not exceed the maximum recommended semidaily dose. However, prescribing information has not recommended EEG and data are insufficient regarding predictive value of EEG for the occurrence of a first seizure in either a daily fampiridine population or a general population.

COMPARATIVE CLINICAL EFFICACY^{13, 18, 19}

Relevant Endpoints:

- 1) Disability
- 2) Quality of Life
- 3) Clinical Exacerbation/relapse
- 4) Withdrawals due to adverse effects
- 5) Seizure

Study Endpoints:

- 1) Response to treatment: A timed walk responder is defined as a patient with a faster walking speed, as measured by the T25FW, for at least 3 of 4 visits during the DB treatment period than the maximum speed for any of the first 5 off-drug visits. Clinical significance of the timed-walk response was validated using the MSWS-12
- 2) Average change from baseline in MSWS-12 score during treatment period.
- 3) Mean change in walking speed from baseline during the treatment period.

Evidence Table

Ref/Study Design	Drug Regimens	Patient Population ^{1,2}	Duration	Efficacy Results ³ (CI/p-values)	ARR/NRI ⁴ (CI/p-values)	Safety Results (CI/p-values)	ARR/NRI ² (CI/p-values)	Quality Rating/Comments ⁵	
NIS-FE03 Goodman 33 center Phase III 6/05-6/06 MC, DB, PC, RCT	1. FAM 10 mg BID 2. PLA	Inclusion criteria: • Aged 18-70 • clinically defined multiple sclerosis • able to complete two trials of the T25FV in an average time of 8-45 s at screening Exclusion criteria: • onset of multiple sclerosis exacerbation within 60 days of screening • history of seizures or evidence of epileptiform activity on a screening electroencephalogram • any condition that would interfere with the conduct or interpretation of the study • additional restrictions on changes in concomitant medications to avoid related changes in MS symptoms during the trial	224 14 weeks	Treatment period: 1. FAM: 35% [p<0.0001]; OR 4.75; CI: 2.08 to 10.86 2. PLA: 8%	Timed walk responders (TWR): 1. FAM: 4.8% (n=1) OR 4.75; CI: 2.08 to 10.86 2. PLA: 0%	27 / 4 Other analyses: Average change from baseline in MSWS-12 score during treatment period, independent of treatment group: Timed walk responders: -6.84 [-9.65 to -4.02, p=0.002] Timed walk non-responders: 0.05 [-1.48 to 1.57]	Seizure: 1. FAM: 0.4% (n=1) 2. PLA: 0%	0.4 / NA 4.8 / 21 Withdrew due to adverse events: 1. FAM: 4.8% 2. PLA: 0%	Fair Internal validity concerns • The definition of a responder seems arbitrary • Appropriateness of questionnaire used to determine clinical significance of findings unclear • Defined ITT population as all randomized patients who had at least one efficacy assessment of T25FV and MSWS-12 during the DB treatment period • Vague exclusion criteria • Did not report how adherence to treatment was ensured, but stated was 97% • Did not state what concomitant medications, other than immunomodulators, or non-pharmacologic therapies patients were using that may have affected mobility • Patients included in the phase II trial, from which the primary endpoint was derived, were required to be able to complete the T25FV in 8-60 s, but in this trial, the requirement was 8-45 s External validity concerns • In speaking of the drug's mechanism of action, the study stated "only some patients would be expected to have axons susceptible to the drug effects at any given time." Therefore, it is unclear which patients at what time would benefit from this medication and at what point patients who had benefited would stop benefiting • Ambulatory deficits in MS caused by multiple factors, unclear which affected by FAM. • Lack of validation of the primary endpoint and unclear clinical significance of the primary endpoint, e.g., impact on activities of daily living, number of hospitalizations, home care needs, quality of life • Study duration short and lacked follow-up regarding long-term benefit • Patients excluded who have history of seizure and epileptiform activity on EEG • Exclusion criteria so vague that it is unknown whether or not patients who are commonly treated were excluded • Patients predominantly Caucasian • Setting not described

MS-F204	Goodman 39 center 5/07-2/08	1. FAM 10 mg BID 2. PLA	Inclusion and exclusion criteria similar to MS-F203 Patient characteristics: PLA, FAM Age (mean yrs): 51.7, 51.8 Female (%): 62.2, 73.3 White (%): 88.2, 94.2 MS course (%): Relapsing-remitting: 33.6, 35.8 Primary progressive: 17.6, 8.3 Secondary progressive: 47.1, 51.7 Progressive relapsing: 1.7, 4.2 Immunomodulator treatment (%): 83, 83 MS duration (mean yrs): 13.1, 14.43 EDSS score (mean): 5.6, 5.8 T25FW (feet/s): 2.2, 2.1 LEMSFT score (mean): 4.0, 3.9 Ashworth score (mean): 0.8, 0.9 MSWS-12 (mean): 67.7, 73.8 SGI score (mean): 4.4, 4.3	119 Treatment period: 9 weeks Phases: 1. Pre-screening: 1 week 2. SB placebo run-in, beginning 1 week after screening; 2 weeks 3. DB treatment, beginning 3 weeks after screening; 9 weeks (visits 2, 3, 4, 5, and 6 separated by 2 weeks) 4. Follow-up, beginning 12 weeks after screening; 2 weeks (visits 7 & 8, separated by 2 wks)	Timed walk responders: 1. FAM: 42.9% [p<0.0001] 2. PLA: 9.3% Average change from baseline in MSWS-12 during DB treatment period, independent of treatment group: 1. TWR: -0.84 [CI: -0.57 to -2.52, nominal p<0.001] 2. TWNR: 0.85 [CI: -0.72 to 2.43] Average change in walking speed visits 3-6: 1. FAM TWR: 0.51 ft/s (CI: 0.43 to 0.59) 2. FAM TWNR: 0.12 ft/s (CI: 0.05 to 0.19) 3. PLA (TWR + TWNR): 0.17 ft/s [CI: 0.10 to 0.23]	33.6 / 3 Withdrawals due to adverse events: 1. FAM: 3.3% 2. PLA: 3.4%	Seizure: 1. FAM: 0% 2. PLA: 0.84% (n=1) NA	Fair
MS-F202	Goodman 24 center 2/03-12/03	1. FAM 10 mg BID 2. FAM 15 mg BID 3. FAM 20 mg BID 4. PLA	Inclusion criteria: • Aged 18-70 • clinically defined multiple sclerosis • able to complete two trials of the T25FW in an average time of 8-60 s at screening Exclusion criteria: • recent MS relapses or changes in medications Patient characteristics: PLA, FAM, mg, FAM 15 mg, FAM 20 mg; Mean age: 49, 49.8, 47.7, 52.2 % female: 57, 69, 68, 60 % Caucasian: 94, 96, 88, 91 MS course (%): Relapsing-remitting: 28, 19, 30, 16 Primary progressive: 26, 23, 24, 26 Secondary progressive: 47, 58, 46, 58 MS duration (mean yrs): 13.9, 10.7, 11.8, 11.8 EDSS score (mean): 5.87, 5.83, 5.64, 5.74 MSFC scores T25FW (feet/s): 1.87, 1.94, 1.99, 2.04	51 Treatment period: 12 weeks Phases: 1. Screening (visit 0) 2. SB placebo run-in, beginning 1 week after screening; 2 weeks (visits 1 and 2, separated by 1 week) 3. DB dose escalation, beginning 3 weeks after screening; 2 weeks (visits 3 and 4, separated by 1 week) 4. DB stable dose, beginning 5 weeks after screening; 12 weeks (phone visits 5 and 6, separated by 1 week; clinic visits 7, 8, and 9, separated by 4	Mean percent change in walking speed during treatment relative to baseline (placebo run-in) using the T25FW 1. FAM 10 mg: 8% [NS] 2. FAM 15 mg: 11% [NS] 3. FAM 20 mg: 6.5% [NS] 4. PLA: 3% Post-hoc responder analysis (someone whose walking speed for at least three visits during the DB treatment period was faster than the maximum speed measured in the five non-treatment visits): 1. FAM 10 mg: 35.3% 2. FAM 15 mg: 36.0% 3. FAM 20 mg: 38.6% 4. PLA: 8.5%	NA NA NA NA	Seizure: FAM 10 mg: 0% FAM 15 mg: 0% 3. FAM 20 mg: 0.04% 4. PLA: 0% Withdrawal due to adverse events: 1. FAM 10 mg: 0% 2. FAM 15 mg: 0.02% 3. FAM 20 mg: 0.09% 4. PLA: 0.02%	Poor

	9-HPT (dominant hand, s): 33.9, 35.7, 33.5, 35.3 9-HPT (non-dominant hand, s): 35.7, 30.6, 31.3, 37.2 PASAT-3: 45.7, 49.2, 48.7, 47.5 Composite score: -0.10, 0.04, 0.04, 0.01 LEMMT score: 4.05, 3.98, 4, 3.98 Ashworth score: 1.2, 0.88, 0.89, 0.88 MSWS-12 score: 75.7, 76.3, 74.6, 76.8 CGI score: 3.74, 3.82, 3.8, 3.91 SGI score: 4.38, 4.32, 4.36, 4.25	5. Dose reduction, beginning 17 weeks after screening: 1 week (visit 10) 6. Non-treatment washout and follow-up, beginning 18 weeks after screening; 2 weeks (visit 11)			described
--	--	--	--	--	-----------

¹Study design abbreviations: DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PAM = famiprednisone, PLA = placebo.

²MS disability tests: T25FW: timed 25-foot walk (maximum time allowed to complete is 180 s or 0.14 fits) EDSS: expanded disability status scale MSFC: MS functional composite. 9-HPT: 9-hole peg test; PASAT: paced auditory serial addition test.

³LEMMT: lower extremity manual muscle test; MSWS-12: 12-item MS Walking scale, SGI: subject global impression (assesses physical well-being, 1=unable to 7=delighted), CGI: clinical global impression (1=not ill to 7=extremely ill).

⁴Results abbreviations: AFR = absolute risk reduction; TVWR: timed walk responders; TWNR: timed walk non-responders; NNT = number needed to treat; NNH = number needed to harm; CI = confidence interval.

⁵NNT/NNH are reported only for statistically significant results.

⁶Quality Rating: (Good = likely valid, Fair = likely valid/possibly valid, Poor = fairly invalid)

⁷Modified ITT: all randomized subjects who received at least one efficacy evaluation (T25FW for MS-F202 and 203 and T25FW and MSWS-12 for MS-F204) during the DB period.

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications):¹

FAM should not be used in those with a history of seizure or with moderate or severe renal impairment.

Precautions: Those with mild renal impairment may have seizure risk approaching those taking FAM 15 mg bid in clinical trials. FAM should not be taken with any other product containing 4-aminopyridine, such as compounded products. FAM may increase the incidence of urinary tract infections (UTIs).

Tolerability (Drop-out rates, management strategies):¹

Both the product information sheet and the FDA make it unclear how many MS patients have been exposed to FAM, as the reported figures do not add up. The reported figures are as follows: FAM has been evaluated in 917 MS patients.¹ A total of 601 MS patients have been exposed to FAM for at least 1 year, with the majority receiving doses of at least 10 mg bid. A total of 807 MS patients have been exposed to FAM SR (67 in clinical pharmacology trials, 532 in placebo controlled trials, 208 in uncontrolled trials) and 187 patients have been exposed to other forms of FAM, 89 each in clinical pharmacology and in placebo controlled trials.¹⁴

Despite this lack of clarity, FAM has been used on relatively few patients and that time on the market will tell the prevalence of side effects related to treatment.

In open-label extension studies, a dose-dependent increase in the incidence of seizures was seen in patients with MS at rates of 0.41 per 100 person-years (95% CI 0.13–0.96) for FAM 10 mg twice daily and 1.7 per 100 person-years (95% CI 0.21–6.28) for FAM 15 mg twice daily. Patients with a history of seizures or with evidence of epileptiform activity on EEG were excluded from clinical trials. Therefore, FAM product information states the seizure risk in patients with epileptiform activity is unknown and could be “substantially higher than that observed in FAM clinical studies.”¹

Initially, FAM was studied in MS patients using an immediate release formulation, and seizures occurred in 6/178 patients receiving doses greater than 20 mg/day. This side effect is correlated with plasma concentration. The sustained release formulation was developed as a method to control the fluctuations and high peaks in serum levels seen with the immediate release formulation, and thus serious adverse effects.^{14, 20}

Ampyra™ REMS includes a medication guide and annual letters to prescribers and pharmacists describing the proper distribution and safe use of Ampyra™, including warnings about the potential risk of seizure and about the use of compounded formulations.¹

Adverse events resulted in discontinuation in 4% (15/400) of patients treated with FAM 10 mg twice daily and 2% (5/238) of those treated with placebo.¹

Pregnancy/Lactation rating:¹ Pregnancy category C. The effects of FAM on labor and delivery are unknown. The safety of FAM in pregnant and nursing women and in patients less than 18 years old has not been tested. FAM should only be used if the benefit justifies the potential risk to the fetus. In animals, FAM given during pregnancy and lactation leads to decreased offspring viability and growth at doses similar to the MRHD.

Unanswered safety questions:

The risk of FAM to patients who are at increased risk for seizures from brain damage, alcohol use, or concurrent use of other medications that decrease the seizure threshold is unknown. Long-term studies are needed to better define the risk of seizures in MS patients. FAM has not been tested in geriatric patients in sufficient number to make a determination about its safety.

Dose Index (efficacy/toxic):¹

Animal studies have shown no evidence of carcinogenicity at plasma exposures corresponding to 18 times the plasma exposure of humans using the maximum recommended human dose (MRHD), 20 mg daily. However, studies in rats have shown a statistically significant increase in uterine polyps at doses 9 times the MRHD. No evidence of

mutagenicity has been demonstrated from *in vivo* and *in vitro* toxicology assays. No adverse effects on fertility have been observed in male and female rats at doses of 1, 3, and 9 mg/kg/day (relationship to the MRHD not given).

Look-alike / Sound-alike (LA/SA) Error Risk Potential

LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexicomp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexicomp	USP Online	First DataBank	ISMP	Clinical Judgment
LA/SA for dalfampridine	Delavirdine	None		None	None
	Desipramine				
LA/SA for Ampyra	Anakinra	None		None	None

ADVERSE REACTIONS¹

In clinical trials, the most commonly observed adverse reactions—incidence $\geq 2\%$ and at a rate greater than or equal to placebo—reported in the prescribing information for FAM are presented in the following table.

Adverse Reaction	Placebo (N=238)	FAM 10 mg bid (N=400)	NNH
Urinary tract infection	8%	12%	25
Insomnia	4%	9%	20
Dizziness	4%	7%	33
Headache	4%	7%	33
Nausea	3%	7%	25
Asthenia	4%	7%	33
Back pain	2%	5%	33
Balance disorder	1%	5%	25
Multiple sclerosis relapse	3%	4%	100
Paresthesia	3%	4%	200
Nasopharyngitis	2%	4%	50
Constipation	2%	3%	100
Dyspepsia	1%	2%	100
Pharyngolaryngeal pain	1%	2%	100

DOSE & AVAILABILITY ¹		STRENGTH	FORM	ROUTE	FREQUENCY	HEPATIC ADJ.	PEDIATRIC Dose	GERIATRIC Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
10 mg	Extended release tablets		Oral		Twice daily (12 hours apart)	Creatinine clearance should be determined before using FAM. FAM should not be used in those with moderate renal or severe renal impairment*				<ul style="list-style-type: none"> May be taken with or without food. The recommended dose is not to be exceeded. The FDA has required studies to evaluate the efficacy of lower doses.¹³

*Renally impaired patients would need a dose lower than 10 mg twice daily to avoid the risk of adverse effects such as seizure, and a lower dosage form is unavailable. Seizure risk in patients with mild renal impairment is unknown; however, their FAM plasma levels may approach 15 mg twice daily, a dose that might increase seizure risk.

PHARMACOKINETICS¹

Parameter	Result
Oral Bioavailability	96%
C _{max}	17.3 ng/mL to 21.6 ng/mL
Protein Binding	1-3%
Elimination	Primarily renal
Half-Life	5.2-6.5 hours
Metabolism	Minor CYP3E1

After 24 hours, 95.9% of a FAM dose is eliminated in the urine 90.3% unchanged, while 0.5% is eliminated in the feces. Two inactive, minor metabolites are produced.

ALLERGIES/INTERACTIONS²

Drug-Drug: None

Food-Drug: None

Allergy/Cross Reactive Substances: None

REFERENCES

1. Ampyra medication guide. Hawthorne, NY: Acorda Therapeutics, Inc; 2010 Jan.
2. Rietberg MB, Brooks D, Uitdehaag BMJ et al. Exercise therapy for multiple sclerosis. *Cochrane Database Syst Rev*. 2004, Issue 3. Art. No.: CD003980. DOI: 10.1002/14651858.CD003980.pub2.
3. Jara M, Barker G, Henney H. Dalfampridine extended release tablets: 1 year of postmarketing safety experience in the US. *Neuropsychiatric Disease and Treatment*. 2013;9:365-370.
4. Courtney AM, Treadaway K, Remington G et al. Multiple Sclerosis. *Med Clin North Am*. 2009; 93(2): 451-476.
5. Calabresi PA. Multiple sclerosis and demyelinating conditions of the central nervous system. In: Goldman L, Ausiello D., eds. *Cecil Medicine*. 23rd ed. Philadelphia: Saunders Elsevier; 2008. (accessed online from www.mdconsult.com).
6. Snook EM, Moyl RW. Effect of exercise training on walking mobility in multiple sclerosis: a meta-analysis. *Neurorehabil neural repair*. 2009; 23: 108-116.
7. Noseworthy JH, Lucchinetti C, Rodriguez M et al. Multiple sclerosis. *NEM*. 2000; 343(13): 938-952.
8. Kobelt G, Berg J, Atherly D et al. Costs and quality of life in multiple sclerosis. *Neurology*. 2006; 66:1696-1702.
9. Patwardhan MB, Matchar DB, Samsa GP et al. Cost of multiple sclerosis by level of disability: a review of literature. *Mult Scler*. 2005; 11: 232-239.
10. Filippini G, Munari L, Inconvia B et al. Interferons in relapsing remitting multiple sclerosis: a systematic review. *Lancet*. 2003; 361: 545-552.
11. Mitsikostas DD. Methodology of clinical trials in multiple sclerosis. *Neuro Sci*. 2006; 27: S362-S364.
12. Galetta SL, Markowitz C, Lee AG. Immunomodulatory agents for the treatment of relapsing multiple sclerosis: a systematic review. *Arch Intern Med*. 2002; 162: 2161-2169.
13. Pozzilli C and Prosperini L. Clinical markers of therapeutic response to disease modifying drugs. *Neuro Sci*. 2008; 29:S211-S213.
14. Goodman AD, Brown TR, Krupp LB et al. Sustained-release oral fampridine in multiple sclerosis: a randomized, double-blind, controlled trial. *Lancet*. 2009; 373: 732-738.
15. Food and Drug Administration: NDA 22-250: Fampridine AC backgrounder. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM185663.pdf> (accessed February 17, 2010, and January 16, 2010).
16. Coleman C, Sobieraj D., Marinucci L. Minimally important clinical difference of the Timed 25-Foot Walk Test: results from a randomized controlled trial in patients with multiple sclerosis.
17. Rudick RA, Cutter G, Reingold S. The Multiple Sclerosis Functional Composite: a new clinical outcome measure for multiple sclerosis trials. *Mult Scler*. 2002; 8: 359-365.
18. Cohen JA, Cutter GR, Fischer JS et al. Use of the Multiple Sclerosis Functional Composite as an outcome measure in a phase 3 clinical trial. *Arch Neurol*. 2001; 58: 961-967.
19. Hobart JC, Riazi A, Lampert DL et al. Measuring the impact of MS on walking ability: The 12-Item MS Walking Scale (MSWS-12). *Neurology*. 2003; 60: 31-36.
20. Goodman AD, Brown TR, Krupp LB et al. Dose comparison trial of sustained-release fampridine in multiple sclerosis. *Neurology*. 2008; 71: 1134-1141.

21. Gijbels D, Dalgas U, Romberg A, et al. Which walking capacity tests to use in multiple sclerosis? A multicenter study providing the basis for a core set. *Multiple Sclerosis Journal*. 2012; 18(3):364-71.
22. Goodman AD, Brown TR, Edwards KR et al. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol*. 2010; 68(4): 494-502.
23. Van Dieeman HAM, Polman CH, Koetsier JC et al. 4-Aminopyridine in patients with multiple sclerosis: dosage and serum level related efficacy and safety. *Clin Neuropharmacol*. 1993; 16(3): 195-204.

New Drug Evaluation: Saproterin for Phenylketonuria**Month/Year of Review:** May 2013**New drug(s):** Saproterin (Kuvan®)**End date of literature search:** March 2013**Research Questions:**

- What is the evidence saproterin is effective for treatment of phenylketonuria (PKU)?
- What is the evidence saproterin is safe for treatment of phenylketonuria (PKU)?
- Are there subgroups of patients where saproterin may be more effective or safer?

Conclusions:

- There is moderate level of evidence that saproterin can lower the blood phenylalanine (Phe) levels in some patients with PKU in short term (up to 10 weeks)^{1,2}. It is unclear whether the patients whose Phe levels go down will also show clinical outcomes such as improvements in their health, well-being, and neurocognitive function.
- There are no serious adverse events associated with the treatment in short term.
- There is insufficient evidence on the long-term effects of saproterin and no clear evidence of effectiveness in severe PKU.
- There is insufficient evidence on how to identify the type of patients most likely to benefit because there is no standardized clinical protocol to select potential patients who might be responsive to saproterin treatment.

Recommendations:

- Implement saproterin prior authorization criteria due to lack of long term data and clinical significance outcomes data to support deceased blood Phe level associated with improved neurocognitive and/or psychosocial functions. (Appendix 3)
- In light of lack of national treatment consensus, recommend working with metabolic clinic providers in the region to formulate a uniform and practical treatment protocol for managing patients with PKU including the use of saproterin for patients who are likely to respond.
- Recommend saproterin be considered for the "High Cost Marginal Benefit" policy.

Reason for Review:

Saproterin is the only Food and Drug Administration (FDA) approved therapeutic agent for treatment of PKU in conjunction with a Phe-restricted diet. The major benefit appears to be a modest liberation of a phenylalanine-restricted diet, however, its use does not allow complete discontinuation of a restricted diet and not all patients with PKU will respond to the therapy. This review will examine the place in therapy for saproterin including appropriate patient selection for treatment, monitoring parameters for response and long term treatment, and identify relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

Background:

Phenylketonuria (PKU) is a disorder affecting the aromatic amino acid phenylalanine resulted from a deficiency of phenylalanine hydroxylase (PAH). If left untreated, PKU can lead to profound mental retardation, seizures, behavioral problems and other symptoms.^{3,4} It is a form of rare inborn error in amino acid metabolism. The incidence of PKU is approximately 1 in 13,500 to 19,000 births in the US.⁵ The hepatic enzyme PAH catalyzes the conversion of the essential amino acid phenylalanine to tyrosine. Tetrahydrobiopterine (BH4) is a cofactor required for PAH activity.⁶ Due to deficiency in PAH, individuals with PKU have an over abundance of phenylalanine, which plays an integral role in the development of normal brain function. Although the mechanism by which the elevated concentration of phenylalanine causes intellectual disability is unknown, excessive phenylalanine is thought to interfere with brain growth, myelination and neurotransmitter synthesis. Because of widespread neonatal screening, overt clinical manifestations of PKU are rare. In the U.S, the screening typically occurs at 24-48 hours after birth.⁷

Cognitive outcome appears to be correlated with the extent of control of blood phenylalanine concentration, especially during early childhood. However, the blood phenylalanine concentration associated with optimal neuro-developmental outcome is uncertain. No consensus exists among treatment centers in the United States or other countries. The National Institutes of Health Consensus Development Conference on PKU recommended maintaining a blood concentration of 2 to 6 mg/dL (120 to 360 μ mol/L) for affected children through 12 years of age and 2 to 15 mg/dL (120 to 900 μ mol/L) after 12 years of age. However, although data are limited, higher blood phenylalanine concentrations appear to adversely affect brain function, even in adults. Thus, maintenance of lower levels (2 to 10 mg/dL, 120 to 600 μ mol/L) is strongly encouraged during adolescence or even beyond.⁸

The mainstay of therapy in PKU is dietary restriction of phenylalanine. Dietary treatment appears to reverse all signs of PKU except cognitive impairment that has already occurred. The PKU diet consists of a restriction of dietary protein in order to minimize phenylalanine (Phe) intake. It requires supplementation with special medical formulas that supply sufficient essential amino acids, energy, vitamins and minerals. The diet should be started in the first weeks of age and maintained for life.⁹ Since the dietary management of PKU was established 60 years ago,¹⁰ the knowledge of the generic basis of disease and enzymology has allowed for the investigation of novel pharmacologic therapies to directly ameliorate the effects of a mutant enzyme.⁹ Saproterin is a synthetic formulation of BH4, which is FDA-approved to reduce blood Phe concentrations in patients with hyperphenylalaninemia due to BH4-responsive PKU. The clinical trials demonstrated saproterin can lower the blood Phe levels in some patients with PKU. However, there are no sufficient details on how to identify the type of patients that would get improvements. There are different definitions of responses ranging from a 20% to 50% reduction in blood Phe levels.¹¹ Saproterin responsiveness in clinical trials was defined as \geq 30% blood Phe levels reductions, but this definition is arbitrary and many clinicians consider a 20% reduction in Phe clinically beneficial].

Methods:

A Medline (Ovid) literature search was conducted in the past 10 years for new randomized controlled trials (RCT's) and controlled clinical trials comparing medications head-to-head in the treatment of PKU using saproterin/kuvan[®], and limits for humans, English language. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and 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 for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:***Cochrane Collaboration*^{1,2}**

In October 2012, Somaraju et al. conducted a systematic review to assess the safety and efficacy of saproterin in lowering blood phenylalanine concentration in people with PKU. Two placebo-controlled trials were included.^{1,2} One trial administered 10mg/kg/day saproterin in 89 children and adults with phenylketonuria whose diets were not restricted and who had previously responded to saproterin. This trial measured change in blood phenylalanine concentration. The second trial screened 90 children (4 to 12 years) with phenylketonuria whose diet was restricted, for responsiveness to saproterin. Forty-six responders entered the placebo-controlled part of the trial and received 20 mg/kg/day saproterin. This trial measured change in both phenylalanine concentration and protein tolerance. Both trials reported adverse events. The trials showed an overall low risk of bias; but both were BioMarin-sponsored. One trial showed a significant lowering in blood phenylalanine concentration in the saproterin group (10 mg/kg/day), mean difference -238.80 μmol/L (95% confidence interval -343.09 to -134.51); a second trial (20 mg/kg/day saproterin) showed a non-significant difference, mean difference -51.90 μmol/L (95% confidence interval -197.27 to 93.47). The second trial also reported a significant increase in supplemental phenylalanine tolerated, mean difference 18.00 mg/kg/day (95% confidence interval 12.28 to 23.72) in the 20 mg/kg/day saproterin group. The authors concluded that there is evidence of short-term benefit from using saproterin in some patients with saproterin-responsive forms of phenylketonuria; blood phenylalanine concentration is lowered and protein tolerance increased. There are no serious adverse events associated with using saproterin in the short term. There is no evidence on the long-term effects of saproterin and no clear evidence of effectiveness in severe phenylketonuria.^{1,2}

CADTH Recommendation¹³

In 2011 the Canadian Expert Drug Advisory Committee (CEDAC), subcommittee of CADTH concluded that there was not enough information to identify the type of individuals with PKU for whom saproterin would provide enough improvement to be cost effective based on the clinical and pharmacoeconomic evidence available up to date. The committee acknowledges that saproterin can lower the Phe levels in the blood of some patients with PKU. In addition, it is not clear whether the patients whose Phe levels go down will also show important improvements in their health and well-being. The committee recommends that saproterin not be listed by Canada's publicly funded drug plans for the treatment of PKU.

Recommendations for Determining Response to Saproterin and its use in Patients with PKU

Clinicians in the field have attempted to develop a uniform and practical approach to the use of saproterin for treating PKU in conjunctions with diet although a national consensus is still lacking. Summary of relevant recommendations developed by these experts are listed below.

Selected Relevant Recommendations by Levy H et al (2007)¹⁴

Patient selection for saproterin responsiveness in order of preference:

- Young patients on diet but not in optimal phenylalanine control
- Patients with mild PKU based on dietary phenylalanine tolerance and initial confirmatory blood phenylalanine concentration, as those are the most likely to respond.
- All other patients with PKU, beginning with younger patients on diet, then older patients struggling with diet or not on diet (but experiencing psychological difficulties), and finally, all patients not yet tested.

Regimen for saproterin responsiveness:

- The initial test dose of should be 20mg/kg daily. The dose may be titrated between 5 and 20mg/kg/day to achieve the desired results and based on tolerability.
 - Before the first dose, a blood specimen for phenylalanine determination must be collected. There should be no change in diet. Subsequent specimens for phenylalanine determination should be collected on day 1,7,14 and 28. The blood should be collected at the same time of day for each patient.
- Determination of responsiveness:
- The most widely accepted standard of response to BH4 is a ≥ 30% reduction in blood phenylalanine level. The authors recognize that a lower degree of responsiveness, e.g. 20% might also be considered sufficient in some individual circumstances.

Optimized Protocol by Blau N et al (2009)¹⁵

The FDA approved algorithm for initiating therapy with saproterin recommends that a measurement of blood Phe is followed by an initial daily dose of saproterin at 10mg/kg/day for one week, at the end of which a repeat blood Phe measurement is taken. If a sufficient reduction in blood Phe level is observed, the dose can be increased to 20mg/day, and blood Phe levels are followed for a total initial treatment period of up to one month. At this time, treatment is stopped for non-responders, while responders entered a dose optimization phase when the dose of saproterin is adjusted based on blood Phe level. Because the initial trial phase is one month, potentially it may create false positive and false negative if patients adjust their diet during trial phase. In 2009 the European working group on PKU proposed an optimized protocol. The protocol suggests administration of single dose of saproterin at 20mg/kg followed by serial measurement of blood Phe during the first 24 hours to determine the initial responders defined as greater than 30% reduction of blood Phe level, and to do a second 24-h test later after second dose on second day for patients who showed a rather slower responsiveness in the first test. After 48 hours responders will enter a dose titration phase.

Recommendations for the use of saproterin in PKU by Cunningham a et al. (2012)¹⁶

In 2011 a group of metabolic diicians who practice in various clinics across the North American in conjunction with physicians with extensive experience in PKU management developed the recommendations in patient selection and determination of saproterin response to the long-term management of patients on saproterin therapy. Target Phe levels, nutritional adequacy, neurocognitive screening and adherence to treatment are addressed to optimize patient outcomes.

Key recommendations:

Patient Selection:

- A trial of saproterin may be offered to all patients with PKU to determine clinical benefit. Patients should be evaluated to ensure their ability to adhere to the treatment protocol over the 1-2 month trial period.

- Special consideration is warranted for the following patient population: patient with mild PKU; infants and young children; pregnant women and late-treated and untreated adults.

Baseline Assessment:

- Blood Phe concentration: ideally 3 or more blood Phe levels within the month prior to the start of the trial.
 - Concurrent medications, supplements assessment and mental health screening
- Implementation of saproterin and monitoring during a trial phase:
- An initial dose of 20mg/kg/day is recommended. The dose may be titrated between 5 and 20mg/kg/day
 - Blood Phe level should be performed prior to initiation of treatment and weekly thereafter until completion of the trial. For infants and young children, a blood Phe test is best obtained at day 1 or 2 of the trial. Blood sample should be obtained at a consistent time of the day that is at least 2 hours after food intake.
 - Patients should be instructed not to make any lifestyle changes and maintain their usual diet.

Determination of clinical benefit of saproterin:

- Reduced blood Phe levels: Although in clinical trials, a ≥ 30% decrease in blood Phe concentration was used to define saproterin response, a smaller reduction may be clinical meaningful if accompanied with an increase in dietary Phe tolerance and/or an improvement in neurocognitive/psychosocial functioning.
- Increased dietary Phe tolerance
- Improved neurocognitive and/or psychosocial functioning
- Improved blood Phe stability

New Drug Evaluation:

FDA approved indications:

Saproterin (Kuvan®) was FDA approved to reduce blood Phe levels in patients with hyperphenylalaninemia (HPA) due to BH4-responsive PKU in conjunction with a Phe-restricted diet.

Clinical Efficacy Data:

There were two double blind, placebo controlled studies evaluated the efficacy and safety of saproterin in patients with PKU.^{1,2} The first randomized clinical trial by Levy et al.¹ was a phase III, multicenter, randomized, double-blind, placebo controlled trial, that included 88 patients who received at least one dose of study drug. There were 41 patients in treatment group received oral doses of saproterin 10mg/kg and 47 patients received placebo once daily for 6 weeks. The patients enrolled in this study were pediatric and adult patients who were screened to show responsiveness, defined as a reduction of 30% or more in blood phenylalanine concentration after 8 days of treatment with saproterin at a dose of 10mg/kg per day. The primary endpoint was mean difference between treatment groups in blood phenylalanine concentration at six weeks. Analysis was on an intention-to-treat basis. The second randomized clinical trial conducted by Trefz et al.² was also a phase III, randomized, double blind, placebo controlled study screen for saproterin response among 90 children aged 4 – 12 years of age in part 1. In part 2, 46 responsive subjects were randomized (3:1) to saproterin 20mg/kg/day, or placebo for 10 weeks while continuing on a Phe-restricted diet. After 3 weeks, a dietary Phe supplement was added every 2 weeks if Phe control was adequate. Responders in part 1, were arbitrarily defined as those who achieved at least 30% reduction in blood Phe concentrations between day 1 and day 8, had blood Phe level of ≤ 300 μmol/L on day 8. The primary endpoint was daily Phe supplement tolerated by the saproterin group at week 10 compared with week 0. The Phe supplement tolerated was defined as the cumulative

increase or decrease in Phe supplement prescribed in part 2 at the last visit at which the subject had adequate blood Phe control, defined as a blood Phe concentration < 360 $\mu\text{mol/L}$.

Comparative Clinical Efficacy

Relevant Endpoints: 1) Neurocognitive and/or psychosocial functioning
2) Quality of life

Study Endpoints: 1) Mean differences between treatment groups in blood Phe level
2) The Phe supplement tolerated by the treatment group

Evidence Table

Ref/ Study Design	Drug/ Regimens	Patient Population	N	Dura- tion	Efficacy Results (C, p-values)	ARR/ NNT (CI, p-values)	Safety Results (CI, p-values)	TARR/ NNH (CI, p-values)	Quality Rating/ Comments
Levy et. al. ¹	S: Saproterin 10mg/kg/day P: placebo	Mean age (S/P): 21.5/19.5 Female (S/P): 3.4%/49%	N = 88 P: 47 S: 41	6 weeks Mean differences between treatment groups in blood Phe level at week 6 ($\mu\text{mol/L}$): S: -245 (CI: -350 to -141; p < 0.0001)	Primary endpoint NA	Any events (S/P): 51%/63% (p = 0.80)	Serious tx related events: None recorded in either group.	NA	Quality Rating: Good

Trefz et al. ²	S: Saproterin 20mg/kg/day Phase III, DB, p: placebo PC, RCT; MC	Part 2: Mean age (S/P): 7.7/7. S: 33 P: 12 Female (S/P): 39%/50%	N= 46* S: 33 P: 12 *One pt did not receive any study drug.	Part 2 Primary endpoint Daily Phe supplement tolerated at week 10, compared with week 0 (mg/kg/day): S: 20.9 (15.4 to 26.4; p <0.001) P: 2.9 (p = NS)	NA	Any events (S/P); 27%/25% (CI, p not reported)	NA	Quality Rating: Good
	Part 1: screening phase (open label)	Mean blood Phe < 300 receive μmol/L (S/P): 48%/42%		Serious tx related events: None recorded in either group.		Internal Validity: RoB Selection: Randomization was done using a computer-generated interactive response system. Sample size is small for all groups. Performance: Blinding of patients and study monitors.		
	Part 2: responsive subjects were randomized (DB phase)	Baseline dietary Phe intake at week 0 (mg/kg/day), mean (SD): 16.3 (8.4)*/16.8 (7.6)^ *N=30, ^N=9		Secondary endpoint Difference in blood Phe level in Saproterin group between week 3 and week 0 (μmol/L): S: -148.5 (-196 to -101; p < 0.001) P: 0 (-251 to 58; p = 0.2)	NA	Discontinuation due to tx: None recorded in either group.	External Validity : Recruitment: Multicenter international study. Patient characteristics: Similar baseline characteristics with exception of gender for which the treatment groups differed. Outcomes: Short-term only; not true effectiveness outcomes.	
		The mean difference of the saproterin and placebo groups in the amount of Phe supplement tolerated at week 10 (mg/kg/day): 17.7 ± 4.5 (p < 0.001)		Common Tx related events (S/P): Headache: 21% (8%) Rhinorrhea: 21% (0%) Cough: 15% (0%)				

Clinical Safety:

In 4 clinical trials, there were approximately 600 individuals with PKU took saproterin. In about 80% of cases, the length of the treatment was about 8 days. No subjects stopped treatment due to side effects in these trials. There were no serious side effects in study by Levy et.al; in part two of Trefz et al study, there were two serious side effects were reported (Streptococcal infection in saproterin group and appendicitis in placebo group). Overall, the adverse events from saproterin were mostly mild; the most common ones in saproterin-treated individuals included: headache, upper respiratory tract infection (common cold), and cough.

References:

1. Levy HL, Milanowski A, Chakrapani A, et al. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study. *The Lancet.* 11;370(9586):504–510.
2. Trefz FK, Burton BK, Longo N, et al. Efficacy of Sapropterin Dihydrochloride in Increasing Phenylalanine Tolerance in Children with Phenylketonuria: A Phase II, Randomized, Double-Blind, Placebo-Controlled Study. *The Journal of Pediatrics.* 2009;154(5):700–707.e1.
3. Otaf A Bodamer. Overview of phenylketonuria. Up to Date. 2013. Available at: http://www.uptodate.com/contents/overview-of-phenylketonuria?source=search_result&search=phenylketonuria&selectedTitle=1%7E140. Accessed March 23, 2013.
4. Pitt DB, Danks DM. The natural history of untreated phenylketonuria over 20 years. *J Paediatr Child Health.* 1991;27(3):189–190.
5. Anon. National Institutes of Health Consensus Development Conference Statement: phenylketonuria: screening and management, October 16-18, 2000. *Pediatrics.* 2001;108(4):972–982.
6. Hoeks MPA, Den Heijer M, Janssen MCH. Adult issues in phenylketonuria. *Neth J Med.* 2009;67(1):2–7.
7. Blau N, Hennermann JB, Langenbeck U, Lichter-Konecki U. Diagnosis, classification, and genetics of phenylketonuria and tetrahydrobiopterin (BH4) deficiencies. *Molecular Genetics and Metabolism.* 2011;104, Supplement:S2–S9.
8. Anon. National Institutes of Health Consensus Development Conference Statement: phenylketonuria: screening and management, October 16-18, 2000. *Pediatrics.* 2001;108(4):972–982.
9. Bélanger-Quintana A, Burlina A, Harding CO, Muntau AC. Up to date knowledge on different treatment strategies for phenylketonuria. *Molecular Genetics and Metabolism.* 2011;104, Supplement:S19–S25.
10. WOOLF LI. Excretion of conjugated phenylacetic acid in phenylketonuria. *Biochem J.* 1951;49(1):ix–x.
11. Fiege B, Blau N. Assessment of Tetrahydrobiopterin (BH4) Responsiveness in Phenylketonuria. *The Journal of Pediatrics.* 2007;150(6):627–630.
12. Somaraju UR, Merrin M. Sapropterin dihydrochloride for phenylketonuria (review). *The Cochrane Collaboration.* 2012. Available at: http://ovidsp.tx.ovid.com.liboff.ohsu.edu/sp-3.8.1a/ovidweb.cgi?WebLinkFrameset=1&S=FFEDFPLLIIDOLMMNCOKLDGCHMFJAA00&returnUrl=ovidweb.cgi%3f%26full%2bText%3dL%257cS.sh.33.52%257c0%257c00075320-100000000-06626%26S%3dFFEDFPLLIIDOLMMNCOKLDGCHMFJAA00&directlink=http%3a%2f%2fgraphics.tx.ovid.com%2fovftpd%2fFDDNCGLDMMI00%2ffs046%2fovft%2fliive%2fgv023%2f00075320%2f00075320-100000000-06626.pdf&filename=Sapropterin+dihydrochloride+for+phenylketonuria&pdf_key=FPDDNCGLDMMI00&pdf_index=/fs046/ovft/live/gv023/00075320/00075320-100000000-06626. Accessed March 14, 2013.

13. CEDAC. kuvan_plain-language_rec_march-15-2011_e.pdf. 2011. Available at: http://www.caadth.ca/media/cdr/relatedinfo/kuvan_plain-language_rec_march-15-2011_e.pdf. Accessed March 15, 2013.
14. Levy H, Burton B, Cederbaum S, Scriver C. Recommendations for evaluation of responsiveness to tetrahydrobiopterin (BH4) in phenylketonuria and its use in treatment. *Molecular Genetics and Metabolism*. 2007;92(4):287–291.
15. Blau N, Bélanger-Quintana A, Demirkol M, et al. Optimizing the use of sapropterin (BH4) in the management of phenylketonuria. *Molecular Genetics and Metabolism*. 2009;96(4):158–163.
16. Cunningham A, Bausell H, Brown M, et al. Recommendations for the use of sapropterin in phenylketonuria. *Molecular Genetics and Metabolism*. 2012;106(3):269–276.
17. Anon. Kuvan Prescribing Information. Available at: <http://www.kuvan.com/KuvanPI.pdf>. Accessed April 2, 2013.

Appendix 1: Specific Drug Information¹⁷

CLINICAL PHARMACOLOGY

Saproterin is a synthetic form of BH4, the cofactor for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates Phe through an oxidative reaction to form tyrosine. In patients with PKU, PAH activity is absent or deficient. Treatment with BH4 can activate residual PAH enzyme, improve normal oxidative metabolism of Phe, and decrease Phe levels in some patients.

PHARMACOKINETICS

The absorption and elimination pharmacokinetics of mirabegron are dose-dependent.

Parameter	Result
Oral Bioavailability	Unknown
Protein Binding	Unknown
Elimination	Unknown
Half-Life	6.7 hours
Metabolism	CYP450

DOSE & AVAILABILITY

Strength	Form	Route	Frequency	Renal Ad.	Hepat/CAD	Enteral	Other Dosing Considerations
100mg	Tab	PO	Daily	Not defined	> 4 years of age, same as adult dose.	Not defined	Administered with food to increase absorption, preferably at the same time every day. Saproterin tablets should be dissolved in 4-8 oz. of water or apple juice and taken within 15 minutes of dissolution.

DRUG SAFETY

Serious (REMs, Black Box Warnings, Contraindications): There are no Serious Drug Safety concerns or contradictions for saproterin at this time.

Warnings and Precautions: Treatment with saproterin should be directed by physicians knowledgeable in the management of PKU. Patients need to be monitored for blood Phe levels. Active management of dietary phe intake while taking saproterin is required to ensure adequate Phe control and nutritional balance. Drugs known to affect folate metabolism such as MTX, and their derivatives should be used with caution while taking saproterin. In addition, caution should be used when concurrent use of saproterin and levodopa and drugs affecting nitric oxide-mediated vasorelaxation (e.g., PDE-5 inhibitors such as sildenafil, vardenafil or tadalafil).

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
No look-alike/sound-alike drugs have been found to have error risk potential.

Adverse Reactions

The most serious reactions during saproterin administration (regardless of relationship to treatment) were gastritis, spinal cord injury, streptococcal infection, testicular carcinoma, and urinary tract infection. The table below summarized the treatment-emergent adverse reactions that occurred in at least 4% of patients treated with saproterin in two double-blind, placebo-controlled clinical trials.

	Placebo N (%)	Saproterin N (%)
Number of Patients	59	74
Any Adverse Reaction	42 (71)	47 (64)
Headache	8 (14)	11 (15)
Upper Respiratory Tract Infection	14 (24)	9 (12)
Rhinorrhea	0	8 (11)
Pharyngolaryngeal pain	1 (2)	7 (10)
Diarrhea	3 (5)	6 (8)
Vomiting	4 (7)	6 (8)
Cough	3 (5)	5 (7)
Pyrexia	4 (7)	5 (7)
Contusion	1 (2)	4 (5)
Abdominal Pain	5 (8)	4 (5)
Rash	4 (7)	4 (5)
Nasal congestion	0	3 (4)

Appendix 2: Abstracts of potentially relevant randomized controlled trials and/or systematic reviews

1. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study Harvey L Levy, MD, Andrzej Milanowski, MD Anupam Chakrapani, MD, Maureen Cleary, MD, Friedrich K Trefz, MD, Chester B Whitley, MD, François Feillet, MD, Annette S Feigenbaum, FRCPC, Judith D Bebbchuk, ScD, Heidi Christ-Schmidt, MSE, Alex Dorenbaum, MD, for the Sapropterin Research Group

Summary

Background: Early and strict dietary management of phenylketonuria is the only option to prevent mental retardation. We aimed to test the efficacy of sapropterin, a synthetic form of tetrahydrobiopterin (BH4), for reduction of blood phenylalanine concentration.

Methods: We enrolled 89 patients with phenylketonuria in a Phase III, multicentre, randomised, double-blind, placebo-controlled trial. We randomly assigned 42 patients to receive oral doses of sapropterin (10 mg/kg) and 47 patients to receive placebo, once daily for 6 weeks. The primary endpoint was mean change from baseline in concentration of phenylalanine in blood after 6 weeks. Analysis was on an intention-to-treat basis. The study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov), number NCT00104247.

Findings: 88 of 89 enrolled patients received at least one dose of study drug, and 87 attended the week 6 visit. Mean age was 20 (SD 9.7) years. At baseline, mean concentration of phenylalanine in blood was 843 (300) µmol/L in patients assigned to receive sapropterin, and 888 (323) µmol/L in controls. After 6 weeks of treatment, patients given sapropterin had a decrease in mean blood phenylalanine of 236 (257) µmol/L, compared with a 3 (240) µmol/L increase in the placebo group ($p<0.0001$). After 6 weeks, 18/41 (44%) patients (95% CI 28–50) in the sapropterin group and 4/47 (9%) controls (95% CI 2–20) had a reduction in blood phenylalanine concentration of 30% or greater from baseline. Blood phenylalanine concentrations fell by about 200 µmol/L after 1 week in the sapropterin group and this reduction persisted for the remaining 5 weeks of the study ($p<0.0001$). 11/47 (23%) patients in the sapropterin group and 8/41 (20%) in the placebo group experienced adverse events that might have been drug-related ($p=0.80$). Upper respiratory tract infections were the most common disorder.

Interpretation: In some patients with phenylketonuria who are responsive to BH4, sapropterin treatment to reduce blood phenylalanine could be used as an adjunct to a restrictive low-phenylalanine diet, and might even replace the diet in some instances.

2. Efficacy of Sapropterin Dihydrochloride in Increasing Phenylalanine Tolerance in Children with Phenylketonuria: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study. Friedrich K. Treitz, MD, Nicola Longo, MD, PhD, Mercedes Martinez-Pardo Casanova, MD, Daniel J. Gruskin, MD, Alex Dorenbaum, MD, Emil D. Kakkis, MD, PhD, Eric A. Crombez, MD, Dorothy K. Grange, MD, Paul Harmatz, MD, Mark H. Lipson, MD, Andrzej Milanowski, MD, PhD, Linda Marie Randolph, MD, Jerry Vockley, MD, PhD, Chester B. Whitley, MD, PhD, Jon A. Wolff, MD, Judith Bebbchuk, ScD, Heidi Christ-Schmidt, MSE, Julia B. Hennermann, MD. Sapropterin Study Group

Objective: To evaluate the ability of sapropterin dihydrochloride (pharmaceutical preparation of tetrahydrobiopterin) to increase phenylalanine (Phe) tolerance while maintaining adequate blood Phe control in 4- to 12-year-old children with phenylketonuria (PKU).

Study design: This international, double-blind, randomized, placebo-controlled study screened for sapropterin response among 90 enrolled subjects in Part 1. In Part 2, 46 responsive subjects with PKU were randomized (3:1) to sapropterin, 20 mg/kg/d, or placebo for 10 weeks while continuing on a Phe-restricted diet. After 3 weeks, a dietary Phe supplement was added every 2 weeks if Phe control was adequate.

Result: The mean ($\pm SD$) Phe supplement tolerated by the sapropterin group had increased significantly from the pretreatment amount (0 mg/kg/d) to 20.9 (± 15.4) mg/kg/d ($P < .001$) at the last visit at which subjects had adequate blood Phe control (<360 $\mu\text{mol/L}$), up to week 10. Over the 10-week period, the placebo group tolerated only an additional 2.9 (± 4.0) mg/kg/d Phe supplement; the mean difference from the sapropterin group ($\pm SE$) was $17.7 \pm 4.5 \text{ mg/kg/d}$ ($P < .001$). No severe or serious related adverse events were observed.

Conclusions: Sapropterin is effective in increasing Phe tolerance while maintaining blood Phe control and has an acceptable safety profile in this population of children with PKU.

3. Sapropterin dihydrochloride for phenylketonuria, Usha Rani Somaraju, Marcus Merrin. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: CD008005. DOI: 10.1002/14651858.CD008005.pub3. Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

A B S T R A C T

Background: Phenylketonuria results from a deficiency of the enzyme phenylalanine hydroxylase. Dietary restriction of phenylalanine keeps blood phenylalanine concentration low. Most natural foods are excluded from diet and supplements are used to supply other nutrients. Recent publications report a decrease in blood phenylalanine concentration in some patients treated with sapropterin dihydrochloride. We examined the evidence for the use of sapropterin dihydrochloride to treat phenylketonuria.

Objectives: To assess the safety and efficacy of sapropterin dihydrochloride in lowering blood phenylalanine concentration in people with phenylketonuria.

Search methods: We identified relevant trials from the Group's Inborn Errors of Metabolism Trials Register. Date of last search: 29 June 2012. We also searched ClinicalTrials.gov and Current controlled trials. Last search: 23 July 2012. We contacted the manufacturers of the drug (BioMarin Pharmaceutical Inc.) for information regarding any unpublished trials.

Selection criteria: Randomized controlled trials comparing sapropterin with no supplementation or placebo in people with phenylketonuria due to phenylalanine hydroxylase deficiency.

Data collection and analysis: Two authors independently assessed trials and extracted outcome data.

Main results: Two placebo-controlled trials were included. One trial administered 10mg/kg/day sapropterin in 89 children and adults with phenylketonuria whose diets were not restricted and who had previously responded to sapropterin. This trial measured change in blood phenylalanine concentration. The second trial screened 90 children (4 to 12 years) with phenylketonuria whose diet was restricted, for responsiveness to sapropterin. Forty-six responders entered the placebo-controlled part of the trial and received 20 mg/kg/day sapropterin. This trial measured change in both phenylalanine concentration and protein tolerance. Both trials reported adverse events. The trials showed an overall low risk of bias; but both are Biomarin-sponsored. One trial showed a significant lowering in blood phenylalanine concentration in the sapropterin group (10 mg/kg/day), mean difference -238.80 μ mol/L (95% confidence interval -343.09 to -134.51); a second trial (20 mg/kg/day sapropterin) showed a non-significant difference, mean difference -51.90 μ mol/L (95% confidence interval -197.27 to 93.47). The second trial also reported a significant increase in phenylalanine tolerance, mean difference 18.00 mg/kg/day (95% confidence interval 12.28 to 23.72) in the 20 mg/kg/day sapropterin group.

Authors' conclusions: There is evidence of short-term benefit from using sapropterin in some patients with sapropterin-responsive forms of phenylketonuria; blood phenylalanine concentration is lowered and protein tolerance increased. There are no serious adverse events associated with using sapropterin in the short term. There is no evidence on the long-term effects of sapropterin and no clear evidence of effectiveness in severe phenylketonuria.

Appendix 3: Suggested PA Criteria

Saproterin (Kuvan)			
Approval Criteria - Initial	Record ICD-9 code		
1. What is the diagnosis?	Yes: Go to #3.	No: Pass to RPh, Deny for investigational use.	
2. Does member have a diagnosis of tetrahydrobiopterin- (BH4-) responsive phenylketonuria?	Yes: Go to #4	No: Deny and recommend Phe-restricted diet.	
3. Is member currently on a Phe-restricted diet and unable to achieve target blood phenylalanine level?	Yes: Approve for 2 months.	No: Request information from provider.	
Approval Criteria - Renewal			
1) Does member have documented one of the following treatment response: a) ≥ 30% decrease in blood Phe concentration compared with baseline b) At least 20% decrease in blood Phe concentration compared with baseline with one of the following: i) Increased dietary Phe tolerance ii) Improved neurocognitive and/or psychosocial functioning iii) Improved blood Phe stability	Yes: Approve for 12 months.	No: Deny for lack of treatment response.	



Oregon State Drug Use Research & Management Program

Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079

College of Pharmacy Phone 503-945-5220 | Fax 503-947-1119



Opioid Dependency Treatment: Abbreviated Class Review

Month/Year of Review: July 2013

Drugs Included: buprenorphine (Subutex™), buprenorphine/naloxone (Suboxone™), naltrexone (Vivitrol™, Revia™), and methadone (Dolophine™)

Current Management: Prior authorization criteria is in place for buprenorphine (Appendix 1) to expand access to opioid addiction treatment, deny for use in pain and/or below the line indications. Methadone for opioid maintenance therapy is covered in opioid dependence treatment clinics.

Research Questions:

- What is the efficacy and safety evidence of different pharmacologic treatment options for opioid dependence when compared to placebo or non-pharmacological interventions?
- What is the comparative efficacy and safety evidence comparing different pharmacologic treatment options for opioid dependence?
- Are there subgroups of patients where one treatment option may be more effective or safer?

Conclusions:

- There is moderate level evidence from a Cochrane review that methadone is more effective than non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use as measured by self-report and urine/hair analysis (6 RCTs, RR = 0.66 95% CI 0.56-0.78), but not different in criminal activity (3 RCTs, RR=0.39; 95%CI: 0.12-1.25) or mortality (4 RCTs, RR=0.48; 95%CI: 0.10-2.39).¹
- There is moderate level evidence from a meta-analysis (20 RCTs, n=2112) comparing buprenorphine, methadone, clonidine and lofexidine that buprenorphine and methadone appear to be the most effective detoxification treatments.²
- There is moderate level evidence from a Cochrane review (24 RCTs, n=4497) that buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but it is less effective than methadone delivered at adequate dosages.³
- There is insufficient evidence comparing the sublingual film of buprenorphine/naloxone to sublingual tablets.
- There is moderate evidence from a Cochrane review (13 RCTs, n=1158) comparing oral naltrexone versus placebo or no pharmacological treatments that there was difference for all the primary outcomes considered.⁴ The authors concluded that the studies conducted have not allowed an adequate evaluation of oral naltrexone treatment in the field of opioid dependence.
- There is insufficient evidence comparing naltrexone intramuscular implant to the oral formulation and placebo.⁵
- There is low quality evidence from a recent review that buprenorphine and methadone maintenance showed no differences in maternal outcomes, however buprenorphine resulted in a significant reduction in the severity of and duration of neonatal abstinence syndrome (NAS).⁶

- There is insufficient evidence from a review that examined the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions on retaining adolescents in treatment, reducing the use of substances and reducing health and social status.⁷

Recommendations:

- Methadone should remain available for maintenance in opioid dependency clinics.
- Continue to require PA for all buprenorphine and buprenorphine/naltrexone products to ensure the diagnosis is for the treatment of opioid dependence.
- Evaluate price for buprenorphine and buprenorphine/naloxone products for PDL placement.
- Naltrexone should be non-preferred due to insufficient evidence of effectiveness.

Reason for Review:

There are several agents available for the treatment of opioid dependency. However none of these agents are currently on the Preferred Drug List (PDL). This review will examine their place in the therapy for PDL placement.

Background:

Opioid dependence is a cluster of physiological, behavioral, and cognitive phenomena. Use of an opioid is a much higher priority for an individual than other behaviors.⁸ People have suffered from opioid dependence for centuries. Historically, opium was used, while more recently it is heroin or prescription pain relievers. The prevalence of prescription opioid abuse in the US has increased in the past decade.⁹ In 2008, among the population of the United States aged 12 or older, nonmedical use of prescription pain relievers was the second most prevalent type of illicit drug use, after marijuana use.¹⁰ This is an increasing problem in Oregon. The rate of past year nonmedical use of prescription pain relievers among those aged 12 or older was 4.6% nationally whereas Oregon ranked the highest at 6.4% in combined 2010 and 2011 data.¹¹ Arkansas, Colorado, Oregon, and Washington were ranked in the top States in three age groups.¹¹ A study of age-adjusted unintentional drug poisoning mortality rates from 1999-2004 in urban and rural areas of the US showed that prescription opioids have replaced heroin as a leading drug for fatal overdose.¹² Health care costs of opioid dependence are over one billion dollars in the US annually.¹³ Costs to society include lost work productivity due to intoxication or complications of use, health care costs for uninsured users with medical complications, prosecution and incarceration expenses for criminal offenses, and economic and psychological costs to the victims of crimes. Additional costs arise from transmission of diseases such as HIV and hepatitis to sexual contacts who are not themselves drug users.

Opioid dependence is a chronic relapsing disorder. Goals of therapy are to prevent abstinence syndrome, reduce opioid cravings and block the euphoric effects of illicit opioid use.¹⁴ Patients with opioid dependence who have gone through the acute withdrawal period from opioid typically require long-term maintenance treatment. Treatment options include non-pharmacological, abstinence-based treatment or maintenance with opioid agonists (e.g. methadone or buprenorphine) and opioid antagonists (e.g. naltrexone). Treatment with an antagonist prevents the user from experiencing recreational effects with subsequent opioid use and it helps to extinguish continued opioid use and reinforces abstinence. Alternatively, opioid agonists, suppress craving and

withdrawal symptoms. Although when patients are on agonist therapy they are physically dependent upon methadone or buprenorphine, they are more likely to refrain from abusing other drugs. Agonist therapy is not equivalent to addiction to methadone or buprenorphine. Some patients remain on opioid maintenance for many years, while others can be tapered off agonist therapy.

Oregon Administrative Rules define standards for outpatient opioid treatment programs. An opioid treatment program is a program that dispenses and administers opioid agonist medications in combination with counseling and supportive services. When used for the treatment of opioid addiction, methadone may only be dispensed in accordance with the OAR standards. A maintenance dose is determined by a physician experienced in addiction treatment and is adequate to achieve the desired effects for 24 hours. A decision on dispensing opioid treatment medications to patients for unsupervised use is made by the program medical director. Methadone can only be administered in oral form to reduce its potential for abuse.

Methods:

A MEDLINE Ovid search was conducted using the terms: opioid dependence, methadone, buprenorphine, naloxone, and naltrexone. The search was limited to meta-analysis, English language, and to studies conducted in humans in the last 10 years. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA) and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

Methadone

Methadone is the most frequently used medication in the treatment of opioid dependence. Methadone maintenance became a major public health initiative to treat opioid dependence in the early 1970s.¹⁵ It remains to be the best researched treatment for this problem.¹ It is a long-acting full opioid agonist. It binds to the mu opioid receptors on the surfaces of brain cells, which mediate the analgesic and other effects of opioids. Methadone produces a range of mu agonist effects similar to short-acting opioids. When appropriately dosed, it produces cross-tolerance for short acting opioids such as morphine and heroin, consequently suppressing withdrawal symptoms and opioid cravings.¹⁵

Methadone maintenance has been demonstrated repeatedly to be safe and effective when used with appropriate safeguards and physical social services.¹⁶ Long-term side effects include constipation, weight gain, decreased libido, and menstrual irregularities (resulting from hyperprolactinemia).¹⁵ Methadone has been shown to increase QT intervals in at least two studies.^{17,18} Prescribers should be aware of potential QT prolongation effects of methadone, especially at high doses. In addition, prescribers should be aware of interactions with other medications that also have QT prolonging properties such as azole antifungals, or medications that slow the elimination of methadone.

Systematic Reviews: (See Appendix 2 for abstract)

Cochrane Collaboration Review by Matick RP et al.¹ In this 2009 meta-analysis, all randomized controlled clinical trials of methadone maintenance therapy compared with either placebo maintenance or other non-pharmacological therapy for the treatment of opioid dependence were reviewed. Eleven studies (n=1969) met the criteria for inclusion in this review, all were randomized clinical trials, two were double-blind. The sequence generation was inadequate in one study, adequate in five studies and unclear in the remaining studies. The allocation of concealment was adequate in three studies and unclear in the remaining studies. Methadone was more effective than non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use as measured by self-report and urine/hair analysis (6 RCTs, RR = 0.66 95% CI 0.56-0.78), but not different in criminal activity (3 RCTs, RR=0.39; 95%CI: 0.12-1.25) or mortality (4 RCTs, RR=0.48; 95%CI: 0.10-2.39). The authors concluded methadone is an effective maintenance therapy intervention for the treatment of heroin dependence as it retains patients in treatment and decreases heroin use better than treatments that do not utilize opioid replacement therapy but did not show a superior effect on criminal activity or mortality. The authors noted that that the doses of methadone used in the randomized clinical trials are probably slightly higher than are being used currently in routine clinical practice in some parts of the world. This relative under dosing in clinical practice may lead to a reduction in the effectiveness of methadone, as the response to methadone treatment is dose-dependent. In addition, the authors recognized that methadone treatment in these trials was often provided with substantial ancillary services. These ancillary services have included counseling, psycho-social services, medical services and often psychiatric care. The quality of the therapeutic relationship with staff in methadone clinics plus the intensity of these ancillary services, combined with the dose of methadone prescribed will all act to enhance the outcome for methadone treatment.

Buprenorphine and buprenorphine/naloxone

The U.S. Food and Drug Administration (FDA) approved sublingual buprenorphine in 2002 to expand access to treatment of opioid dependence to areas lacking methadone clinics. Buprenorphine is a synthetic opioid. It is a partial mu receptor agonist and antagonist at the kappa receptor. In the 1990s, researchers determined that buprenorphine does not activate mu receptors fully (i.e. low intrinsic activity) and results in a ceiling effect, which prevents larger dose of buprenorphine from producing greater agonist effects.¹⁹ As a result, it has a higher margin of safety for death by respiratory depression. Buprenorphine is available alone (sublingual tablets) or combined with naloxone (sublingual tablets or films). The combination product was developed because buprenorphine abuse by injection was reported outside the United States. Buprenorphine alone precipitates withdrawal symptoms in most opioid addicted patients and the addition of naloxone increases this likelihood.¹⁵

The sublingual film was approved in 2010 to make it harder to crush into powder and snort and therefore minimize abuse and misuse. There was no new efficacy data provided for approval and it was determined that an advisory committee meeting was unnecessary for the new formulation.²⁰ The sublingual tablet formulation has been used off label for the treatment of chronic pain.^{21,22}

Johnson et al. reviewed several studies evaluating the efficacy of buprenorphine for maintenance treatment lasting up to 1 year.²³ These studies showed that daily doses of 8 to 16mg buprenorphine are safe and well tolerated. Studies comparing buprenorphine and methadone suggested that 8mg or 16 mg of sublingual buprenorphine daily is equivalent to approximately 60mg of methadone per day.²³ The efficacy and safety of buprenorphine -naloxone

combination used in office-based setting was shown in a randomized double blinded clinic trial.²⁴ In addition, there are two systematic reviews comparing buprenorphine with other opioid dependence treatment options.

Meta-analysis by Meader N² (May, 2010)

The aim of this systematic review was to compare the efficacy of methadone, buprenorphine, clonidine and lofexidine (not available in the US) for opioid detoxification. Randomized clinical trials (RCTs) that included opioid dependent participants over a mean age of 16 receiving opioid detoxification using buprenorphine, methadone, clonidine, or lofexidine were included in the systematic review. Included studies were quality assessed and the completion of treatment data was extracted by the author and a research assistant independently. Mixed treatment comparison methods were used to synthesize the data. There were 23 RCTs included in the systematic review (and 20 included in the meta-analysis) comprising a total of 2112 participants. Buprenorphine and methadone were ranked as the most effective methods of opioid detoxification followed by lofexidine and clonidine respectively. The author concluded that buprenorphine and methadone appear to be the most effective detoxification treatments. While the analysis suggests buprenorphine is the most effective method of detoxification there is some uncertainty on whether it is more effective than methadone and requires further research to confirm this result.

Cochrane Review by Mattick RP et al.³ (Issue 2, 2008)

The review evaluated the effects of buprenorphine maintenance against placebo and methadone maintenance in retaining patients in treatment and in suppressing illicit drug use. Authors separately and independently evaluated the papers and extracts data for meta-analysis. Twenty four studies met the inclusion criteria (4497 participants), all were randomized clinical trials, all but six were double-blind. The method of allocation concealment was not clearly described in the majority (20) of the studies, but where it was reported the methodological quality was good. Buprenorphine was superior to placebo in retention of patients in treatment at low doses ($RR=1.50$; 95% CI: 1.19 - 1.88), medium ($RR=1.74$; 95% CI: 1.06 - 2.87), and high doses ($RR=1.74$; 95% CI: 1.02 - 2.96). However, only medium and high dose buprenorphine suppressed heroin use significantly above placebo. Buprenorphine given in flexible doses was less effective than methadone in retaining patients in treatment ($RR=0.80$; 95% CI: 0.68 - 0.95), but no different in suppression of opioid use for those who remained in treatment. Low dose methadone is more likely to retain patients than low dose buprenorphine ($RR=0.67$; 95% CI: 0.52 - 0.87). Medium dose buprenorphine does not retain more patients than low dose methadone, but may suppress heroin use better. There was no advantage for medium dose buprenorphine over medium dose methadone in retention ($RR=0.79$; 95% CI: 0.64 - 0.99) and medium dose buprenorphine was inferior in suppression of heroin use. The authors concluded that buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but it is less effective than methadone delivered at adequate dosages.

Naltrexone

Naltrexone is a highly effective opioid antagonist that binds to mu-receptors. It has a higher affinity for mu receptors than has heroin, morphine, or methadone. It displaces those drugs from receptors and blocks their effects. As a result, it can precipitate withdrawal in patients who have not been abstinent from short-acting opioids for at least 7 days and have not been abstinent from long-acting ones, such as methadone, for at least 10 days.¹⁶ Naltrexone displaces buprenorphine to a lesser degree, but when used in higher doses, it overrides buprenorphine's activity as well. Naltrexone has no narcotic effects, there are no withdrawal symptoms when discontinued, nor does naltrexone have abuse potential. Naltrexone in all forms carries a black-

box warning for hepatotoxicity and warnings for use in patients with elevated hepatic enzymes and acute hepatitis. The FDA approved naltrexone in tablet form for maintenance treatment in 1984 based on its pharmacological effects without requiring evidence showing efficacy in the clinical trials. Despite of its potential advantages, it has little impact on the treatment of opioid dependence in the United States due to poor patient compliance.¹⁶ In 2010 an extended release once monthly intramuscular injection of naltrexone under the trade name Vivitrol® was approved by FDA to overcome the poor compliance.

The FDA approval was based on a randomized, controlled trial⁵ in Russia over 6 months and examined 3 medication groups: (1) 1000-mg naltrexone implant and oral placebo (NI+OP, n=102); (2) placebo implant and 50-mg oral naltrexone hydrochloride (PI+ON, n=102); or (3) placebo implant and oral placebo (PI+OP, n=102). The primary outcome was percentage of patients retained in treatment without relapse. By month 6, 54 (52.9%) in the NI+OP group compared with 16 (15.7%) in the PI+ON group (survival analysis, log-rank test, $P < .001$) and 11 (10.8%) in the PI+OP group ($P < 0.001$) remained in treatment without relapse. The PI+ON vs. PI+OP comparison showed a non-significant trend favoring the PI+ON group ($P = .07$). Counting missing test results as positive, the proportion of urine screening tests yielding negative results for opioids was 63.6% (95% CI, 60%-66%) for the NI+OP group; 42.7% (40%-45%) for the PI+ON group; and 34.1% (32%-37%) for the PI+OP group ($P < .001$, Fisher exact test, compared with the NI+OP group). The implant is more effective than oral naltrexone or placebo. More patients in the NI+OP than in the other groups develop wound infections or local irritation, but none are serious and all resolve with treatment.

A Cochrane review by Minozzi et al.⁴ included 13 randomized control trials, total 1158 participants, compared naltrexone versus placebo or no pharmacological treatments, no statistically significant difference were noted for all the primary outcomes considered. The only outcome statistically significant in favor of naltrexone is re-incarceration, RR 0.47 (95%CI 0.26-0.84), but results come only from two studies. Considering only studies were patients were forced to adhere to a statistical significant difference in favor of naltrexone was found for retention and abstinence, RR 2.93 (95%CI 1.66-5.18). Comparing naltrexone versus psychotherapy in the two considered outcomes, no statistically significant difference was found in the single study considered. Naltrexone was not superior to benzodiazepines and to buprenorphine for retention and abstinence and side effects. The findings of this review suggest that oral naltrexone did not perform better than treatment with placebo or no pharmacological agent with respect to the number of participants reincarcerated during the study period. If oral naltrexone is compared with other pharmacological treatments such as benzodiazepine and buprenorphine, no statistically significant difference was found. The percentage of people retained in treatment in the included studies is however low (28%). The authors concluded that the studies conducted have not allowed an adequate evaluation of oral naltrexone treatment in the field of opioid dependence. Consequently, maintenance therapy with naltrexone cannot yet be considered a treatment which has been scientifically proved to be superior to other kinds of treatment.

Management of Opioid Dependent in Adolescents

Unlike older adults, opioid dependence in adolescents and young adults present some unique characteristics, such as differences in routes of administration (i.e., intranasally and by smoking), which makes harder to detect some physical markers of opioid use (e.g., track marks); shorter abuse history and different attitudes towards addiction and the recovery process.¹⁵ In 2009 a Cochrane review by Minozzi et al. examined the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions on retaining adolescents in treatment, reducing the use of substances and reducing health and social status.⁷ There were two randomized and

controlled clinical trials met review inclusion criteria with total of 187 participants. One study (n=37) compared methadone with levo-alpha acetyl methadol (LAAM, manufacturer ceased production in 2004 in the U.S.) for maintenance treatment lasting 16 weeks after which patients were detoxified; the other (n=150) compared maintenance treatment with buprenorphine/naloxone with detoxification with buprenorphine. No meta-analysis was performed because the two studies assessed different comparisons. Self-reported opioid use at 1 year follow up was significantly lower in the maintenance group even if both groups reported high level of opioid use and more patients in the maintenance group were enrolled in other addiction treatment at 12 month follow up. It is difficult to draw conclusions about the use of maintenance pharmacological interventions from only two trials. The authors attributed the lack of evidence to the potential difficult of conducting trial with young people due to practical and ethical reasons.

Management of Opioid Dependence in Pregnancy

Treatment of opioid dependence in pregnancy is unique because of many challenges in the management of this patient population including the medical risks of illicit substance use in pregnancy, psychological comorbidity, and the psychosocial stressors that frequently interfere with prenatal treatment and addiction recovery.²⁵ In 1998, a National Institutes of Health consensus panel recommended methadone maintenance as the standard of care for pregnant women with opioid addiction.²⁶ Recently a review article by Park EM et. al. reviewed the management of the opioid dependent pregnant women and paid special focus on the use of buprenorphine.²⁷ The authors reviewed the efficacy and safety comparing buprenorphine and methadone during pregnancy and decreased severity of fetal withdrawal symptoms based on a double blind, double dummy, randomized controlled trial of 175 pregnant women in pregnancy through 28 days postpartum.⁶ The study results showed no differences between buprenorphine and methadone groups in maternal outcomes including caesarian sections rates, study discontinuation, anesthesia, and medical complications. However buprenorphine group resulted in a significant reduction in the severity of and duration of neonatal abstinence syndrome (NAS). The overall proportion of infants who developed NAS symptoms requiring opioid treatment was not significant different ($p = 0.26$) between two treatment groups. However, infants exposed to buprenorphine requiring 89% less morphine (1.1mg vs. 10.4mg) and spent an average 43% less time in the hospital (10.0 vs. 17.5 days).⁶ The authors acknowledged buprenorphine emerged as a new and effective alternative to methadone maintenance treatment

Treatment Guidelines:

In addition to robust and comprehensive treatment guidelines/protocols developed by the Substance Abuse and Mental Health Services Administration (SAMHSA), there are several other guidelines developed by several other agencies. CADTH published a review of major evidence based guideline recommendations with a special interest in the recommendations for treatment of opioid dependence in small clinic settings, rural area and remote communities.²⁸ There were five guidelines included in the review: 1) Canadian Centre for Addiction and Mental Health (CCMH), 2) US Department of Defense (DoD) and The Department of Veterans Affairs (VA), 3) British Association for Psychopharmacology, 4) World Health Organization (WHO), and 5) World Federation of Societies of Biological Psychiatry (WFSBP). All five guidelines provided recommendations for treatment of opioid dependence, 3 provided recommendations for the detoxification or treatment of opioid dependent pregnant women, none provided recommendations on the detoxification or treatment of opioid dependence in settings such as small clinics, rural, or remote areas, none of the guidelines provided specific recommendations for youth or people with co-occurring mental health issues. All guidelines were assessed for quality using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument. All five included guidelines were developed by professional association or expert committee based on systematic literature reviews. Some recommendations in VA/DOD guideline, BAP guideline, or WFSBP guideline were not directly accompanied with

supporting evidence and/or the strength of the recommendations. Most of the recommendations for pregnant women were based on low quality evidence or standard of care. One guideline was developed in Canada and provided recommendations for buprenorphine/naloxone treatment for opioid dependence, but not for overall treatment for opioid dependence. The key recommendations from five guidelines were:

- The patient should be assessed with DSM-IV-TR criteria and the patient should meet the diagnostic criteria for opioid dependence prior to initiating maintenance opioid agonist treatment.

- Methadone maintenance treatment was consistently recommended as a standard treatment for opioid dependence. Buprenorphine or buprenorphine/naloxone was also recommended as appropriate treatment, especially where the methadone uptake is limited by issues of access or patient disinterest. While use in rural areas was not specifically discussed in the cited literature, this may represent one setting with limited access to methadone where buprenorphine or buprenorphine/naloxone treatment may be preferred.
- Psychosocial intervention was recommended as a supportive treatment in conjunction with opioid agonist maintenance treatment.
- Ultra-rapid detoxification was not recommended.
- Oral naltrexone treatment was recommended for patients who are highly motivated to remain abstinent.
- Detoxification should be avoided during pregnancy, especially in the first trimester.
- Methadone or buprenorphine, but not buprenorphine/naloxone combination, maintenance therapy were recommended for pregnant women. However, it should be noted that most of the recommendations on treatment for pregnant opioid dependent women were based on low quality evidence or standard of care.

A recent released clinical practice guideline on the use of buprenorphine/naloxone for opioid dependence from AHRQ recommended the following²⁹:

- Once a patient is diagnosed with opioid dependence and is deemed appropriate for opioid agonist treatment, prescribers are encouraged to consider prescribing either buprenorphine/naloxone or methadone in order to increase retention in treatment and decrease opioid misuse. (**Level I, Grade A**)
- Buprenorphine/naloxone maintenance treatment can be prescribed to patients in either a primary care setting or in a specialized addiction treatment setting. (**Level I, Grade A**)
- Prior to initiating maintenance opioid agonist treatment the patient should meet the diagnostic criteria for opioid dependence. (**Level III, Grade A**)
- The decision to initiate opioid agonist therapy with either buprenorphine/naloxone or methadone maintenance should be guided by the individual clinical circumstances and the patient's preferences. (**Level III, Grade I**)
- A physician should have a structured approach, such as the one suggested in the clinical considerations (see section 3 of the original guideline document), to initiating buprenorphine/naloxone maintenance treatment in order to stabilize a patient at their maintenance dose as rapidly as possible while at the same time avoiding over sedation or precipitated withdrawal. (**Level III, Grade A**)
- Prior to initiation of buprenorphine/naloxone treatment, the patient must provide informed consent and there must be physician documentation that the patient has been informed of the physical dependence on the medication and possible long-term nature of the maintenance treatment. (**Level III, Grade A**)

- Once a stable maintenance dose is achieved, physicians can consider nondaily dosing of buprenorphine/naloxone as effective as daily dosing of buprenorphine/naloxone with respect to retention in treatment and reduction in illicit drug use. (**Level I, Grade A**)
- When monitoring a patient on buprenorphine/naloxone maintenance, the physician should adopt a patient-centred urine drug testing strategy that maximizes clinical utility while avoiding testing without indication. (**Level III, Grade I**)
- In making decisions regarding the provision of take-home doses of buprenorphine/naloxone, providers should use a clinical risk stratification strategy (as described in the clinical considerations) that aims to support patient autonomy while at the same time respecting patient and public safety. (**Level III, Grade A**)

Buprenorphine/naloxone may be preferred over methadone to treat opioid dependence in the following patient populations:

- When methadone is absolutely or relatively contraindicated, such as:
 - Presence of, history of or increased risk of prolonged QT interval (**Level I, Grade A**)
 - History of methadone allergy (**Level III, Grade A**)
 - History of significant side effects on methadone such as:
 - Sexual side effects on methadone (**Level II-2, Grade B**)
 - Severe sedation or constipation with methadone (**Level III, Grade C**)
 - Increased risk of toxicity from a full mu agonist:
 - If suspect a lower tolerance to opioids (**Level III, Grade B**)
 - If concurrent heavy or unstable use of sedating drugs/medication (**Level II-3, Grade B**)
 - If elderly (**Level III, Grade B**)
 - If significant respiratory illness (**Level III, Grade B**)

Methadone may be preferred over buprenorphine/naloxone in the following patient populations:

- Pregnancy (specifically avoiding the naloxone component in the buprenorphine/naloxone combination product) (**Level III, Grade A**)
- Clinical situations where opioid withdrawal during induction is particularly hazardous – i.e., cardiovascular instability (**Level III, Grade B**)
- Prior inability to stabilize on buprenorphine/naloxone maintenance treatment (**Level III, Grade B**)
- History of abusing buprenorphine/naloxone via injection (**Level III, Grade A**)
- Patient side effects with or allergy to buprenorphine/naloxone or to excipients including aceulfame (**Level III, Grade A**)
- Patients experiencing dry mouth of severity that would interfere with dissolution and absorption of sublingual buprenorphine/ naloxone tablets (dry mouth may be due to side effects of concurrent medications, chemotherapy, or conditions causing dry mouth, e.g., Sjögren's syndrome) (**Level III, Grade A**)
- Past history of successful stabilization with methadone (**Level III, Grade I**)
- Patient choice and access, in particular patients with limited financial resources that make reliable long-term use of buprenorphine/naloxone uncertain (**Level III, Grade B**)

References:

1. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2009. Available at: <http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD002203.pub2/abstract>. Accessed May 24, 2013.
2. Meader N. A comparison of methadone, buprenorphine and alpha2 adrenergic agonists for opioid detoxification: A mixed treatment comparison meta-analysis. *Drug Alcohol Depend*. 2010;108(1-2):110–114. doi:10.1016/j.drugalcdep.2009.12.008.
3. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2008. Available at: <http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD002207.pub3/abstract>. Accessed May 24, 2013.
4. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2011. Available at: <http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD001333.pub4/abstract>. Accessed May 24, 2013.
5. Moeller. Long-Acting Injectable Naltrexone for the Management of Patients with Opioid Dependence. *Subst Abuse Res Treat*. 2011:1. doi:10.4137/SART.S5452.
6. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. 2010;363(24):2320–2331. doi:10.1056/NEJMoa1005359.
7. Minozzi S, Amato L, Davoli M. Maintenance treatments for opiate dependent adolescent. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2009. Available at: <http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD007210.pub2/abstract>. Accessed May 24, 2013.
8. Praveen KT, Law F, O’Shea J, Melichar J. Clinical Evidence Handbook: Opioid Dependence - September 15, 2012 - American Family Physician. 2012. Available at: <http://www.aafp.org.liboff.ohsu.edu/afp/2012/0915/p565.html>. Accessed May 18, 2013.
9. Cicero TJ, Inciardi JA, Muñoz A. Trends in Abuse of OxyContin® and Other Opioid Analgesics in the United States: 2002-2004. *J Pain*. 2005;6(10):662–672. doi:10.1016/j.jpain.2005.05.004.
10. SAMHSA. Substance Abuse Treatment Admissions Involving Abuse of Pain Relievers: 1998 and 2008 |SAMHSA. 2010. Available at: <http://store.samhsa.gov/product/Substance-Abuse-Treatment-Admissions-Involving-Abuse-of-Pain-Relievers-1998-and-2008/TEDS10-0715>. Accessed May 24, 2013.

11. SAMHSA. The NSDUH Report: State Estimates of Nonmedical Use of Prescription Pain Relievers. 2013. Available at: <http://www.samhsa.gov/data/2k12/NSDUH115/sr115-nonmedical-use-pain-relievers.htm>. Accessed May 24, 2013.
12. Paulozzi LJ, Xi Y. Recent changes in drug poisoning mortality in the United States by urban–rural status and by drug type. *Pharmacoepidemiol Drug Saf*. 2008;17(10):997–1005. doi:10.1002/pds.1626.
13. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. Effective medical treatment of opiate addiction. *JAMA*. 1998;280(22):1936–1943. doi:10.1001/jama.280.22.1936.
14. Krambeer LL, von Mcknelly W Jr, Gabrielli WF Jr, Penick EC. Methadone therapy for opioid dependence. *Am Fam Physician*. 2001;63(12):2404–2410.
15. SAMHSA. TIP 43: Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs | SAMHSA. 2008. Available at: <http://store.samhsa.gov/product/TIP-43-Medication-Assisted-Treatment-for-Opioid-Addiction-in-Opioid-Treatment-Programs/SMA12-4214>. Accessed May 24, 2013.
16. O'Connor PG, Fiellin DA. Pharmacologic treatment of heroin-dependent patients. *Ann Intern Med*. 2000;133(1):40–54.
17. Krantz MJ. Heterogeneous impact of methadone on the QTc interval: what are the practical implications? *J Addict Dis*. 2008;27(4):5–9. doi:10.1080/10550880802324317.
18. Martell BA, Arnsten JH, Ray B, Gourevitch MN. The impact of methadone induction on cardiac conduction in opiate users. *Ann Intern Med*. 2003;139(2):154–155.
19. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther*. 1994;55(5):569–580.
20. Suboxone Film PI. SUBOXONE Film. Available at: http://www.suboxone.com/patients/about_suboxone/about_suboxone_film.aspx#15. Accessed June 1, 2013.
21. Rosenblum A, Cruciani RA, Strain EC, et al. Sublingual buprenorphine/naloxone for chronic pain in at-risk patients: development and pilot test of a clinical protocol. *J Opioid Manag*. 2012;8(6):369–382. doi:10.5055/jom.2012.0137.
22. Malinoff Herbert L, L BR, Wilson Geoffrey. Sublingual Buprenorphine Is Effective in the Treatment of Ch...□: American Journal of Therapeutics. *Am J Ther*. 2005. Available at: http://journals.lww.com/americantherapeutics/FullText/2005/09000/Sublingual_Buprenorphine_Is_Effective_in_the.2.aspx. Accessed June 26, 2013.

23. Johnson RE, Strain EC, Amass L. Buprenorphine: how to use it right. *Drug Alcohol Depend.* 2003;70(2, Supplement):S59–S77. doi:10.1016/S0376-8716(03)00060-7.
24. Fudala PJ, Bridge TP, Herbert S, et al. Office-Based Treatment of Opiate Addiction with a Sublingual-Tablet Formulation of Buprenorphine and Naloxone. *N Engl J Med.* 2003;349(10):949–958. doi:10.1056/NEJMoa022164.
25. Bell J, Harvey-Dodds L. Pregnancy and injecting drug use. *BMJ.* 2008;336(7656):1303–1305. doi:10.1136/bmj.39514.554375.AE.
26. Effective medical treatment of opiate addiction. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. *Jama J Am Med Assoc.* 1998;280(22):1936–1943.
27. Park EM, Meltzer-Brody S, Suzuki J. Evaluation and management of opioid dependence in pregnancy. *Psychosomatics.* 2012;53(5):424–432. doi:10.1016/j.psym.2012.04.003.
28. CADTH, Rapid Response: Treatment for Opioid Dependency: A Review of Guidelines. Available at: <http://www.cadth.ca/media/pdf/htis/sept-2012/RC0390%20Opioid%20Dependency%20Guidelines%20Final.pdf>. Accessed June 9, 2013.
29. Handford C, et al. National Guideline Clearinghouse | Buprenorphine/naloxone for opioid dependence: clinical practice guideline. 2011. Available at: <http://guideline.gov/content.aspx?f=rss&id=39351&osrc=12>. Accessed May 24, 2013.

Appendix 1: Buprenorphine Prior Authorization Criteria

Goal(s):

- Expand access to opioid addiction treatment
- Treatment of pain remains a priority, including e.g. addicts with injury & illness. Buprenorphine would need to be held during opioid treatment, esp. long-acting opioids. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction, TIP 40, available at <http://www.samhsa.gov> or <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat5>

Initiative: Asthma Controller PDL

Length of Authorization: up to 6 months; 2 months if MD prescribing for immediate need pending certification.

Requires PA:

- Non-preferred drugs

Brand	Generic	GCN
Suboxone	buprenorphine/naloxone	51640, 051641
Subutex	buprenorphine	029312, 029313

Covered alternatives: See PDL list at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria	
1. What is diagnosis being treated?	Document ICD-9:
2. Is diagnosis one of the following? 304.00 Opioid type dependence unspecified use 304.01 Opioid type dependence continuous use 304.70 Opioid type dependence continuous use unspecified use 304.71 Combinations of opioid type drug with other drug dependence continuous	<p>Yes: Go to 3.</p> <p>No: PASS TO RPH, Deny for medical appropriateness.</p>

3. Is prescriber a Physicians Assistant or Nurse Practitioner? (NPs & PAs may not prescribe.)	Yes: PASS TO RPH Deny for medical appropriateness.
4. Does prescribing physician have a Drug Addiction Treatment Act (DATA) - 2000 waiver ID number (also termed a special X-DEA license or certification)? OR Prescriber provides copy of SAMSHA certification request pending with "Immediate Need" checked? (Once MD meets criteria SAMHSA may take 45 days to process.) <i>Note: Physicians do not have to list their license on the SAMHSA Buprenorphine Physician Locator web site, which is publicly available. Pharmacists may call the Buprenorphine Information Center at 1-866-BUP-CSAT to verify unlisted or application under review prescribers.</i>	Yes: Document number or attach copy of SAMSHA request to PA record. Go to 5.
5. Does MD qualify for waiver from separate registration? a) Must have a valid DEA license AND b) board certified in addiction medicine OR c) employed by an opioid treatment program OR d) federally employed physicians (e.g. IHS or VA)	Yes: Go to 6. No: PASS TO RPH, Deny for medical appropriateness. Encourage physician to get training & register at SAMHSA http://buprenorphine.samhsa.gov/howto.html or FAX "Intent" form to 240-276-1630 at DEA.
Approval Criteria	Yes: PASS TO RPH. Deny for medical appropriateness.
6. Is patient concurrently on long-acting opioids (check claim record & inform prescriber of any current claims)? Examples of long-acting opioids include: methadone (e.g. Dolophine, Methadose) levodromoran long-acting morphine (e.g. MS Contin, Oramorph SR, Kadian, Avinza) long-acting oxycodone (e.g. OxyContin) fentanyl patches (e.g. Duragesic) Opana XR	NO: Go to 7. DO NOT GIVE methadone, or any long-acting opiate CONCURRENTLY with buprenorphine. If currently on methadone, reduce to stable state of 30 mg methadone equivalent (methadone 40 = buprenorphine 6mg), then wait 24 hours to initiate buprenorphine
7. Is patient concurrently on other opioids (check claim record and prescriber of any current claims in STC 40)?	Yes: Pass to RPH; Deny for medical appropriateness. No: Go to #8

	If MD can provide rationale for concurrent therapy document in PA and record and continue to #8.	
8. Is dose < 24mg/day (may average every other day therapy, ie. 48 mg qod)?	Yes: Go to #9	No: Pass to RPH; deny for medical appropriateness.
9. What is patients' pharmacy of choice? Document pharmacy name and NPI or address in PA record. Lock patient into their pharmacy of choice for 6 months. Use reason code: Suboxone	Inform prescriber patient will be locked to a single pharmacy for all prescriptions. Go to #10	
10. What is the expected length of treatment? Document treatment length in PA record.	a) If prescriber is waiting for SAMSHA certification subsequent approvals dependent on certification: Approve x 2 months. b) If prescriber is certified: Approve for anticipated length of treatment or 6 months, whichever is shorter.	

Appendix 2: Abstract of Selected Systemic Reviews and RTC Trial

1. **Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence**
Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD002209. DOI: 10.1002/14651858.CD002209.pub2.

Background: Methadone maintenance was the first widely used opioid replacement therapy to treat heroin dependence, and it remains the best-researched treatment for this problem. Despite the widespread use of methadone in maintenance treatment for opioid dependence in many countries, it is a controversial treatment whose effectiveness has been disputed.

Objectives: To evaluate the effects of methadone maintenance treatment (MMT) compared with treatments that did not involve opioid replacement therapy (i.e., detoxification, offer of drug-free rehabilitation, placebo medication, wait-list controls) for opioid dependence.

Search methods: We searched the following databases up to Dec 2008: the Cochrane Controlled Trials Register, EMBASE, PubMed, CINAHL, Current Contents, Psychlit, CORK [www.vt.su/adap/cork], Alcohol and Drug Council of Australia (ADCA) [www.adca.org.au], Australian Drug Foundation (ADF-VIC) [www.adf.org.au], Centre for Education and Information on Drugs and Alcohol (CEIDA) [www.ceida.net.au], Australian Bibliographic Network (ABN), and Library of Congress databases, available NIDA monographs and the College on Problems of Drug Dependence Inc. proceedings, the reference lists of all identified studies and published reviews; authors of identified RCTs were asked about other published or unpublished relevant RCTs.

Selection criteria: All randomised controlled clinical trials of methadone maintenance therapy compared with either placebo maintenance or other non-pharmacological therapy for the treatment of opioid dependence.

Data collection and analysis: Reviewers evaluated the papers separately and independently, rating methodological quality of sequence generation, concealment of allocation and bias. Data were extracted independently for meta-analysis and double-entered.

Main results: Eleven studies met the criteria for inclusion in this review, all were randomised clinical trials, two were double-blind. There were a total number of 1969 participants. The sequence generation was inadequate in one study, adequate in five studies and unclear in the remaining studies. The allocation of concealment was adequate in three studies and unclear in the remaining studies. Methadone appeared statistically significantly more effective than non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use as measured by self report and urine/hair analysis (6 RCTs, RR = 0.66 95% CI 0.56-0.78), but not statistically different in criminal activity (3 RCTs, RR=0.39; 95%CI : 0.12-1.25) or mortality (4 RCTs, RR=0.48, 95%CI: 0.10-2.39).

Authors' conclusions: Methadone is an effective maintenance therapy intervention for the treatment of heroin dependence as it retains patients in treatment and decreases heroin use better than treatments that do not utilise opioid replacement therapy. It does not show a statistically significant superior effect on criminal activity or mortality.

2. **Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone.**
Fidala PJ, Bridge TP, Herbert S, Williford WO, Collins J, Raisch D, Casadonte P, Goldsmith RJ, Ling W, Maltkerneker U, McNicholas L, Renner J, Stine S, Tusel D; Buprenorphine/Naloxone Collaborative Study Group. N Engl J Med. 2003 Sep 4;349(10):949-58.

BACKGROUND: Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone has been proposed, but its efficacy and safety have not been well studied.

METHODS: We conducted a multicenter, randomized, placebo-controlled trial involving 326 opiate-addicted persons who were assigned to office-based treatment with sublingual tablets consisting of buprenorphine (16 mg) in combination with naloxone (4 mg), buprenorphine alone (16 mg), or placebo given daily for four weeks. The primary outcome measures were the percentage of urine samples negative for opiates and the subjects' self-reported craving for opiates. Safety data were obtained on 461 opiate-addicted persons who participated in an open-label study of buprenorphine and naloxone (at daily doses of up to 24 mg and 6 mg, respectively) and another 11 persons who received this combination only during the trial.

RESULTS: The double-blind trial was terminated early because buprenorphine and naloxone in combination and buprenorphine alone were found to have greater efficacy than placebo. The proportion of urine samples that were negative for opiates was greater in the combined-treatment and buprenorphine groups (17.8 percent and 20.7 percent, respectively) than in the placebo group (5.8 percent, $P<0.001$ for both comparisons); the active-treatment groups also reported less opiate craving ($P<0.001$ for both comparisons with placebo). Rates of adverse events were similar in the active-treatment and placebo groups. During the open-label phase, the percentage of urine samples negative for opiates ranged from 35.2 percent to 67.4 percent. Results from the open-label follow-up study indicated that the combined treatment was safe and well tolerated.

CONCLUSIONS: Buprenorphine and naloxone in combination and buprenorphine alone are safe and reduce the use of opiates and the craving for opiates among opiate-addicted persons who receive these medications in an office-based setting.

3. **A comparison of methadone, buprenorphine and alpha(2) adrenergic agonists for opioid detoxification: a mixed treatment comparison meta-analysis.** [Review] [39 refs] Meader N. Drug & Alcohol Dependence. 108(1-2):110-4, 2010 Apr 1.

OBJECTIVES: The aim of this systematic review was to compare the efficacy of methadone, buprenorphine, clonidine and lofexidine for opioid detoxification. Mixed treatment comparison meta-analyses were used to synthesise the data as it is designed for data sets where limitations in standard pairwise meta-analyses make comparisons difficult to interpret.

DATA SOURCES: A systematic search was conducted using the following databases: CENTRAL, CINAHL, Embase, HMIC, Medline and PsycINFO.

REVIEW METHODS: RCTs that included opioid dependent participants over a mean age of 16 receiving opioid detoxification using buprenorphine, methadone, clonidine or lofexidine were included in the systematic review. Included studies were quality assessed and the completion of treatment data was extracted by the author and a research assistant independently. Mixed treatment comparison methods were used to synthesise the data.

RESULTS: There were 23 RCTs included in the systematic review (and 20 included in the meta-analysis) comprising a total of 2112 participants. Buprenorphine and methadone were ranked as the most effective methods of opioid detoxification followed by lofexidine and clonidine respectively.

CONCLUSION: Buprenorphine and methadone appear to be the most effective detoxification treatments. While the analysis suggests buprenorphine is the most effective method of detoxification there is some uncertainty on whether it is more effective than methadone and requires further research to confirm this result.

4. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence
Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD002207. DOI: 10.1002/14651858.CD002207.pub3.

Background: Buprenorphine has been reported as an alternative to methadone for maintenance treatment of opioid dependence, but differing results are reported concerning its relative effectiveness indicating the need for an integrative review.

Objectives: To evaluate the effects of buprenorphine maintenance against placebo and methadone maintenance in retaining patients in treatment and in suppressing illicit drug use.

Search methods: We searched the following databases up to October 2006:Cochrane Drugs and Alcohol Review Group Register, the Cochrane Controlled Trials Register, MEDLINE, EMBASE, Current Contents, Psychlit, CORK , Alcohol and Drug Council of Australia, Australian Drug Foundation, Centre for Education and Information on Drugs and Alcohol, Library of Congress databases, reference lists of identified studies and reviews, authors were asked about any other published or unpublished relevant RCT.

Selection criteria: Randomised clinical trials of buprenorphine maintenance versus placebo or methadone maintenance.

Data collection and analysis: Authors separately and independently evaluated the papers and extracted data for meta-analysis.

Main results: Twenty four studies met the inclusion criteria (4497 participants), all were randomised clinical trials, all but six were double-blind. The method of allocation concealment was not clearly described in the majority (20) of the studies, but where it was reported the methodological quality was good. Buprenorphine was statistically significantly superior to placebo medication in retention of patients in treatment at low doses ($RR=1.50$; 95% CI: 1.19 - 1.88), medium ($RR=1.74$; 95% CI: 1.06 - 2.87), and high doses ($RR=1.74$; 95% CI: 1.02 - 2.96). The high statistical heterogeneity prevented the calculation of a cumulative estimate. However, only medium and high dose buprenorphine suppressed heroin use significantly above placebo. Buprenorphine given in flexible doses was statistically significantly less effective than methadone in retaining patients in treatment ($RR=0.80$; 95% CI: 0.68 - 0.95), but no different in suppression of opioid use for those who remained in treatment. Low dose methadone is more likely to retain patients than low dose buprenorphine ($RR=0.67$; 95% CI: 0.52 - 0.87). Medium dose buprenorphine over medium dose methadone in retention ($RR=0.79$; 95% CI: 0.64 - 0.99) and medium dose buprenorphine was inferior in suppression of heroin use.

Authors' conclusions: Buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but it is less effective than

methadone delivered at adequate dosages.

5. Oral naltrexone maintenance treatment for opioid dependence

Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database of Systematic Reviews 2011, Issue 4. Art. No.: CD001333. DOI: 10.1002/14651858.CD001333.pub4.

Background: Research on clinical application of oral naltrexone agrees on several things. From a pharmacological perspective, naltrexone works. From an applied perspective, the medication compliance and the retention rates are poor.

Objectives: To evaluate the effects of naltrexone maintenance treatment versus placebo or other treatments in preventing relapse in opioid addicts after detoxification.

Search methods: We searched: Cochrane Central Register of Controlled Trials (CENTRAL - The Cochrane Library issue 6 2010), PubMed (1973-June 2010), CINAHL (1982- June 2010). We inspected reference lists of relevant articles and contacted pharmaceutical producers of naltrexone, authors and other Cochrane review groups.

Selection criteria: All randomised controlled clinical trials which focus on the use of naltrexone maintenance treatment versus placebo, or other treatments to reach sustained abstinence from opiate drugs

Data collection and analysis: Three reviewers independently assessed studies for inclusion and extracted data. One reviewer carried out the qualitative assessments of the methodology of eligible studies using validated checklists.

Main results: Thirteen studies, 1158 participants, met the criteria for inclusion in this review. Comparing naltrexone versus placebo or no pharmacological treatments, no statistically significant difference were noted for all the primary outcomes considered. The only outcome statistically significant in favour of naltrexone is re-incarceration, RR 0.47 (95%CI 0.26-0.84), but results come only from two studies. Considering only studies were patients were forced to adherence a statistical significant difference in favour of naltrexone was found for retention and abstinence, RR 2.93 (95%CI 1.66-5.18). Comparing naltrexone versus psychotherapy, in the two considered outcomes, no statistically significant difference was found in the single study considered. Naltrexone was not superior to benzodiazepines and to buprenorphine for retention and abstinence and side effects. Results come from single studies.

Authors' conclusions: The findings of this review suggest that oral naltrexone did not perform better than treatment with placebo or no pharmacological agent with respect to the number of participants re-incarcerated during the study period. If oral naltrexone is compared with other pharmacological treatments such as benzodiazepine and buprenorphine, no statistically significant difference was found. The percentage of people retained in treatment in the included studies is however low (28%). The conclusion of this review is that the studies conducted have not allowed an adequate evaluation of oral naltrexone treatment in the field of opioid dependence. Consequently, maintenance therapy with naltrexone cannot yet be considered a treatment which has been scientifically proved to be superior to other kinds of treatment.

6. Maintenance treatments for opiate dependent adolescent
Minozzi S, Amato L, Davoli M. Maintenance treatments for opiate dependent adolescent. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD007210. DOI: 10.1002/14651858.CD007210.pub2. Editorial Group: Cochrane Drugs and Alcohol Group

Background: The scientific literature examining effective treatments for opioid dependent adults clearly indicates that pharmacotherapy is a necessary and acceptable component of effective treatments for opioid dependence. Nevertheless no studies have been published which systematically assess the effectiveness of the pharmacological maintenance treatment among adolescent.

Objectives: To assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions on retaining adolescents in treatment, reducing the use of substances and reducing health and social status.

Search methods: We searched the Cochrane Drugs and Alcohol Group's trials register (august 2008), MEDLINE (January 1966 to august 2008), EMBASE (January 1980 to august 2008), CINHAL (January 1982 to august 2008) and reference lists of articles.

Selection criteria: Randomised and controlled clinical trials comparing any maintenance pharmacological interventions alone or associated with psychosocial intervention with no intervention, placebo, other pharmacological intervention included pharmacological detoxification or psychosocial intervention in adolescent (13-18 years).

Data collection and analysis: Two reviewers independently assessed trial quality and extracted data.

Main results: Two trials involving 187 participants were included. One study compared methadone with LAAM for maintenance treatment lasting 16 weeks after which patients were detoxified, the other compared maintenance treatment with buprenorphine - naloxone with detoxification with buprenorphine. No meta-analysis has been performed because the two studies assessed different comparisons. Maintenance treatment seems more efficacious in retaining patients in treatment but not in reducing patients with positive urine at the end of the study. Self reported opioid use at 1 year follow up was significantly lower in the maintenance group even if both group reported high level of opioid use and more patients in the maintenance group were enrolled in other addiction treatment at 12 month follow up.

Authors' conclusions: It is difficult to draft conclusions on the basis of only two trials. One of the possible reason for the lack of evidence could be the difficulty to conduct trial with young people due to practical and ethic reasons.

7. **Neonatal abstinence syndrome after methadone or buprenorphine exposure.**
Jones HE, Kaltenbach K, Heit SH, Stine SM, Coyle MG, Arria AM, O'Grady KE, Selby P, Martin PR, Fischer G. N Engl J Med. 2010 Dec 9;363(24):2320-31. doi: 10.1056/NEJMoa1005359.

Background: Methadone, a full mu-opioid agonist, is the recommended treatment for opioid dependence during pregnancy. However, prenatal exposure to methadone is associated with a neonatal abstinence syndrome (NAS) characterized by central nervous system hyperirritability and autonomic nervous system dysfunction, which often requires medication and extended hospitalization. Buprenorphine, a partial mu-opioid agonist, is an alternative treatment for opioid dependence but has not been extensively studied in pregnancy.

Methods: We conducted a double-blind, double-dummy, flexible-dosing, randomized, controlled study in which buprenorphine and methadone were compared for use in the comprehensive care of 175 pregnant women with opioid dependency at eight international sites. Primary outcomes were the number of neonates requiring treatment for NAS, the peak NAS score, the total amount of morphine needed to treat NAS, the length of the hospital stay for neonates, and neonatal head circumference.

Results: Treatment was discontinued by 16 of the 89 women in the methadone group (18%) and 28 of the 86 women in the buprenorphine group (33%). A comparison of the 131 neonates whose mothers were followed to the end of pregnancy according to treatment group (with 58 exposed to buprenorphine and 73 exposed to methadone) showed that the former group required significantly less morphine (mean dose, 1.1 mg vs. 10.4 mg; $P < 0.0091$), had a significantly shorter hospital stay (10.0 days vs. 17.5 days, $P < 0.0091$), and had a significantly shorter duration of treatment for the neonatal abstinence syndrome (4.1 days vs. 9.9 days, $P < 0.003125$) (P values calculated in accordance with pre-specified thresholds for significance). There were no significant differences between groups in other primary or secondary outcomes or in the rates of maternal or neonatal adverse events.

Conclusions: These results are consistent with the use of buprenorphine as an acceptable treatment for opioid dependence in pregnant women. (Funded by the National Institute on Drug Abuse; ClinicalTrials.gov number, NCT00271219.).



© Copyright 2012 Oregon State University. All Rights Reserved

Oregon State Drug Use Research & Management Program

Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079

College of Pharmacy Phone 503-947-5220 | Fax 503-947-1119



Abbreviated Class Update: Long-Acting Opioids (LAOs)

Month/year of Review: July 2013

New drug(s): morphine/naltrexone (Embeda™) August 2009
 hydromorphone (Exalgo™) March 1, 2010
 buprenorphine (Butrans™) June 30, 2010
 tapentadol (Nucynta ER™) August 25, 2011
 oxymorphone (Opana ER) new formulation December 9, 2011

End date of literature search: May 2013

Manufacturer:
 Alpharma King
 Mallinckrodt, Inc.
 Purdue Pharma LP
 Janssen
 Endo Pharma

Oregon PDL status	Drug	Trade name(s)	Forms evaluated in review	Recommended usual dosing frequency (times per day)
N	buprenorphine	Butrans™	ER transdermal film	Every 7 days
Y	fentanyl	Duragesic™	ER transdermal film	Every 72 hours
N	hydromorphone	Exalgo™	ER oral tablet	1
N	levorphanol	Generic	Oral tablet	3-4
Y	methadone	Generic, Dolophine™	Oral tablet	2-3
N	morphine sulfate	Generic Avinza™ Kadian™ Generic Generic MS Contin™ Oramorph SR™ *	ER oral capsule ER oral capsule ER oral capsule ER oral capsule ER oral tablet ER oral tablet	1 1-2 1-2 1-2 2-3 2-3
Y				
Y				
Y				
N	morphine sulfate and naltrexone hydrochloride	Embeda™	ER oral capsule	1-2
N	oxycodone	OxyContin™	ER oral tablet	2
N	oxymorphone	Opana ER™	ER oral tablet	2
N	tapentadol	Nucynta ER™	ER oral tablet	2

Abbreviations: ER, extended release; MS, morphine sulfate; SR, sustained release.

*Discontinued

Additionally, there is a maximum dose prior authorization (PA) required for doses greater than 100 morphine equivalent doses (MED) on all LAOs. Duplication of LAOs is not allowed except for cross-titration. Methadone carries an additional PA for initial doses above 20mg per day when prescribed for pain. Methadone for addiction treatment is also covered via professional claims.

Research Questions:

- Is there any new evidence about comparative effectiveness of different long-acting opioids, in reducing pain and improving functional outcomes in adult patients being treated for chronic non-cancer pain?
- Is there any new evidence about comparative harms (including addiction and abuse) of different long-acting opioids in adult patients being treated for chronic non-cancer pain?
- Are there subpopulations of patients (specifically by race, age, sex, socioeconomic status type of pain, or comorbidities) with chronic non-cancer pain for which one long-acting opioid is more effective or associated with less harm?

Conclusions:

- There continues to be insufficient comparative evidence to establish differences in effectiveness among the LAOs. Morphine and fentanyl have the most evidence of efficacy against placebo per DynaMed. Treatment guidelines consistently recommend morphine as first-line with fentanyl patches recommended for patients who cannot tolerate oral medications.
- There continues to be insufficient comparative evidence to establish differences in safety among the LAOs. All LAOs carry FDA Black Box warnings for increased risk of death and risk of abuse and misuse. However, methadone alone carries the warning of accumulation and was associated with more than 30% of opioid related deaths in Oregon.
- There is insufficient comparative evidence in subpopulations to differentiate drugs.

Recommendations:

- Remove methadone from preferred status due to safety concerns.
- A form of morphine ER should remain a preferred option and relative cost of the different formulations evaluated in executive session to determine preference.
- All other drugs should be evaluated in executive session for relative cost.

Reason for Review: Oregon has not reviewed the literature in this class since 2006. Since then, the Drug Effectiveness Review Project (DERP) completed Update #6 (July 2011 with searches through January 2011)¹ and a recent literature scan for new information (searches through April 2013).² Additionally, the FDA published the Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS)³ in response to a CDC report⁴ of increasing deaths associated with all prescription opioids. Finally, Oregon Health Authority executives requested the committee specifically evaluate the safety of methadone in light of the 2012 Oregon Medical Examiner report.⁵

Previous HRC Conclusions (2006):

- There is insufficient evidence to draw any conclusions about the comparative efficacy of long-acting opioids.
- There is insufficient evidence to draw conclusions about incidence and nature of adverse effects, including discontinuation rates and addiction and abuse of long-acting opioids
- There is insufficient evidence to support differences in efficacy or adverse effects in sub-populations by race and ethnicity, age, gender, or type of pain in this class of drugs.
- Even though evidence does not demonstrate a difference between long-acting opioids or between long-acting opioids when compared to other drugs, limitations of studies currently available for review preclude a confident conclusion that no differences exist. It is possible that better controlled studies may yet demonstrate such differences.

Background: Long-acting opioids are indicated for moderate to severe chronic (at least 3 to 6 months) pain, which impairs function or quality of life, where the benefits outweigh risks and no alternative has a better risk/benefit profile. Opioids have been endorsed by the American Pain Society/American Academy of Pain Medicine,⁶ the Canadian Pain Society^{7,8} and others,^{9,10,11} as appropriate treatment for refractory chronic non-cancer pain, in the general population and in older patients, when used judiciously and according to guidelines. The World Health Organization's (WHO) "analgesic ladder,"¹² originally published in the mid-1980s, outlines an approach to pain control that has widely influenced cancer pain management and subsequently many of the strategies used in nonmalignant pain.¹³

Previous DERP reports^{14,15} have established there was insufficient evidence to distinguish differences in effectiveness or harms between LAOs when used to treat adult nonmalignant pain. In the absence of sufficient evidence, Oregon Health Plan preference has been established with cost. Several new drugs have been approved [i.e. morphine/naltrexone (Embeda™), hydromorphone (Exalgo™), buprenorphine (Butrans™), tapentadol (Nucynta ER™) and a new formulation of oxymorphone (Opana ER)].

In July 2012, the Centers for Disease Control published a report⁴ of the Drug Abuse Warning Network 2011 data¹⁶ indicating, that despite a reduction since 2007, methadone used for pain relief was associated with 31.4% of opioid pain reliever deaths and almost 40% of single-drug

Abbreviated Class Update: Long-Acting Opioids (LAOs)

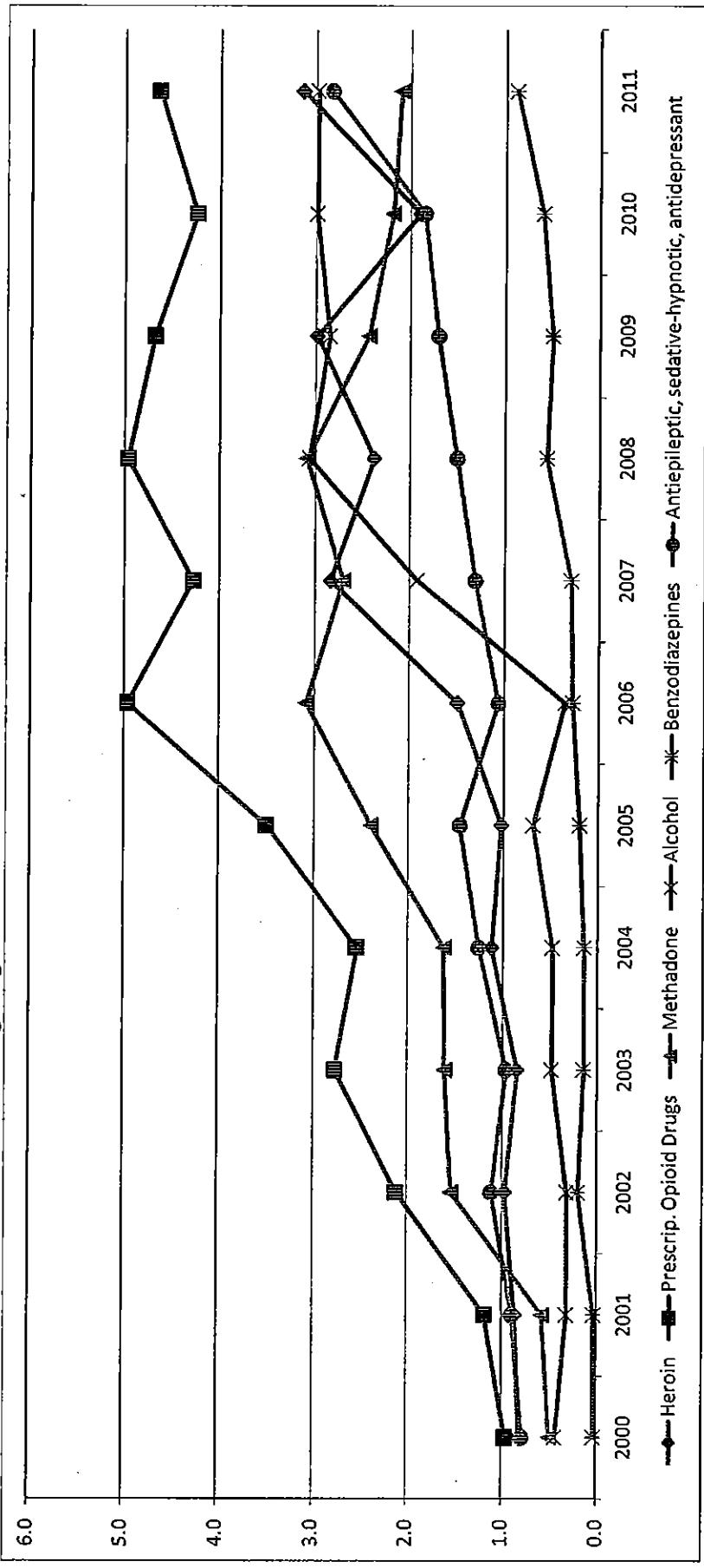
opioid pain reliever deaths in 2010. The overdose death rate for methadone was significantly higher than any other opioid. CDC recommended, “*For chronic non-cancer pain, methadone should not be considered a drug of first choice by prescribers or insurers.*”¹⁴ This report and its recommendation have been widely reported in the lay press.^{17,18,19} Unintentional drug poisonings were the fourth highest cause of death (9.4 per 100,000) in Oregon in 2007 (motor vehicle deaths were second at 12.1 per 100,000).²⁰ Prescription opioids represented 53% of all deaths due to poisoning by drugs in 2008 and methadone led all opioids.²⁰ The most recent Oregon Medical Examiner’s Report⁵ confirms a recent downward trend from a peak in 2007 for methadone deaths, decreasing 20% from 100 in 2011 to 78 in 2012. This decrease was attributed to the implementation of the 2010 Prescription Drug Monitoring Program (PDMP) in Oregon.⁵ Despite the PDMP, oxycodone-related deaths rose from 56 in 2011 to 66 in 2012. The PDMP data in Figure 1 was presented at the National Governor’s Association (NGA) Prescription Drug Misuse and Abuse Workgroup meeting in December 2012.²¹ Methadone was linked to 30% of drug overdose deaths in Oregon and Medicaid was over-represented in the data generally.²¹ However, the issue appears complex: 30% of patients did not have an opioid prescription; misuse or abuse contributed to 77% of deaths and 52% of patients had a history of mental illness.²¹

The FDA responded to the CDC report by publishing their efforts to “Address the Misuse and Abuse of Opioids.”²² It is a multi-pronged approach ranging from the encouragement of abuse-deterring formulations (e.g. OxyContin²³) to implementing a REMS³ program for *all* LAOs (notably not singling out methadone). The REMS program requires all manufacturers of LAOs to ensure that training is made available to prescribers of LAOs and that patient medication guides are dispensed with all prescriptions. All of the LAOs carry at least one FDA Black Box warning of high potency and risk of respiratory depression, risk of misuse and abuse, cautions about appropriate patient selection, cautions against crushing or mixing with alcohol or accumulation.

Abbreviated Class Update: Long-Acting Opioids (LAOs)

Figure 1: Overdose death rate by drug type per 100,000 in Oregon 2000-2011²¹

Note: a person can have more than 1 contributing drug related to their death



Methods:

A Medline literature search ending May 2013 for new systematic reviews and randomized controlled trials (RCT's) that compared long-acting opioids in head to head trials was done. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and 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 for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, three recent systematic reviews^{1,24,25} comparing opioid treatments, three updated chronic pain treatment guidelines^{7,8,9,10} and three RCTs comparing tapentadol ER to oxycodone ER were included in this review.

Systematic Reviews:

The 2011 DERP Report¹ identified 10 head-to-head trials comparing two or more LAOs but still concluded the evidence was insufficient to determine if there are differences in effectiveness or harms among the drugs. Eight trials found no significant difference in pain relief or function. The two that found a significant difference were rate poor quality. The authors noted the included studies were relatively small, short and had important methodological flaws. Tapentadol ER was not included in the literature searches.

The DynaMed²⁴ review notes that not only is the comparative evidence lacking for this class but, that evidence of efficacy of the individual opioids is weak overall, with the best evidence for morphine ER tablets and transdermal fentanyl. It cites Level 2 (moderate) evidence that morphine ER (Avinza™) may be more effective than oxycodone ER (OxyContin™) in enabling patients with low back pain to return to work (n=266).²⁴ No comparative evidence of harms is presented outside the FDA labeling for each drug. However, three citations that associate the risk of death to increased opioid doses and that were previously reviewed by the Oregon DUR Board when considering the current LAO high dose limits are provided.^{26,27,28}

Cochrane evaluated the use of methadone for chronic non-malignant pain and concluded that three studies (n=181) provided very limited evidence of efficacy.²⁵ No conclusions could be drawn on the differences in efficacy or safety between methadone and placebo or other opioids (i.e. morphine, oxycodone or transdermal fentanyl).²⁵

New Guidelines:

The National Institute of Clinical Excellence published guidance on the use of strong opioids for pain in palliative care in 2012.¹⁰ Morphine ER is recommended first-line unless the oral route is not viable, then fentanyl patches are recommended. The recommendations are based upon low-quality evidence from RCTs and expert opinion. The guideline does not cover all aspects of pain management, including second-line approaches.

The Canadian guidelines^{7,8} for chronic nonmalignant pain were updated and published in 2011. The guidelines include recommendations on opioid indications, selection, titration, precautions and monitoring. Only selection recommendations are reported here. After a failed trial of either codeine or tramadol, morphine is recommended for patients without renal impairment. Oxycodone or hydromorphone are not recommended for patients at higher risk of opioid misuse or addiction. Methadone is only available to prescribers with a written Health Canada exemption because it is considered hazardous due to its bioaccumulation. Fentanyl is recommended only for patients already stabilized on 60-90 mg of MED for two weeks. Doses about 200mg MED of any opioid are not recommended.

The United States Veterans Administration and Department of Defense published guidelines on opioid therapy for chronic pain in 2010.⁹ Drug selection recommendations are reported from this very comprehensive document. The authors report there is no evidence to recommend any specific opioid but recommend to base drug selection in a shared-decision making model to match the individual's needs and specific medical conditions. However, both fentanyl (not in opioid naïve patients) and methadone (arrhythmia risk) receive cautionary statements. Morphine ER is recommended as first-line, oxycodone ER is recommended second-line. The guidelines include a summary table of the evidence for opioids in special populations which is reproduced in Appendix 1.

Randomized Controlled Trials: Three trials^{29,30,31} evaluating tapentadol ER were identified. Two were 12-week non-inferiority trials versus oxycodone ER in osteoarthritis²⁹ and low back pain³⁰ and the third was safety and tolerability study for up to one year.³¹ However, only 52% took a study medication for 6 months. Evidence from these trials is insufficient to indicate tapentadol is more effective or safer than other LAOs. A summary is in Table 1 below and the abstracts are in Appendix 2.

Table 1: Potentially relevant comparative trials

Study	Comparison	Population	Primary Outcome	Results
Afifalo 2010 RCT	tapentadol ER 100-250mg BID vs. oxycodone ER 20-50mg BID vs. placebo	Osteoarthritis	Change from baseline on average daily pain intensity on 11-pt numerical scale at 12- weeks or last observation carried forward.	n=1023 (loss to f/u n=7) T vs. P least square means = -0.7[-1.04, 0.33] O vs. P least square means = -0.3 [-0.68, 0.02]
DB				

Abbreviated Class Update: Long-Acting Opioids (LAOs)

Buynak 2010 RCT 1:1:1	tapentadol ER 100-250mg BID vs. oxycodone ER 20-50mg BID vs. placebo	Low back pain average daily pain intensity on 11-pt numerical scale at 12- weeks or last observation carried forward.	Change from baseline on average daily pain intensity on 11-pt numerical scale at 12- weeks or last observation carried forward.	n=981 T vs. P least square means = -0.8 [-1.22, - 0.47] O vs. P least square means = -0.9 [-1.24, - 0.49]
Wild 2010 RCT 4:1	tapentadol ER 100-250mg BID vs. oxycodone ER 20-50mg BID vs. placebo	Osteoarthritis or low back pain	Safety and tolerability assessments for up to 1 year.	N=1121 (loss to f/up n=4) Withdrawal for ADE: T: 203 (22.7%) O: 82 (36.8%)

New Safety Alerts, Indications:

July 2012: FDA approved a risk evaluation and mitigation strategy (REMS)³ for extended-release and long-acting opioid medications. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS. This REMS will use a single, shared system for the elements to ensure safe use and the REMS assessments. This single shared system is known as the ER/LA Opioid REMS.

The updated labels include information on ER/LA prescription opioid analgesics abuse potential, the risk of life-threatening respiratory depression, and consumer-friendly information on the safe use and disposal of ER/LA opioid analgesics.

References:

- Carson S. *Long-acting Opioid Analgesics: Final Update 6 Report*. Oregon Health & Science University; 2011.
- Carson S, Low A, Smith B, Chou R. Drug Class Review Long-Acting Opioid Analgesics. *Update*. 2008. Available at: http://derp.ohsu.edu/final/Opioids_final_report_update%2006_Jul_11.pdf. Accessed June 19, 2013.
- Food and Drug Administration Center for Drug Evaluation and Research. EXTENDED-RELEASE (ER) AND LONG-ACTING (LA) OPIOID ANALGESICS RISK EVALUATION AND MITIGATION STRATEGY (REMS). <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm315112.htm>. 2012. Available at: <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf>. Accessed June 17, 2013.

Abbreviated Class Update: Long-Acting Opioids (LAOs)

4. Morbidity and Mortality Weekly Report. Vital Signs: Risk for Overdose from Methadone Used for Pain Relief — United States, 1999–2010. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6126a5.htm?s_cid=mm6126a5_w. 2012. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6126a5.htm?s_cid=mm6126a5_w. Accessed June 17, 2013.
5. Gunson K. Oregon State Police News Releases Oregon State Medical Examiner Releases 2012 Drug-Related Death Statistics. 2013. Available at: http://www.oregon.gov/osp/NEWSR/_Pages/news/06_04_2013_2012_drug_deaths_ME.aspx. Accessed June 17, 2013.
6. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113–130. doi:10.1016/j.jpain.2008.10.008.
7. Kahan M, Mailis-Gagnon A, Wilson L, Srivastava A, National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 1: general population. *Can Fam Physician*. 2011;57(11):1257–1266, e407–418.
8. Kahan M, Wilson L, Mailis-Gagnon A, Srivastava A, National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 2: special populations. *Can Fam Physician*. 2011;57(11):1269–1276, e419–428.
9. The Management of Opioid Therapy for Chronic Pain Working Group. Management of Opioid Therapy for Chronic Pain. US Department of Veterans Affairs: Department of Defense. 2010. Available at: http://www.healthquality.va.gov/cot/cot_310_full.pdf. Accessed June 19, 2013.
10. Bennett MI, Graham J, Schmidt-Hansen M, Prettyjohns M, Arnold S, Guideline Development Group. Prescribing strong opioids for pain in adult palliative care: summary of NICE guidance. *BMJ*. 2012;344:e2806.
11. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the Management of Chronic Severe Pain in the Elderly: Consensus Statement of an International Expert Panel with Focus on the Six Clinically Most Often Used World Health Organization step III Opioids (Buprenorphine, Fentanyl, Hydromorphone, Methadone, Morphine, Oxycodone). *Pain Practice*. 2008;8(4):287–313. doi:10.1111/j.1533-2500.2008.00204.x.
12. World Health Organization. WHO | WHO's pain ladder for adults. WHO. Available at: <http://www.who.int/cancer/palliative/painladder/en/index.html>. Accessed June 19, 2013.

Abbreviated Class Update: Long-Acting Opioids (LAOs)

13. Bajwa ZH, Smith HS. Overview of the treatment of chronic pain. *UpToDate*. 2012. Available at: http://www-upToDate.com.liboff.ohsu.edu/contents/overview-of-the-treatment-of-chronic-pain?source=search_result&search=chronic+pain+management&selectedTitle=1%7E150. Accessed June 17, 2013.
14. Chou R. Drug Class Review on Long-Acting Opioid Analgesics. 2006. Available at: http://derp.ohsu.edu/final/nsaids_final_report_update%2034.pdf. Accessed June 20, 2013.
15. Chou R, Carson S. Drug class review on long-acting opioid analgesics. 2008. Available at: http://derp.ohsu.edu/final/op_final_report_update%205.pdf. Accessed June 20, 2013.
16. Substance Abuse and Mental Health Services Administration. Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits. *US DEPARTMENT OF HEALTH AND HUMAN SERVICES*. 2013. Available at: <http://www.samhsa.gov/data/2k13/DAWN2k11ED/DAWN2k11ED.htm>. Accessed June 17, 2013.
17. Bakalar N. Many Fatal Overdoses Linked to Methadone - NYTimes.com. *NY Times*. 2012. Available at: <http://well.blogs.nytimes.com/2012/07/09/many-fatal-overdoses-linked-to-methadone/>. Accessed June 17, 2013.
18. Methadone Causes 30% Of Painkiller Overdose Deaths. 2012. Available at: <http://www.medicalnewstoday.com/articles/247398.php>. Accessed June 17, 2013.
19. Cuti J. Methadone Realities · Think Out Loud. *Oregon Public Broadcasting*. 2011. Available at: <http://www.opb.org/thinkoutloud/shows/methadone-realities/>. Accessed June 17, 2013.
20. Public Health Division. Oregon Injury Prevention Plan 2011-2015. *Oregon Health Authority*. 2010. Available at: <http://public.health.oregon.gov/diseasesconditions/injuryfatalitydata/documents/oregoninjurypreventionplan.pdf>. Accessed June 17, 2013.
21. Millet L. Prescription Opioid Overdose and Misuse in Oregon.pptx. 2012.
22. Research C for DE and. Information by Drug Class - FDA's Efforts to Address the Misuse and Abuse of Opioids. Available at: <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337852.htm>. Accessed June 19, 2013.

23. Press Announcements - FDA approves abuse-deterrent labeling for reformulated OxyContin. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm348252.htm>. Accessed June 19, 2013.
24. DynaMed. DynaMed: Opioids for chronic pain. *DynaMed*. 2013. Available at: <http://web.ebscohost.com.liboff.ohsu.edu/dynamed/detail?vid=3&sid=66448eff-e5db-4c50-ab49-3cc13d4f51d7%40sessionmgr113&hid=113&bdata=JnNpdGU9ZHIuYW1lZC1saXZJnNjb3BIPXNpdGU%3d#db=dme&AN=361112>. Accessed June 17, 2013.
25. Haroutunian S, McNicol ED, Lipman AG. Methadone for chronic non-cancer pain in adults. In: The Cochrane Collaboration, McNicol ED, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: <http://doi.wiley.com/10.1002/14651858.CD0008025.pub2>. Accessed June 17, 2013.
26. Bohner ASB, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011;305(13):1315–1321. doi:10.1001/jama.2011.370.
27. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*. 2011;171(7):686–691. doi:10.1001/archinternmed.2011.117.
28. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*. 2010;152(2):85–92. doi:10.1059/0003-4819-152-2-201001190-00006.
29. Afilalo M, Etropolski M, Kuperwasser B, et al. Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clinical Drug Investigation*. 2010;30(8):489–505. doi:<http://dx.doi.org/10.2165/11533440-00000000-00000>.
30. Buynak R, Shapiro D, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. [Erratum appears in Expert Opin Pharmacother. 2010 Nov;11(16):2773]. *Expert Opinion on Pharmacotherapy*. 2010;11(11):1787–804. doi:<http://dx.doi.org/10.1517/14656566.2010.497720>.
31. Wild J, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. *Pain Practice*. 2010;10(5):416–27. doi:<http://dx.doi.org/10.1111/j.1533-2500.2010.00397.x>.

Abbreviated Class Update: Long-Acting Opioids (LACs)

Appendix 1:9

Table 3: Use of Opioids for Chronic Pain in Special Populations

Medication	Standard Category	Recreational Use		Healthcare Use		Based on Addiction	Based on Dependence	Side effects	Effectiveness
		C ^a	C ^b	B ^c	B ^c				
Codine (#)		C ^a	* ^d	*	*	*	*	*	
Fentanyl transdermal	+	+	+	C ^a	UC (C)	* and ↓	*	*	
Hydrocodone		C ^a	PC			*	*		
Hydromorphone (OS, R)	+ (ES)	B ^c	PC	* and ↓		*	(ND)		? less effective
Methadone (E)	+ (OS)	B ^c	PC	* and ↓		*			
Morphine (OS, ES)	+ (ES)	C ^a	PC			*			
Morphine SR/CR (S-1a); ER (C-4b)									
Oxycodone (OS)	+ (OS)	B ^c	PC			*	or *	(ND)	
Oxycodone CR (12h)						*	and ↓	*	? less effective
Oxyimphene		B ^c	PC	*	*	*	(ND)		
Oxyimphene ER (12h)		C ^a	PC	*	*	*	(ND)		
Propoxyphene		C ^a	*	*	*	*	*	*	
Triparanol		C ^a	*	*	*	*	*	*	
Tramadol		C ^a	PC	* and ↓	* and ↓	*	(ND)	*	? and ↓
Tramadol ER (C-4b)						*	(ND)	*	? less effective

Abbreviated Class Update: Long-Acting Opioids (LAOs)

- (a) Estimates of risk of opioid therapy in pregnancy and while breastfeeding may be based on expectations of maintenance or short-term use.
- (b) Use of chronic opioid therapy during pregnancy or while breastfeeding should be approached with caution.
- (c) Codeine is metabolized to morphine by CYP 2D6; both pass into breast milk in small amounts usually considered clinically insignificant; however, caution in known or suspected ultra-rapid metabolizers of CYP 2D6 substrates. 2006 case report of death in a nursing infant of CYP 2D6 ultra-rapid metabolizer mother associated with high morphine levels in breast milk [Karen et al., 2006].
- (d) Manufacturer does not recommend use while breast-feeding. Classified as contraindicated by the American Academy of Pediatrics.
- (e) Fentanyl citrate available as transmucosal lozenges, buccal tablets.
- (f) Methadone is the only long-acting opioid available as an oral solution. See Appendix E, Tables E1 and E2 and Appendix F Methadone Dosing Recommendations for Treatment of Chronic Pain for further details and references.
- (g) Dosing Recommendations for Treatment of Chronic Pain for further details and references.
- (h) Product information.

CR = Controlled release
 OS = Oral solution
 RS = Rectal suppository
 SR = Sustained release
 TDS = Transdermal system
 RBD = Removed by dialysis
 ND = No data

♦ = Recommended
 ♦ = Use with caution
 ↓ = Reduce dose
 ✕ = Not recommended
 ? less effective = counteraction to the active metabolite may be decreased.
 Impact on analgesic efficacy unknown.

PREGNANCY Risk Categories
 A = controlled studies show no risk
 B = no evidence of risk in humans
 C = Risk cannot be ruled out, but potential benefits may justify potential risk
 D = Positive evidence of risk; however, potential benefits may outweigh potential risk

X = Contraindicated in pregnancy.
 *Human data suggest risk in 3rd trimester [Briggs et al., 2008]
 ? Human data suggest risk in 3rd trimester [Briggs et al., 2008]
 Risk category D if prolonged gestation or high doses at term [Briggs et al., 2008]

लूप अन्तर्वार्षिक खोजक्रम
 UC = usually compatible; either not expected into human breast milk in clinically significant amounts or not expected to cause toxicity in infants
 NC = probably compatible; no or limited human data
 ♦ = potential toxicity, no or limited human data
 ✕ = not recommended due to potential toxicity, no or limited human data
 CT = contraindicated; potential for severe toxicity based on animal and/or human data

Appendix 2: Abstracts of potentially relevant randomized controlled trials and/or systematic reviews

Authors : Afilalo M, Etropolski MS, Kuperwasser B, Kelly K, Okamoto A, Van Hove I, Steup A, Lange B, Rauschkolb C, Haeussler J.
Title: Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study.
Source: Clinical Drug Investigation. 30(8):489-505, 2010.

BACKGROUND: Tapentadol is a novel, centrally acting analgesic with mu-opioid receptor agonist and norepinephrine reuptake inhibitor activity.

OBJECTIVE: to evaluate the efficacy and safety of Tapentadol extended release (ER) compared with oxycodone controlled release (CR) for management of moderate to severe chronic osteoarthritis-related knee pain.

METHODS: this was a randomized, double-blind, active- and placebo-controlled, parallel-arm, multicentre, phase III study during which patients received Tapentadol ER, oxycodone CR or placebo for a 3-week titration period followed by a 12-week maintenance period. The study was carried out at sites in Australia, Canada, New Zealand and the US. A total of 1030 patients with chronic osteoarthritis-related knee pain were randomized to receive Tapentadol ER 100-250 mg twice daily, oxycodone HCl CR 20-50 mg twice daily or placebo. Primary endpoints (as determined prior to initiation of the study) were the changes from baseline in average daily pain intensity (rated by patients on an 11-point numerical rating scale) over the last week of maintenance and over the entire 12-week maintenance period; last observation carried forward was used to impute missing values after early treatment discontinuation.

RESULTS: efficacy and safety were evaluated for 1023 patients. Tapentadol ER significantly reduced average pain intensity from baseline to week 12 of the maintenance period versus placebo [least squares mean [LSM] difference [95% CI], -0.7 [-1.04, -0.33]], and throughout the maintenance period (-0.7 [-1.00, -0.33]). Oxycodone CR significantly reduced average pain intensity from baseline throughout the maintenance period versus placebo [LSM difference [95% CI], -0.3 [-0.67, -0.00]) but not at week 12 (-0.3 [-0.68, 0.02]). A significantly higher percentage of patients achieved > or =50% improvement in pain intensity in the Tapentadol ER group (32.0% [110/344]) compared with the placebo group (24.3% [82/337]; p = 0.027), indicating a clinically significant improvement in pain intensity, while a significantly lower percentage of patients achieved > or =50% improvement in pain intensity in the oxycodone CR group (17.3% [59/342]; p = 0.023 vs. placebo). In the placebo, Tapentadol ER and oxycodone CR groups, respectively, 61.1% (206/337), 75.9% (261/344) and 87.4% (299/342) of patients reported at least one treatment-emergent adverse event (TEAE); incidences of gastrointestinal-related TEAEs were 26.1% (88/337), 43.0% (148/344) and 67.3% (230/342).

CONCLUSION:

treatment with Tapentadol ER 100-250 mg twice daily or oxycodone HCl CR 20-50 mg twice daily was effective for the management of moderate to severe chronic osteoarthritis-related knee pain, with substantially lower incidences of gastrointestinal-related TEAEs associated with treatment with Tapentadol ER than with oxycodone CR.

Abbreviated Class Update: Long-Acting Opioids (LAOs)

Authors: Buynak R, Shapiro DY, Okamoto A, Van Hove I, Rauschkolb C, Steup A, Lange B, Lange C, Etropolski M.
Title: Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase II study. [Erratum appears in Expert Opin Pharmacother. 2010 Nov;11(16):2773]
Source: Expert Opinion on Pharmacotherapy. 11(11):1787-804, 2010 Aug.

OBJECTIVE: To evaluate the efficacy and safety of tapentadol extended release (ER) for the management of moderate to severe chronic low back pain.

DESIGN: Patients (N = 981) were randomized 1:1:1 to receive tapentadol ER 100 - 250 mg b.i.d., oxycodone HCl controlled release (CR) 20 - 50 mg b.i.d., or placebo over 15 weeks (3-week titration period, 12-week maintenance period).

MAIN OUTCOME MEASURES: Efficacy was assessed as change from baseline in average pain intensity (11-point NRS) at week 12 of the maintenance period and throughout the maintenance period; last observation carried forward was used to impute missing pain scores. Adverse events (AEs) were monitored throughout the study.

RESULTS: Tapentadol ER significantly reduced average pain intensity versus placebo at week 12 (least squares mean difference vs. placebo [95% confidence interval], -0.8 [-1.22, -0.47]; p < 0.001) and throughout the maintenance period (-0.7 [-1.06, -0.35]; p < 0.001). Oxycodone CR significantly reduced average pain intensity versus placebo at week 12 (-0.9 [-1.24, -0.49]; p < 0.001) and throughout the maintenance period (-0.8 [-1.16, -0.46]; p < 0.001). Tapentadol ER was associated with a lower incidence of treatment-emergent AEs (TEAES) than oxycodone CR. Gastrointestinal TAEAs, including constipation, nausea, and vomiting, were among the most commonly reported TAEAs (placebo, 26.3%; tapentadol ER, 43.7%; oxycodone CR, 61.9%). The odds of experiencing constipation or the composite of nausea and/or vomiting were significantly lower with tapentadol ER than with oxycodone CR (both p < 0.001).

CONCLUSIONS: Tapentadol ER (100 - 250 mg b.i.d.) effectively relieved moderate to severe chronic low back pain over 15 weeks and had better gastrointestinal tolerability than oxycodone HCl CR (20 - 50 mg b.i.d.).

Authors: Wild JE, Grond S, Kuperwasser B, Gilbert J, McCann B, Lange B, Steup A, Haufel T, Etropolski M, Rauschkolb C, Lange R.
Title: Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain.
Source: Pain Practice. 10(5):416-27, 2010 Sep-Oct.
Abstract: BACKGROUND: Tapentadol is a novel, centrally acting analgesic with 2 mechanisms of action: -opioid receptor agonism and norepinephrine reuptake inhibition. This randomized, open-label phase 3 study (ClinicalTrials.gov Identifier: NCT00361504) assessed the long-term safety and tolerability of tapentadol extended release (ER) in patients with chronic knee or hip osteoarthritis pain or low back pain.

METHODS: Patients were randomized 4:1 to receive controlled, adjustable, oral, twice-daily doses of tapentadol ER (100 to 250 mg) or oxycodone HCl controlled release (CR; 20 to 50 mg) for up to 1 year. Efficacy evaluations included assessments at each study visit of average pain intensity (11-point numerical rating scale) over the preceding 24 hours. Treatment-emergent adverse events (TEAES) and discontinuations were monitored throughout the study.

Author: Kathy L. Ketchum
Version: 6/26/2013 6:02 AM

P&T Date: July 27, 2012
15

Abbreviated Class Update: Long-Acting Opioids (LAOs)

- RESULTS:** A total of 1,117 patients received at least 1 dose of study drug. Mean (standard error) pain intensity scores in the tapentadol ER and oxycodone CR groups, respectively, were 7.6 (0.05) and 7.6 (0.11) at baseline and decreased to 4.4 (0.09) and 4.5 (0.17) at endpoint. The overall incidence of TEAEs was 85.7% in the tapentadol ER group and 90.6% in the oxycodone CR group. In the tapentadol ER and oxycodone CR groups, respectively, TEAEs led to discontinuation in 22.1% and 36.8% of patients; gastrointestinal TEAEs led to discontinuation in 8.6% and 21.5% of patients.
- CONCLUSION:** Tapentadol ER (100 to 250 mg bid) was associated with better gastrointestinal tolerability than oxycodone HCl CR (20 to 50 mg bid) and provided sustainable relief of moderate to severe chronic knee or hip osteoarthritis or low back pain for up to 1 year. 2010 World Institute of Pain.



Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079

Oregon State Phone 503-947-5220 | Fax 503-947-1119

College of Pharmacy

© Copyright 2012 Oregon State University. All Rights Reserved



Month/Year of Review: July 2013

PDL Classes: ADHD

Date of Last Review: Drug December 2011

Source Document: Drug Effectiveness Review Project

Current Status of PDL Class:

- **PREFERRED AGENTS:** AMPHETAMINE ASPARTATE/AMPHETAMINE/D-AMPHETAMINE TABLET, DEXMETHYLPHENIDATE CPMP 50-50 (FOCALIN XR®), DEXTROAMPHETAMINE TABLETS (DEXEDRINE®), FOCALIN® (BRAND ONLY), LISDEXAMFETAMINE (VYVANSE®), METHYLPHENIDATE HCL TABLETS, methylphenidate ER
- **NON-PREFERRED AGENTS:** AMPHETAMINE ASPARTATE/AMPHETAMINE/D-AMPHETAMINE ER, DEXTROAMPHETAMINE ER, DEXTROAMPHETAMINE SOLUTION (PROCENTRA), METHAMPHETAMINE HCL TABLETS, METHYLPHENIDATE TRANSDERMAL (DAYTRANA®), METHYLPHENIDATE HCL CD CPMP 30-70, METHYLPHENIDATE ER CPMP 50-50, METHYLPHENIDATE HCL SOLUTION, METHYLPHENIDATE XR (QUILLIVANT XR®), METHYLPHENIDATE HCL CHEWABLE TABLET, METHYLPHENIDATE ER DESTROAMPHETAMINE/AMPHETAMINE, DEXTROAMPHETAMINE/AMPHETAMINE (ADDERALL XR®)
- **NON-PREFERRED VOLUNTARY AGENTS:** ATOMOXETINE (STRATTERA®), CLONIDINE HCL (KAPVAY®), GUANFACINE HCL (INTUNIV®)

Previous Recommendation:

- Due to a lack of comparative efficacy or effectiveness data, do not consider extended release formulations of clonidine and guanfacine as clinically superior to other stimulant and non-stimulant ADHD treatments.
- There is a lack of long term evidence to support any differences between stimulants and atomoxetine.

Current PA criteria:

Prior authorization is required for non-preferred drugs to ensure coverage only for OHP covered diagnoses and restrict to doses supported by the medical literature. This PA does not concern drugs in STC 07 or 11; however, these drugs are not to be encouraged. See specific criteria in Appendix 2.

Methods:

A Medline OVID search was conducted with the following search terms: amphetamine, amphetamines, d-amphetamine, dextroamphetamine, dexamphetamine, lisdexamfetamine, lisdexamphetamine, amphetamine salts, methylphenidate, dexmethylphenidate, dextromethylphenidate, Ritalin, Metadate, Concerta, Focalin, Adderall, Vyvanse, Quillivant, Daytrana, stimulants, central nervous system stimulants, guanfacine, clonidine, alpha adrenergic blockers, Intuniv, Kapvay, atomoxetine, Strattera, attention deficit and hyperactivity disorder, ADHD, and narcolepsy. The search was limited to English language articles of controlled trials conducted on humans published from 2011 to May week two 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Trials (Appendix 2):

A total of 245 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, seven relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Brams¹ et al studied the safety and efficacy of extended release dextromethylphenidate at different doses, 20 mg vs. 30 mg, in children with ADHD (n=157) aged 6 to 12 years old. This was a good quality, double-blind, randomized, cross-over study with subjects randomized to one of three treatments for three 7 day periods; all children received 20 mg, 30 mg of dexmethylphenidate and placebo. The setting was a classroom laboratory where children were observed for 12 hours. The primary efficacy outcome measure was change in the average Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-Combined score from pre-dose to (the average of 10, 11, and 12 hours' score) post-dose for 30 mg versus 20 mg. The SKAMP scale is a 13-item instrument designed to measure target classroom manifestations of ADHD. Dexmethylphenidate 30 mg was shown to have a significantly improved SKAMP score (difference in least mean square: -2.45, p=0.002) over the 20 mg dose and (-8.97, p<0.001) placebo. Safety was assessed by symptom questionnaires given to subjects and parents, as well as vital signs and measurements collected at visits. Most common adverse events were decreased appetite, headache, abdominal pain, and tachycardia. No significant difference was seen between the two treatment groups in adverse events.

Jafarinia² et al compared ADHD symptom improvement in children (n=44) aged 6 to 17 years old treated with bupropion or methylphenidate for six weeks. Efficacy was measured by a change in the symptom measurement tool the Teacher and Parent Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) from baseline to week six. No significant difference was found between the two groups on the ADHD-RS-IV parent (mean difference -0.5, p = 0.609) and teacher (-1.4, p = 0.612) scores at week six. Adverse event frequency was not statistically different between the two groups in this fair quality study.

Weisler³ et al conducted a study comparing a novel histamine H3 receptor antagonist (bavistin) with traditional ADHD medications for symptom control over 42 weeks. This good quality, randomized, double-blind, placebo-controlled, multi-center trial evaluated three dosages of bavistin (1 mg, 3 mg or 10 mg) with atomoxetine (80 mg), methylphenidate (54 mg) and placebo; 430 adult patients were randomized. The primary outcome was mean change from baseline in the total ADHD-RS-IV score at day 42. None of the bavistin groups showed a significance difference from placebo in their score difference; statistical analysis was performed only for the 10 mg strength (mean difference: -8.8 vs. -12.2, p = 0.161). Mean change from baseline in the total ADHD-RS-IV score at day 42 was superior to placebo in the atomoxetine (-15.3) and methylphenidate (-15.7) groups (both, p< 0.005). Methylphenidate and atomoxetine were not compared with each other.

Dopfner⁴ et al compared the efficacy of two methylphenidate modified release formulations in a multi-center crossover trial. Children (n=113) with ADHD were randomized to two different 22% immediate release (IR) formulations of methylphenidate (Concerta or Medikinct), and a 50% IR formulation (Medikinct) in turn for three weeks. The primary endpoint was improvement from baseline in SKAMP score as measured during the first three hours of schooling by the kids' teachers. Medikinct 50% IR was found to be significantly superior to Concerta in improving SKAMP scores (p=0.0009). Medikinct 22% IR was found to be noninferior to Concerta. This was a poor quality trial with many discrepancies in allocation concealment, randomization and data collection.

Yildiz⁵ et al conducted an open-label study to compare the efficacy and safety of atomoxetine and methylphenidate for ADHD. Children (n=25) aged 8 to 14 years old were randomized to 12 weeks of treatment with either medication. Efficacy was measured by the Clinical Global Impression Scales Severity and Improvement (CGI-S, CGI-I). These instruments are designed to record illness severity and the response to the intervention. Safety was assessed through parent observation of adverse effects and collection of results from physical examinations including vital signs, EKGs, and labs. At week twelve, 63.6% of atomoxetine and 83.3% of methylphenidate subjects were considered treatment responders on the CGI scale. This was not statistically significant (p=0.076). No difference was found between the two medications on a parent rated behavior assessment tool (T-DSM-IV), or in discontinuations due to adverse effects. Nervousness, nausea and anorexia were the most common reported adverse events for both medications. Both atomoxetine and methylphenidate groups had a significant decrease in weight from baseline but there was no statistical difference between treatments. This was a poor quality study with many opportunities for bias.

Date: July 2013

Spencer⁶ et al compared the efficacy of extended release methylphenidate in patients currently on an immediate release formulation. Adults (n=53) with ADHD were randomized to receive equivalent doses of the ER preparation or to continue their IR regimen and were assessed for six weeks. The primary endpoint was improvement in the Adult ADHD Investigator System Symptom Report (AISRS) Scale. At the end of the study no difference was seen in the AISRS scores for the ER and IR groups (11.2 vs. 10.7, p= 0.8). This was a poor quality study with allocation, blinding and randomization all poorly explained or not performed.

Stein⁷ et al conducted a fair quality, crossover study to compare the efficacy of extended release methylphenidate with extended release amphetamine salts in children with ADHD. For eight weeks, children (n=65) aged 9 to 17 years old were randomized to each medication for four weeks with a week of placebo use within the drug period. Change in the ADHD-RS-IV was the primary endpoint. Although both groups saw significant improvement in ADHD-RS-IV score (p<0.001), when compared there was no statistical difference between treatment groups (p=0.855).

New drugs:

None

New Formulations/Indications:

A new formulation of methylphenidate was approved in September 2012. Quillivant XR™ is an extended-release oral suspension indicated for adults and children aged six and older for the treatment of ADHD and is available as a 5mg/ml oral suspension.⁸ This is the first liquid formulation of the drug that is available as once-daily. A short-acting oral solution is currently available (Methyltin®).

There are currently no available head to head trials. Approval was based on a single double-blind crossover trial in 45 children aged 6-12 in a laboratory classroom setting.⁹ The primary endpoint was the SKAMP rating system (evaluates school-related problems such as following class rules, interacting with classmates and teachers, and performance of classroom tasks). The primary endpoint measured at 4 hours post dose. Mean SKAMP scores were significantly better with the drug than with placebo at all post-dose assessment times (7.12 vs. 19.58, respectively; p<0.0001). Over the average 41 days, 93.3% experienced a treatment-emergent and 3 subjects experienced a severe treatment-emergent adverse event (affect lability, aggression, and initial insomnia).⁹

Lisdexamfetamine dimesylate (Vyvanse®) capsules were approved in January 2012 for maintenance treatment in Adults with ADHD.

New FDA safety alerts:

In November 2012, the FDA issued a drug safety communication regarding stimulant use in children and young adults with ADHD. Results from a large, recently completed study did not show any association between use of certain ADHD medications (amphetamine derivatives and methylphenidate) and adverse cardiovascular events (stroke, heart attack, and sudden cardiac death). The FDA recommends patients on these medications should still continue to be monitored for any abnormal increase in heart rate or blood pressure.¹⁰

In September 2011, the FDA updated the safety labeling for Vyvanse (lisdexamphfetamine) to include the psychiatric disorder dermatillomania as an adverse reaction.¹¹

New Systematic Reviews: (Appendix 2)

Three new systematic reviews were identified. Please see Appendix 2 for the full abstracts.

Many patients with ADHD also have a diagnosis of oppositional defiant disorder (ODD) but little investigation has been focused on if comorbid ODD affects the efficacy of ADHD medication. Van Wyk¹² et al assessed how ODD, inattention, and hyperactivity-impulsivity affect the response to atomoxetine versus methylphenidate. Seven randomized control

Date: July 2013

trials (n=1,391) conducted on children with ADHD aged 6 to 16 years old were included in the systematic review. Trials were a mix of double-blinded and open label studies at least six weeks in length; a total of 42.7% of patients in the atomoxetine and 38.2% in the methylphenidate cohort had an ODD diagnosis. The primary outcome was a $\geq 40\%$ reduction in the ADHD Rating Scale-IV (ADHD-RS-IV). For patients with ODD, the mean difference (atomoxetine minus methylphenidate) in response rates for patients with ODD was 0.6% (95% CI = -11.9% to 13.1%). Response rate differences for patients meeting the threshold for inattention or hyperactivity-impulsivity were -3.1% (95% CI = -11.5% to 5.3%) and -4.9% (95% CI = -14.3% to 4.4%), respectively. Comorbid ODD did not alter ADHD symptom response to atomoxetine or methylphenidate. Individual trial quality was rated as fair to good. For the most part randomization and blinding procedures were transparent, however two trials were open-label and not all trials explained procedures for allocation concealment.

Hanwella¹³ et al performed a systematic review with head to head randomized clinical trials comparing the efficacy of atomoxetine versus methylphenidate for ADHD symptom improvement. The meta analysis combined nine double-blind and open label randomized control trials with children (n=2762) with ADHD aged 6 to 16 years old. Trials were at least 3 weeks in length. The outcome studied was a comparison in change in ADHD-RS-IV score. The standardized mean difference (SMD) was used as a measure of effect size. Analysis did not find a significant difference in efficacy between methylphenidate and atomoxetine (SMD = 0.09, 95% CI -0.08 to 0.26). Synthesis of data from eight trials found no significant difference in response rates (RR = 0.93 95% CI 0.76 to 1.14). Excluding open label trials did not significantly alter the effect size (SMD = 0.08, 95% CI -0.04 to 0.21). Individual trial quality was evaluated for the presence of randomization, description of outcome measures, inclusion and exclusion criteria; the authors found all included trials to rate more than 12 on the Detsky quality scale. However, because three of the included studies were open label and allocation concealment was not evaluated, the individual quality of the trials may be considered fair at best.

The Cochrane Collection¹⁴ conducted a systematic review to examine the efficacy and safety of use of amphetamines in adults with ADHD. Randomized controlled trials comparing the efficacy of amphetamine derivatives (dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts) against placebo or an active intervention were included. A total of seven studies were analyzed with 1091 adult subjects; all studies included a placebo as a comparator. Three studies had an additional active comparator: guanfacine, modafinil and paroxetine. The average trial length was 8.1 weeks. The primary efficacy outcome was measured as standard mean difference (SMD) in a composite proportion of patients achieving a reduction of ADHD symptom severity $\geq 30\%$ on the ADHD-RS-IV, patients achieving a Clinical Global Impression-Improvement (CGI-I) score of 1 or 2, or Clinical Global Impression (CGI) at study end. Amphetamines improved ADHD symptom severity (SMD = -0.72; 95% CI -0.87 to -0.57). The three amphetamine derivatives investigated were all efficacious for reducing ADHD symptoms. Change in dose did not appear associated with differences in efficacy nor was there any difference between immediate and sustained drug release formulations. When amphetamines were compared to guanfacine, modafinil or paroxetine, they were not found to statistically superior. Amphetamines were associated with higher attrition due to adverse events. The quality of all trials was assessed as low to very low by the authors with high risk of bias likely for all outcomes.

Guidelines:

The updated guidelines for ADHD from the American Academy of Pediatrics¹⁵ and the American Academy of Family Physicians¹⁶ were reviewed. No changes regarding the use of ADHD medications were found.

Recommendations:

- There is insufficient evidence that the new methylphenidate formulation (Quillivant XR[®]) has improved efficacy or safety or other formulations.
- There is no new clinical evidence to make changes to current PDL status.
- Evaluate comparative costs in executive session.

Date: July 2013

References:

1. Brams M, Turnbow J, Pestreich L, et al. A Randomized, Double-Blind Study of 30 Versus 20 mg Dexmethylphenidate Extended-Release in Children With Attention-Deficit/Hyperactivity Disorder. *Journal of Clinical Psychopharmacology*. 2012;32(5):637–644. doi:10.1097/JCP.0b013e3182677825.
2. Jafarinia M, Mohammadi M-R, Modabbernia A, et al. Bupropion versus methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder: randomized double-blind study. *Human Psychopharmacology: Clinical and Experimental*. 2012;27(4):411–418. doi:10.1002/hup.2242.
3. Welsler RH, Pandina GJ, Daly EJ, Cooper K, Gassmann-Mayer C. Randomized Clinical Study of a Histamine H3 Receptor Antagonist for the Treatment of Adults with Attention-Deficit Hyperactivity Disorder. *CNS Drugs*. 2012;26(5):421–434. doi:10.2165/11631990-00000000-00000.
4. Döpfner M, Ose C, Fischer R, Ammer R, Scherag A. Comparison of the Efficacy of Two Different Modified Release Methylphenidate Preparations for Children and Adolescents with Attention-Deficit/Hyperactivity Disorder In a Natural Setting: Comparison of the Efficacy of Medikinet® Retard and Concerta® —a Randomized, Controlled, Double-Blind Multicenter Clinical Crossover Trial. *Journal of Child and Adolescent Psychopharmacology*. 2011;21(5):445–454. doi:10.1089/cap.2010.0082.
5. Yıldız O, Sismanlar SG, Memik NC, Karakaya I, Agaoglu B. Atomoxetine and Methylphenidate Treatment In Children with ADHD: The Efficacy, Tolerability and Effects on Executive Functions. *Child Psychiatry & Human Development*. 2010;42(3):257–269. doi:10.1007/s10578-010-0212-3.
6. Spencer TJ, Mick E, Surman CBH, et al. A Randomized, Single-Blind, Substitution Study of OROS Methylphenidate (Concerta) In ADHD Adults Receiving Immediate Release Methylphenidate. *Journal of Attention Disorders*. 2010;15(4):286–294. doi:10.1177/1087054710367880.
7. Stein MA, Waldman ID, Charney E, et al. Dose Effects and Comparative Effectiveness of Extended Release Dexmethylphenidate and Mixed Amphetamine Salts. *Journal of Child and Adolescent Psychopharmacology*. 2011;21(6):581–588. doi:10.1089/cap.2011.0018.
8. QUILLIVANT XR (methylphenidate hydrochloride) Label - 202100lbl.pdf. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202100lbl.pdf. Accessed May 28, 2013.
9. SB Wigal et al. NWP06, an extended release oral suspension of methylphenidate, Improved attention-deficit/hyperactivity disorder symptoms compared with placebo in a laboratory classroom study. *J Child Adolesc Psychopharmacol* 2013 Jan 5 {epub}.
10. Drug Safety and Availability > FDA Drug Safety Communication: Safety Review Update of Medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in adults. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm279858.htm>. Accessed May 27, 2013.
11. Safety Information > Vyvanse (lisdexamfetamine dimesylate) Capsules. Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm234015.htm>. Accessed May 28, 2013.
12. Van Wyk GW, Hazell PL, Kohn MR, Granger RE, Walton RJ. How Oppositionality, Inattention, and Hyperactivity Affect Response to Atomoxetine Versus Methylphenidate: A Pooled Meta-Analysis. *Journal of Attention Disorders*. 2011;16(4):314–324. doi:10.1177/1087054710389989.
13. Hanwella R, Senanayake M, de Silva V. Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. *BMC Psychiatry*. 2011;11(1):176. doi:10.1186/1471-244X-11-176.
14. Castells X, Ramos-Quiroga JA, Bosch R, Nogueira M, Casas M. Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults. In: The Cochrane Collaboration, Castells X, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2011. Available at: <http://doi.wiley.com/10.1002/14651858.CD007813.pub2>. Accessed May 27, 2013.
15. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *PEDIATRICS*. 2011;128(5):1007–1022. doi:10.1542/peds.2011-2654.
16. Post RE, Kurlansik SL. Diagnosis and management of adult attention-deficit/hyperactivity disorder. *Am Fam Physician*. 2012; 85(9):890–896.

Date: July 2013

Appendix 1: Prior Authorization Criteria

Central Nervous System (CNS) Stimulants

Goal(s):

- Cover stimulants only for OHP covered diagnoses (e.g. ADHD, narcolepsy)
- Restrict to doses supported by medical literature and promote preferred drugs in class
- The long-term effects of stimulants are unknown. Adverse events are more frequently associated with high doses. However, effectiveness is not linearly associated with dose and promote preferred drugs in class.

Initiative: CNS Stimulants (Non-PDL & Excessive Dose)

Length of Authorization: up to 12 months

Requires PA :

- Non-preferred drugs

Covered alternatives: See PDL list at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

- PA does NOT concern drugs in STC 07 or 11 ; however, these drugs are not to be encouraged. The State is prohibited from prior authorizing Class 11 drugs by statute. These include :
 - Armodafinil (Nuvigil)
 - Atomoxetine (Strattera)
 - Modafanil (Provigil)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code	
2. Is diagnosis one of the following?: ADHD (ICD9 314-314.01); Narcolepsy (ICD9 341); Drug-induced sedation (ICD9 292.89)?	Yes: Go to #4	No: Go to #3
3. Is the diagnosis above the line? Unspecified hypersomnia (ICD9 780.54) and Obesity treatment (278.0-278.1) are below the line.	Yes: Pass to RPH; Deny, (Not covered by OHP)	No: Go to #4
4. Is the drug requested preferred?	Yes: Go to #7	NO: Go to #5
5. Is this continuation of therapy (claim indicating prescription filled within prior 90 days)?	Yes: Document prior therapy in PA record. Go to #7	No: Go to #6
6. Will the provider consider a change to a preferred product? Message: <ul style="list-style-type: none">- Preferred products do not require a PA- Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T Committee).	Yes: Inform provider of covered alternatives	No: Go to #7
7. Is the dose greater than limits in table below?	Yes: Go to #8	No: Approve for up to 1 year.

Date: July 2013

8. Is the prescriber a psychiatrist?	Yes: Approve for up to 1 year.	No: Go to #9
9. Is the patient <18 years old?	Yes: Go to #10	No: Pass to RPH; Deny, (Medical Appropriateness). Dose exceeds maximum recommended dose.
10. How much does the patient weight?	Document the patient's weight and continue to #11	
11. Is the patient receiving an accumulative dose that EXCEEDS 2mg/kg/day of methylphenidate products or EXCEEDS 0.5mg/kg/day of amphetamine products?	Yes: Pass to RPH; Deny. (Medical Appropriateness) – Dose exceeds maximum recommended dose. Consider switching to an alternative stimulant drug class or assessing compliance with the current therapy.	No: Approve for up to 1 year.

Date: July 2013

Appendix 2: RCT Abstracts

Brams M, Turnbow J, Pestreich L, et al. A Randomized, Double-Blind Study of 30 Versus 20 mg Dexmethylphenidate Extended-Release in Children With Attention-Deficit/Hyperactivity Disorder. *Journal of Clinical Psychopharmacology*. 2012; 32(5):637–644. doi:10.1097/JCP.0b013e3182677825.

The objective of this study was to evaluate the safety and efficacy of dexmethylphenidate extended-release (d-MPH-ER) 30 versus 20mg in children with attention-deficit/hyperactivity disorder (ADHD) in a 12-hour laboratory classroom setting. In a randomized, double-blind, 3-period _ 3-treatment, crossover study, children aged 6 to 12 years with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnosed ADHD previously stabilized on MPH (40Y60 mg/d) or D-MPH (Combined score from predose to 10, 11, and 12 hours postdose) compared with D-MPH-ER 20mg (2.02; P=0.002). Most common adverse events (Q3% in any group) were decreased appetite (6.1%, 4.9%, and 0%), headache (4.3%, 4.3%, and 1.9%), abdominal pain (3.7%, 3.1%, and 3.1%), and tachycardia (1.2%, 3.1%, and 0.6%) for D-MPH-ER 30 mg, D-MPH-ER 20 mg, and placebo, respectively). Significantly greater improvement in ADHD symptoms was noted with D-MPH-ER 30 mg compared with D-MPH-ER 20 mg at hours 10 through 12. Tolerability was comparable between doses. Dexmethylphenidate extended-release 30-mg dose may provide further benefit to patients who do not maintain optimal symptom control later in the day with D-MPH-ER 20 mg.

Jafarinia M, Mohammadi M-R, Modabbernia A, et al. Bupropion versus methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder: randomized double-blind study. *Human Psychopharmacology: Clinical and Experimental*. 2012; 27(4):411–418. doi:10.1002/hup.2242.

Objective To compare the safety and efficacy of bupropion with methylphenidate in children and adolescents with attention-deficit/ hyperactivity disorder (ADHD).

Methods In a 6-week randomized double-blind study, 44 patients with a DSM-IV-TR diagnosis of ADHD were randomly assigned to receive bupropion 100–150 mg/day (100 mg/day for <30 kg and 150 mg/day for >30 kg) or methylphenidate 20–30 mg/day. Symptoms were assessed using Teacher and Parent Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) at baseline and weeks 3 and 6.

Results Forty patients had at least one post-baseline measurement, and 38 patients completed the trial. No significant difference was found between the two groups on the Parent and Teacher ADHD-RS-IV scores ($|F(1, 38) = 0.266, p = 0.609|$ and $|F(1, 38) = 0.001, p = 0.972|$, respectively). By week 6, 18 patients (90%) in each group achieved response on the Parent scale (Fisher's exact test p-value = 1.0). With the Teacher ADHD-RS-IV used, eight (40%) patients in the bupropion group and 12 (60%) patients in the methylphenidate group achieved response by week 6 ($w2(1) = 1.600, p = 0.206$). Headache was observed more frequently in the methylphenidate group. Frequency of other side effects was not significantly different between the two groups.

Conclusions Bupropion has a comparable safety and efficacy profile with methylphenidate in children and adolescents with ADHD.

Weisler RH, Pandina GJ, Daly EJ, Cooper K, Gassmann-Mayer C. Randomized Clinical Study of a Histamine H3 Receptor Antagonist for the Treatment of Adults with Attention-Deficit Hyperactivity Disorder. *CNS Drugs*. 2012;26(5):421–434. doi:10.2165/11631990-00000000-00000.

Background: Psychostimulants, including methylphenidate and amphetamine preparations, are commonly prescribed for the treatment of attention-deficit hyperactivity disorder (ADHD) in children and adults. Histamine H3 receptors reside on non-histamine neurons and regulate other neurotransmitters (e.g. acetylcholine, noradrenaline (norepinephrine)) suggesting that H3 antagonists have the potential to improve attention and impulsivity. Research indicates that H3 receptor antagonists due to their novel mechanism of action may have a unique treatment effect offering an important alternative for the treatment of ADHD. Bavisant (JNJ-31001074) is a highly selective, orally active antagonist of the human H3 receptor with a novel mechanism of action, involving wakefulness and cognition, with potential as a treatment for ADHD.

Objective: The objective of this study was to evaluate the efficacy, safety and tolerability of three dosages of bavisant compared with placebo in adults with ADHD.

Study design: This randomized, double-blind, placebo- and active-controlled, parallel-group, multicentre study evaluated three dosages of bavisant (1 mg/day, 3 mg/day or 10 mg/day) and two active controls in adults with ADHD. The study consisted of a screening phase of up to 14 days, a 42-day double-blind treatment phase and a 7-day post-treatment follow-up phase. Efficacy and safety assessments were performed.

Setting: The study was conducted at 37 study centres in the US from April 2009 through January 2010.

Participants: Men and women aged 18–55 years with an established diagnosis of ADHD as confirmed by clinician and self-report diagnostic measures were enrolled.

Intervention: Participants were randomly assigned equally to one of six treatment groups: placebo, bavisant 1 mg/day, 3 mg/day or 10 mg/day, atomoxetine hydrochloride 80 mg/day or osmotic-release oral system (OROS) methylphenidate hydrochloride 54 mg/day.

Main outcome measure: The primary efficacy endpoint was the change in the Attention Deficit Hyperactivity Disorder Rating Scale, Version IV (ADHRS-IV) total score from baseline (day 1) to the end of the treatment phase (day 42), and included all randomized participants who received one or more doses of study drug and had baseline and one or more post-baseline assessments (intent-to-treat [ITT] population). Safety assessments included treatment-emergent adverse events (TEAEs), laboratory tests and ECG readings.

Results: 430 participants were randomized, 424 received one or more doses of study medication and 335 (78%) of those randomized completed the study. Study participants had a mean age of 33.9 years and were predominantly White men. Mean treatment duration ranged from 31.4 to 38.8 days across groups. Mean change from baseline in the total ADHRS-IV score at day 42 (primary efficacy endpoint) was -8.8 in the placebo group versus -9.3, -11.2 and -12.2 in the bavisant 1 mg/day, 3 mg/day and 10 mg/day groups, respectively; the change in the 10 mg/day group was not statistically superior to placebo ($p = 0.161$), and hence statistical comparisons of the 1 mg/day and 3 mg/day groups with placebo based on a step-down closed testing procedure were not performed. Mean change from baseline in the total ADHRS-IV score at day 42 was superior to placebo in the atomoxetine (-15.3) and OROS methylphenidate (-15.7) groups ($p < 0.005$). Secondary efficacy assessments demonstrated a similar pattern with a non-significant trend towards improvement in the bavisant groups. The two lower dosages showed a good tolerability profile, but the higher dosage of bavisant was less well tolerated, as evidenced by the incidence of total TEAEs (61.8%, 82.4%, 89.0%), and discontinuations due to TEAEs (4.4%, 7.4%, 19.2%) in the bavisant 1 mg/day, 3 mg/day and 10 mg/day groups, respectively, compared with 58.9% and 2.7%, respectively on placebo. In the atomoxetine and OROS methylphenidate groups, the incidence of total TEAEs was 83.8% and 82.4% and discontinuations due to TEAEs was 10.8% and 8.8%, respectively.

Conclusion: Bavisant, a highly selective, wakefulness-promoting H3 antagonist, did not display significant clinical effectiveness in the treatment of adults with ADHD.

Döpfner M, Ose C, Fischer R, Ammer R, Scherag A. Comparison of the Efficacy of Two Different Modified Release Methylphenidate Preparations for Children and Adolescents with Attention-Deficit/Hyperactivity Disorder in a Natural Setting: Comparison of the Efficacy of Medikinct® Retard and Concerta®—a Randomized, Controlled, Double-Blind Multicenter Clinical Crossover Trial. *Journal of Child and Adolescent Psychopharmacology*. 2011;21(5):445–454. doi:10.1089/cap.2010.0082.

Objective: The comparison of the efficacy of Medikinct retard and Concerta trial was a multisite, randomized, double-blind, crossover trial that aimed at comparing the effects of two different modified release methylphenidate preparations (Medikinct retard: 50% immediate release (IR); Concerta: 22% IR) in a natural setting across the day in 113 randomized children and adolescents with attention-deficit/hyperactivity disorder (age range 6–16 years). The duration of the study per patient was 3 weeks.

Date: July 2013

Methods: The primary outcome variable was the German version of the "Swanson, Kotkin, Agler, M-Flynn, and Pelham scale" in the first 3 hours of school as assessed by teachers.

Results: Medikinct retard with a higher IR component than Concerta (and an equivalent daily dose) was superior to Concerta ($p = 0.0009$), and Medikinct retard with similar IR components in the morning as Concerta (but a lower daily dose) was noninferior to Concerta with regard to the primary outcome. Further, exploratory analyses on teacher and parent ratings on attention-deficit/hyperactivity disorder and on externalizing symptoms during the day revealed no evidence for the superiority of Concerta over Medikinct retard in an equivalent daily dosage throughout the day.

Conclusion: Children and adolescents may be treated with a lower daily dose of Medikinct retard (which has a similar IR component as Concerta) without resulting in a clinically relevant worse effect during school time.

Yıldız O, Sismanlar SG, Memik NC, Karakaya I, Agaoglu B. Atomoxetine and Methylphenidate Treatment in Children with ADHD: The Efficacy, Tolerability and Effects on Executive Functions. *Child Psychiatry & Human Development*. 2010;42(3):257–269. doi:10.1007/s10578-010-0212-3.

The aim of this study was to compare the safety, efficacy, tolerability, and the effects of atomoxetine and OROS-MPH on executive functions in children with ADHD. This study was an open-label study that only included two medication groups. Children were randomized to open-label atomoxetine or OROS-MPH for 12 weeks.

Primary efficacy measures were T-DSM-IV-S, CGI-I and neuropsychological tests battery. Safety assessments included electrocardiogram, adverse events checklist and laboratory tests. According to the endpoint improvement scores of CGI and parents T-DSM-IV-S, treatment responses were not significantly different between the two study groups. OROS-MPH led to a significantly greater reduction in teacher T-DSM-IV-S scale scores. OROS-MPH was more effective than atomoxetine on Stroop-5 time and number of corrections. Significant decrease in the percentage of perseverative errors on WCST in the OROS-MPH group was seen ($p = 0.005$). The most frequently reported adverse events in the atomoxetine group were anorexia, nausea, nervousness, weight loss, abdominal pain, and somnolence. In the OROS-MPH group, patients most frequently reported anorexia, nervousness, insomnia, headache, nausea, and weight loss. When all these results are considered, although both drugs can be considered effective in ADHD treatment, more remarkable improvement is provided by OROS-MPH based on the rates across informant (i.e., teachers, clinicians) and neuropsychological evaluation.

Spencer TJ, Mick E, Surman CBH, et al. A Randomized, Single-Blind, Substitution Study of OROS Methylphenidate (Concerta) in ADHD Adults Receiving Immediate Release Methylphenidate. *Journal of Attention Disorders*. 2010;15(4):286–294. doi:10.1177/1087054710367880.

Objective: The main aim of this study was to examine the efficacy, tolerability, and compliance of an extended-release formulation of methylphenidate (OROS-MPH) in adults with ADHD receiving immediate-release methylphenidate (IR-MPH).

Method: Participants were outpatient adults with ADHD who were stable on IR-MPH-administered TID. Participants were randomized (4:1) to equipotent doses of OROS-MPH or to continue IR-MPH and were assessed weekly for 6 weeks with the Adult ADHD Investigator System Symptom Report Scale (AISRS).

Results: Randomization of 53 IR-MPH responders to IR- or OROS-MPH had no effect on AISRS score at endpoint (11.2 ± 6.9 vs. 10.7 ± 5.1 , $p = .8$). Participants stabilized on IR-MPH and switched to OROS-MPH remained satisfied over 71% of the time. However, the IR-MPH group missed more doses (7.3 ± 6.8 vs. 3.3 ± 4.2 , $p = .02$) than the OROS-MPH group.

Conclusion: Findings showed that adults with ADHD can be successfully switched from an effective regimen of IR-MPH TID to once-daily OROS-MPH. Results also demonstrated better compliance with OROS-MPH than with IR-MPH treatment.

Stein MA, Waldman ID, Charney E, et al. Dose Effects and Comparative Effectiveness of Extended Release Dexmethylphenidate and Mixed Amphetamine Salts. *Journal of Child and Adolescent Psychopharmacology*. 2011;21(6):581–588. doi:10.1089/cap.2011.0018.

Objective: To compare the dose effects of long-acting extended-release dexmethylphenidate (ER d-MPH) and ER mixed amphetamine salts (ER MAS) on attention-deficit/hyperactivity disorder (ADHD) symptom dimensions, global and specific impairments, and common adverse events associated with stimulants.

Methods: Fifty-six children and adolescents with ADHD participated in an 8-week, double-blind, crossover study comparing ER d-MPH (10, 20, 25–30 mg) and ER MAS (10, 20, 25–30) with a week of randomized placebo within each drug period. Efficacy was assessed with the ADHD Rating Scale-IV (ADHD-RS-IV), whereas global and specific domains of impairment were assessed with the Clinical Global Impressions Severity and Improvement Scales and the parent-completed Wechsler Functional Impairment Scale, respectively. Insomnia and decreased appetite, common stimulant-related adverse events, were measured with the parent-completed Stimulant Side Effects Rating Scale.

Results: Both ER d-MPH and ER MAS were associated with significant reductions in ADHD symptoms. Improvement in Total ADHD and Hyperactivity/Impulsivity symptoms were strongly associated with increasing dose, whereas improvements in Inattentive symptoms were only moderately associated with dose. About 80% demonstrated reliable change on ADHD-RS-IV at the highest dose level of ERMAS compared with 79% when receiving ER d-MPH. Decreased appetite and Insomnia were more common at higher dose levels for both stimulants. Approximately 43% of the responders were preferential responders to only one of the stimulant formulations.

Conclusions: Dose level, rather than stimulant class, was strongly related to medication response.

Appendix 3: Abstracts of Meta Analyses

Van Wyk GW, Hazell PL, Kohn MR, Granger RE, Walton RJ. How Oppositionality, Inattention, and Hyperactivity Affect Response to Atomoxetine Versus Methylphenidate: A Pooled Meta-Analysis. *Journal of Attention Disorders*. 2011;16(4):314–324. doi:10.1177/1087054710389989.

Objective: To assess how threshold oppositional defiant disorder (ODD), inattention, and hyperactivity-impulsivity affect the response to atomoxetine versus methylphenidate.

Method: Systematic review of randomized controlled trials (RCTs; ≥6 weeks follow-up). The primary measure was core symptom response—≥40% reduction in ADHD Rating Scale-IV-Parent Version: investigator administered and scored total or domain subscores, as appropriate.

Results: Data from 1,391 children and adolescents (823 atomoxetine, 568 methylphenidate; 7 RCTs) were meta-analyzed. The mean difference in response rates for patients with ODD was 0.6% (95% confidence interval [CI] = -11.9%–13.1%). The "without ODD" patient group showed significant between-trial heterogeneity ($p < .001$). Response rate differences for patients meeting the threshold for inattention or hyperactivity-impulsivity were -3.1% (95% CI = -11.5%–5.3%) and -4.9% (95% CI = -14.3%–4.4%), respectively.

Conclusions: Meeting the threshold criteria for oppositionality, inattention, or hyperactivity-impulsivity did not alter core ADHD symptom response to atomoxetine versus methylphenidate, which was equivalent.

Hanwella R, Senanayake M, de Silva V. Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. *BMC Psychiatry*. 2011;11(1):176. doi:10.1186/1471-244X-11-176.

Date: July 2013

Background: Psychostimulants and non-stimulants are effective in the treatment of ADHD. Efficacy of both methylphenidate and atomoxetine has been established in placebo controlled trials. Direct comparison of efficacy is now possible due to availability of results from several head-to-head trials of these two medications.

Methods: All published, randomized, open label or double blind trials, comparing efficacy of methylphenidate with atomoxetine, in treatment of ADHD in children, diagnosed using DSM-IV™ criteria were included. The outcome studied was ADHRS-IV Parent score. The standardized mean difference (SMD) was used as a measure of effect size.

Results: Nine randomized trials comparing methylphenidate and atomoxetine, with a total of 2762 participants were included. Meta-analysis did not find a significant difference in efficacy between methylphenidate and atomoxetine ($SMD = 0.09$, 95% CI -0.08-0.26) ($Z = 1.06$, $p = 0.29$). Synthesis of data from eight trials found no significant difference in response rates ($RR = 0.93$ 95% CI 0.76-1.14, $p = 0.49$). Sub group analysis showed a significant standardized mean difference favouring OROS methylphenidate ($SMD = 0.32$, 95% CI 0.12-0.53 ($Z = 3.05$, $p < 0.002$)). Immediate release methylphenidate was not superior to atomoxetine ($SMD = -0.04$, 95% CI -0.19-0.12) ($Z = 0.46$, $p = 0.64$). Excluding open label trials did not significantly alter the effect size ($SMD = 0.08$, 95% CI -0.04-0.21) ($Z = 1.27$, $p = 0.20$). All-cause discontinuation was used as a measure of acceptability. There was no significant difference in all cause discontinuation between atomoxetine and methylphenidate ($RR = 1.22$, 95% CI 0.87-1.71). There was significant heterogeneity among the studies ($p = 0.002$, $I^2 = 67\%$). Subgroup analysis demonstrated the heterogeneity to be due to the open label trials ($p \approx 0.001$, $I^2 \approx 81\%$).

Conclusions: In general atomoxetine and methylphenidate have comparable efficacy and equal acceptability in treatment of ADHD in children and adolescents. However OROS methylphenidate is more effective than atomoxetine and may be considered as first line treatment in treatment of ADHD in children and adolescents.

Castells X, Ramos-Quiroga JA, Bosch R, Noguerira M, Casas M. Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults. In: The Cochrane Collaboration, Castells X, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2011. Available at:

<http://doi.wiley.com/10.1002/14651858.CD007813.pub2>. Accessed May 27, 2013.

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 methods 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.

Date: July 2013

Drug Class Review

Controller Medications for Asthma

Preliminary Scan Report #1

April 2013

Last Report: April 2011

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

Scan conducted by:
Rachael Posey, MSLS
Roberta Wines, MPH
Cynthia Feltner, MD, MPH

RTI-UNC Evidence-based Practice Center
Cecil G. Sheps Center for Health Services Research
University of North Carolina at Chapel Hill
725 MLK Blvd, CB# 7590
Chapel Hill, NC 27599-7590

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

Copyright © 2013 by Oregon Health & Science University
Portland, Oregon 97239. All rights reserved.



OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Report

Update #1, April 2011 (searches through September 2010)

Date of Last Preliminary Update Scan Report

None since most recent report

Scope and Key Questions

Researchers at the University of North Carolina wrote preliminary key questions and the eligibility criteria for studies based on the populations, interventions, and outcomes of interest. These were reviewed by representatives of organizations participating in the Drug Effectiveness Review Project (DERP) and posted to the DERP website for public comment. The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma?
2. What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma?
3. Are there subgroups of these patients based on demographics (age, racial groups, gender), asthma severity, comorbidities (drug-disease interactions, including obesity), other medications (drug-drug interactions), smoking status, genetics, or pregnancy for which asthma controller medications differ in efficacy, effectiveness, or frequency of adverse events?

Inclusion Criteria

Populations

- Adults (age >12 years) and children (age ≤12 years) with persistent asthma

Interventions

Table 1. Included interventions

Drug Class	Brand name Administration	Labeled indications	Strength
Beclomethasone dipropionate Inhaled corticosteroid	QVAR® HFA	Asthma (age ≥ 5)	40 mcg/puff 80 mcg/puff
	Vanceril® MDI	Asthma (age ≥ 5)	42 mcg/puff 84 mcg/puff
Budesonide Inhaled corticosteroid	Pulmicort® Flexhaler® DPI	Asthma (age ≥ 6)	90 mcg/dose 180 mcg/dose
	Pulmicort® Respules® Inhalation suspension	Asthma (age 1-8)	0.25 mg/2ml 0.5 mg/2ml 1 mg/2ml
Ciclesonide Inhaled corticosteroid	Alvesco® HFA-MDI	Asthma (age ≥ 12)	80 mcg/puff 160 mcg/puff
Flunisolide Inhaled corticosteroid	AeroBid® MDI AeroBid-M® MDI-menthol	Asthma (age ≥ 6)	250 mcg/puff
	AeroSpan® HFA	Asthma (age ≥ 6)	80 mcg/puff
Fluticasone propionate Inhaled corticosteroid	Bronalide® MDI	Asthma (age ≥ 4)	250 mcg/puff
	Flovent® HFA HFA	Asthma (age ≥ 4)	44 mcg/puff 110 mcg/puff 220 mcg/puff
Fluticasone propionate Inhaled corticosteroid	Flovent Rotadisk® DPI	Asthma (age ≥ 12)	50 mcg/dose 100 mcg/dose 250 mcg/dose
	Flovent Diskus® DPI	Asthma (age ≥ 4 yrs)	50 mcg/dose 100 mcg/dose 250 mcg/dose
Mometasone furoate Inhaled corticosteroid	Asmanex® Twisthaler® DPI	Asthma (age ≥ 4)	110 mcg/dose 220 mcg/dose
Triamcinolone acetonide Inhaled corticosteroid	Azmacort® MDI – with spacer mouthpiece	Asthma (age ≥ 6)	75 mcg/dose
Montelukast Leukotriene modifier	Singulair® Tablets Chewable tablets Granules	Asthma (age ≥ 1)	10 mg 4 mg, 5 mg 4 mg/packet
Zafirlukast Leukotriene receptor antagonist	Accolate® Tablets	Asthma (age ≥ 5 yrs in US); (age ≥ 12 yrs in Canada)	10 mg 20 mg

Drug Class	Brand name Administration	Labeled indications	Strength	
Zileuton 5-lipoxygenase Inhibitor	Zyflo® Tablets Zyflo CR® Extended release tablets	Asthma (age ≥ 12 yrs)	600 mg 600 mg	
Arformoterol Long-Acting Beta-2 Agonist	Brovana® Inhalation solution	Not approved for asthma (COPD only)	15 mcg/2ml	
Formoterol fumarate/ Eformoterol Long-Acting Beta-2 Agonist	Foradil Aerolizer® DPI	Asthma (age ≥ 5 yrs)	12 mcg/capsule	
Salmeterol xinafoate Long-Acting Beta-2 Agonist	Oxis Turbohaler® ^c DPI	Asthma (age ≥ 6 yrs)	6 mcg/puff 12 mcg/puff	
Omalizumab Anti-IgE medication	Xolair® Powder for subcutaneous injection	Serevent Diskus® DPI	Asthma (age ≥ 4 yrs)	50 mcg/blister
Fluticasone propionate/ Salmeterol xinafoate Combination product	Advair Diskus® DPI	Asthma (age ≥ 4 yrs)	100mcg/50mcg 250mcg/50mcg 500mcg/50mcg	
Tiotropium bromide Long-acting anticholinergic	Spiriva® DPI	Advair HFA® HFA	Asthma (age ≥ 12 yrs)	45mcg/21mcg 115mcg/21mcg 230mcg/21mcg
Budesonide/ Formoterol Combination product	Symbicort® HFA	Asthma (age ≥ 12 yrs)	80mcg/4.5mcg 160mcg/4.5mcg	

Abbreviations: DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; MDI = metered dose inhaler.

^aThis product has been discontinued by the manufacturer.

^bThe FDA approved dosing regimen for ciclesonide is twice daily.

^cThis product is not available in the US.

Study designs

- For efficacy/effectiveness outcomes,
 - 1) randomized controlled clinical trials of at least 6 weeks duration and n ≥ 40
 - 2) good quality systematic reviews
- For adverse events/safety:
 - 1) randomized controlled clinical trials of at least 6 weeks duration and n ≥ 40
 - 2) observational studies of at least 6 months duration and n ≥ 100
 - 3) good quality systematic reviews

Comparators

- Any other asthma medication listed above
- Placebo

Efficacy and effectiveness outcomes

- Control of symptoms (e.g., days/nights/frequency of symptoms, rate of asthma exacerbations, frequency of rescue medication use, courses of oral steroids)
- Functional capacity and quality of life (missed school and missed work days, ability to participate in work/school/sports/physical activity, activity limitation, improved sleep/sleep disruption)
- Urgent care services (Emergency department visits/urgent medical care visits)
- Adherence
- Hospitalization
- Mortality

Harms/adverse events outcomes

- Any reported adverse event or harm (e.g., growth suppression, hypothalamus-pituitary-adrenal axis suppression, osteoporosis/fractures, mortality, growth retardation, bone mineral density, ocular toxicity, suppression of the HPA axis, tachycardia, anaphylaxis, death)
- Withdrawals due to adverse events

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from March 27, 2010 through April 2, 2013 using terms for included drugs. To identify trials of newly-approved drugs, we searched from database inception (i.e., did not limit the search start date) through April 2, 2013. We also searched the FDA website (<http://www.fda.gov/medwatch/safety.htm>) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (<http://www.ahrq.gov/>) and the Canadian Agency for Drugs and Technology in Health (<http://www.cadth.ca/>). All citations were imported into an electronic database (EndNote X4) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

New drugs identified in this Preliminary Update Scan

6/22/2010: Dulera®, a combination product of formoterol fumarate and mometasone furoate, was approved for the treatment of asthma in patients 12 years of age and older.

7/1/2011: Arcapta Neohaler® (indacaterol), a long-acting beta2-adrenergic agonist, was approved for the long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is not indicated to treat acute deteriorations of chronic obstructive pulmonary disease or asthma.

4/17/2013: Breo®, a combination product of fluticasone furoate and vilanterol, will be discussed by the Pulmonary-Allergy Drugs Advisory Committee for approval for the long-term maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease.

New Indications

None identified.

New Safety Alerts

Identified in this Preliminary Update Scan

None identified.

Identified in previous Preliminary Update Scan(s)

No scan since most recent report

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan

None identified.

Reviews identified in previous Preliminary Update Scan(s)

No scans have been conducted since the original report.

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches for randomized controlled trials resulted in 300 citations. Of those, there are 43 potentially relevant new publications, including 18 trials comparing two included medications, 20 placebo-controlled trials, and 5 subgroup or secondary analyses of trials included in existing reports (see Appendix A for abstracts). Characteristics of these trials are shown in Tables 2, 3, and 4, below.

Table 2. New head-to-head trials

Study	N, Duration	Population	Comparison	Focus
Inhaled corticosteroids				
Brown, 2012	742, 52 weeks	African American adults with moderate-to-severe asthma	Budesonide vs budesonide + formoterol	Safety and asthma control with a budesonide/formoterol pressurized metered-dose inhaler versus budesonide over 1 year in African American patients
Hoshino, 2012	50, 24 weeks	Asthma patients	Budesonide vs budesonide + formoterol	Effects of budesonide/formoterol versus budesonide alone on airway dimensions and inflammation in individuals with asthma
Spector, 2012	311, 12 weeks	African American adolescents with moderate to severe persistent asthma	Budesonide vs budesonide + formoterol	Efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler versus budesonide dry powder inhaler in adolescent and adult black asthma patients
Zangrilli, 2011	250, 12 week	Hispanic adults with moderate to severe asthma requiring medium- to high-dose inhaled corticosteroids	budesonide vs budesonide + formoterol	Efficacy and safety of budesonide/formoterol with budesonide in an ethnically diverse group of Hispanic participants with asthma previously treated with inhaled corticosteroids
Stelmach, 2011	96, 6 months	Children with newly diagnosed atopic asthma	Budesonide vs montelukast	Effects of a medium and high dose of inhaled corticosteroid and a high-dose inhaled corticosteroid with vitamin D on bone metabolism in children with newly diagnosed atopic asthma
Korn, 2012	160, 6 weeks	Patients with moderate asthma	Ciclesonide vs fluticasone propionate + salmeterol xinafoate	Efficacy of a newly developed fixed combination of ciclesonide and formoterol in comparison to the marketed fixed combination of fluticasone and salmeterol in patients with moderate asthma
Postma, 2011	NR, 52 weeks	Adults with mild persistent asthma	Ciclesonide vs fluticasone propionate + salmeterol xinafoate	Benefits of first-line treatment with ciclesonide and a combination of fluticasone and salmeterol in patients with mild persistent asthma

Study	N, Duration	Population	Comparison	Focus
Katial, 2011	621, 52 weeks	Patients with persistent asthma symptomatic on open-label fluticasone propionate 100 micrograms	Fluticasone vs fluticasone propionate + salmeterol xinafoate	Safety and efficacy of fluticasone propionate/salmeterol combination 250/50 micrograms versus fluticasone propionate 250 micrograms in subjects with persistent asthma symptomatic on open-label FP 100 micrograms
Vaessen-Verberne, 2010	158, 26 weeks	Children with symptomatic asthma	Fluticasone vs fluticasone propionate + salmeterol xinafoate	Noninferiority of salmeterol/fluticasone propionate, 50/100 mug twice a day, in symptom control compared with fluticasone propionate, 200 mug twice a day Diskus in children with symptomatic asthma
Djukanovic, 2010	89, 12 weeks	Asthma patients uncontrolled on short-acting beta(2)-agonists	Fluticasone vs montelukast	Efficacy of adding a leukotriene modifier to an inhaled corticosteroid for clinical and/or anti-inflammatory outcomes in patients symptomatic on short-acting beta(2)-agonists
Weinstein, 2010	728, 12 weeks	Adults with uncontrolled asthma	Mometasone vs formoterol fumarate + mometasone furoate	Efficacy and safety of mometasone furoate/formoterol 400/10 microg versus MF 400 microg administered twice-daily via metered-dose inhaler in patients with asthma uncontrolled on high-dose inhaled corticosteroids
Meltzer, 2010	746, 26 weeks	Adults with not well-controlled asthma on low-dose inhaled corticosteroids	Mometasone vs formoterol vs formoterol fumarate + mometasone furoate	Effect of mometasone furoate/formoterol versus its monocomponents, each administered via metered-dose inhaler, on asthma deteriorations and lung function
Nathan, 2010	781, 12 weeks	Adults with asthma uncontrolled on medium-dose inhaled corticosteroid	Mometasone vs formoterol vs formoterol fumarate + mometasone furoate	Effect of mometasone furoate/formoterol combination, 200/10 microg, administered twice daily on asthma deteriorations and pulmonary function in patients with asthma uncontrolled on medium-dose inhaled corticosteroid
<i>Long-acting beta-2 agonists</i>				

Study	N, Duration	Population	Comparison	Focus
Meltzer, 2010	746, 26 weeks	Adults with not well-controlled asthma on low-dose inhaled corticosteroids	Formoterol vs mometasone vs formoterol fumarate + mometasone furoate	Effect of mometasone furoate/formoterol versus its monocomponents, each administered via metered-dose inhaler, on asthma deteriorations and lung function
Nathan, 2010	781, 12 weeks	Adults with asthma uncontrolled on medium-dose inhaled corticosteroid	Formoterol vs mometasone vs formoterol fumarate + mometasone furoate	Effect of mometasone furoate/formoterol combination, 200/10 microg, administered twice daily on asthma deteriorations and pulmonary function in patients with asthma uncontrolled on medium-dose inhaled corticosteroid
Upworth, 2013	62, 1 year	Children with persistent asthma with the homozygous Arg16 genotype	Salmeterol vs montelukast	Efficacy of using montelukast as an alternative to salmeterol as tailored second-line asthma controller therapy in children expressing the Arg(16) beta(2) receptor genotype
Bateman, 2011	388, 16 weeks	Asthmatic adults with the B16-Arg/Arg genotype	Salmeterol vs tiotropium	Efficacy and safety of the long-acting anticholinergic tiotropium with salmeterol and placebo added to an inhaled corticosteroid in B16-Arg/Arg patients with asthma that was not controlled by inhaled corticosteroids alone.
Peters, 2010	210, NR	Adults with uncontrolled asthma	Salmeterol vs tiotropium	The addition of tiotropium bromide to an inhaled glucocorticoid, as compared with a doubling of the dose of the inhaled glucocorticoid (primary superiority comparison) or the addition of the LABA salmeterol (secondary noninferiority comparison)
Leukotriene modifiers				
Stelmach, 2011	96, 6 months	Children with newly diagnosed atopic asthma	Montelukast vs budesonide	Effects of a medium and high dose of inhaled corticosteroid and a high-dose inhaled corticosteroid with vitamin D on bone metabolism in children with newly diagnosed atopic asthma
Djukanovic, 2010	89, 12 weeks	Asthma patients uncontrolled on short-acting beta(2)-agonists	Montelukast vs fluticasone	Efficacy of adding a leukotriene modifier to an inhaled corticosteroid for clinical and/or anti-inflammatory outcomes in patients symptomatic on short-acting beta(2)-agonists

Study	N, Duration	Population	Comparison	Focus
Upworth, 2013	62, 1 year	Children with persistent asthma with the homozygous Arg16 genotype	Montelukast vs salmeterol	Efficacy of using montelukast as an alternative to salmeterol as tailored second-line asthma controller therapy in children expressing the Arg(16) beta(2) receptor genotype
Anti-IgE therapy				
None				
Combination products				
Brown, 2012	742, 52 weeks	African American adults with moderate-to-severe asthma	Budesonide + formoterol vs budesonide	Safety and asthma control with a budesonide/formoterol pressurized metered-dose inhaler versus budesonide over 1 year in African American patients
Hoshino, 2012	50, 24 weeks	Asthma patients	Budesonide + formoterol vs budesonide	Effects of budesonide/formoterol versus budesonide alone on airway dimensions and inflammation in individuals with asthma
Spector, 2012	311, 12 weeks	African American adolescents with moderate to severe persistent asthma	Budesonide + formoterol vs budesonide	Efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler versus budesonide dry powder inhaler in adolescent and adult black asthma patients
Zangrilli, 2011	250, 12 week	Hispanic adults with moderate to severe asthma requiring medium- to high-dose inhaled corticosteroids	Budesonide + formoterol vs budesonide	Efficacy and safety of budesonide/formoterol with budesonide in an ethnically diverse group of Hispanic participants with asthma previously treated with inhaled corticosteroids
Hozawa, 2011	40, NR	Asthmatic patients with suspected persistent airway inflammation and small airway impairment	Budesonide + formoterol vs fluticasone propionate + salmeterol xinafoate	Effects of budesonide/formoterol delivered by a Turbuhaler® and fluticasone/salmeterol delivered by a Diskus® on small airway function and airway inflammation
Korn, 2012	160, 6 weeks	Patients with moderate asthma	Fluticasone propionate + salmeterol xinafoate vs ciclesonide	Efficacy of a newly developed fixed combination of ciclesonide and formoterol in comparison to the marketed fixed combination of fluticasone and salmeterol in patients with moderate asthma

Study	N, Duration	Population	Comparison	Focus
Postma, 2011	NR, 52 weeks	Adults with mild persistent asthma	Fluticasone propionate + salmeterol xinafoate vs ciclesonide	Benefits of first-line treatment with ciclesonide and a combination of fluticasone and salmeterol in patients with mild persistent asthma
Katyal, 2011	621, 52 weeks	Patients with persistent asthma symptomatic on open-label fluticasone propionate 100 micrograms	Fluticasone propionate + salmeterol xinafoate vs fluticasone	Safety and efficacy of fluticasone propionate/salmeterol combination 250/50 micrograms versus fluticasone propionate 250 micrograms in subjects with persistent asthma symptomatic on open-label FP 100 micrograms
Vaessen-Verberne, 2010	158, 26 weeks	Children with symptomatic asthma	Fluticasone propionate + salmeterol xinafoate vs fluticasone	Noninferiority of salmeterol/fluticasone propionate, 50/100 mug twice a day, in symptom control compared with fluticasone propionate, 200 mug twice a day Diskus in children with symptomatic asthma
Maspero, 2010	404, 52 week	Adults with persistent asthma inadequately controlled on inhaled corticosteroid monotherapy	Formoterol fumarate + mometasone furoate vs fluticasone propionate + salmeterol xinafoate	Long-term safety of mometasone furoate/formoterol administered through metered-dose inhaler in patients with persistent asthma previously on medium- to high-dose inhaled corticosteroid
Weinstein, 2010	728, 12 weeks	Adults with uncontrolled asthma	Formoterol fumarate + mometasone furoate vs mometasone	Efficacy and safety of mometasone furoate/formoterol 400/10 microg versus MF 400 microg administered twice-daily via metered-dose inhaler in patients with asthma uncontrolled on high-dose inhaled corticosteroids
Meltzer, 2010	746, 26 weeks	Adults with not well-controlled asthma on low-dose inhaled corticosteroids	Formoterol fumarate + mometasone furoate vs mometasone vs formoterol	Effect of mometasone furoate/formoterol versus its monocomponents, each administered via metered-dose inhaler, on asthma deteriorations and lung function
Nathan, 2010	781, 12 weeks	Adults with asthma uncontrolled on medium-dose inhaled corticosteroid	Formoterol fumarate + mometasone furoate vs mometasone vs formoterol	Effect of mometasone furoate/formoterol combination, 200/10 microg, administered twice daily on asthma deteriorations and pulmonary function in patients with asthma uncontrolled on medium-dose inhaled corticosteroid

Study	N, Duration	Population	Comparison	Focus
<i>Long-acting anticholinergics</i>				
Bateman, 2011	388, 16 weeks	Asthmatic adults with the B16-Arg/Arg genotype	Tiotropium vs salmeterol	Efficacy and safety of the long-acting anticholinergic tiotropium with salmeterol and placebo added to an inhaled corticosteroid in B16-Arg/Arg patients with asthma that was not controlled by inhaled corticosteroids alone.
Peters, 2010	210, NR	Adults with uncontrolled asthma	Tiotropium vs salmeterol	The addition of tiotropium bromide to an inhaled glucocorticoid, as compared with a doubling of the dose of the inhaled glucocorticoid (primary superiority comparison) or the addition of the LABA salmeterol (secondary noninferiority comparison)

Table 3. New placebo-controlled trials

Study	N, Duration	Population	Comparison	Focus
<i>Inhaled corticosteroids</i>				
Krishnan, 2012	84 and 56, 4 years	Children with mild or moderate asthma	Budesonide	Influence of adherence to study medications on treatment-related differences in outcomes
Pedersen, 2010	2073, 12 weeks	Children (6-11 years) with persistent asthma	Ciclesonide	Efficacy and safety of ciclesonide in children with persistent asthma
Bensch, 2011	218, 52 weeks	Children with mild persistent asthma ranging in age from 4 to 10 years	Flunisolide	Effect of 1 year of inhalation therapy with flunisolide hydrofluoroalkane (HFA) on growth velocity and bone maturation in children with mild persistent asthma
Bateman, 2012	598, 8 weeks	Patients with persistent asthma not controlled by short-acting beta(2) agonists	Fluticasone	Efficacy of inhaled once-daily fluticasone furoate administered in the evening in patients with persistent asthma not controlled by short-acting beta(2) agonists
Bleecker, 2012	622, 8 weeks	Adults with moderate asthma, uncontrolled on low-dose inhaled corticosteroid	Fluticasone	Efficacy and safety of fluticasone furoate administered using a dry powder inhaler in patients with moderate asthma, uncontrolled on low-dose ICS

Study	N, Duration	Population	Comparison	Focus
Busse, 2012	627, 8 weeks	Patients with persistent moderate-to-severe asthma, symptomatic on medium-dose inhaled corticosteroid therapy	Fluticasone	To determine the optimal dose(s) of fluticasone furoate for treating patients with asthma
Guilbert, 2011	NR, 2 years	Children aged 2 and 3 years with recurrent wheezing and positive modified Asthma Predictive Index scores	Fluticasone	Effect of daily inhaled corticosteroid given for 2 years on linear growth in preschool children with recurrent wheezing
Woodcock, 2011	545, 8 weeks	Persistent asthma patients maintained on inhaled corticosteroids for at least 3 months	Fluticasone	Efficacy and safety of fluticasone furoate in patients with persistent asthma
Skoner, 2011	187, 52 weeks	Children aged 4-9 years with asthma	Mometasone	Effects of long-term mometasone furoate delivered via a dry powder inhaler on growth velocity and hypothalamic-pituitary-adrenal axis function in children with asthma
<i>Long-acting beta-2 agonists</i>				
Chuchalin, 2007	156, 7 weeks	Asthma patients	Indacaterol	Safety and tolerability of indacaterol in asthma patients
<i>Leukotriene modifiers</i>				
Philip, 2011	134, 8	Adults with chronic asthma	Montelukast	Efficacy of inhaled montelukast added to inhaled mometasone
Valovirta, 2011	1771, 52 weeks	Children 6 months to 5 years of age with episodic asthma	Montelukast	Regimen-related efficacy of montelukast in treating pediatric episodic asthma
<i>Anti-IgE therapy</i>				
Bardelas, 2012	271, 24 weeks	Adults with persistent allergic asthma inadequately controlled with NHLBI Step 4 or above asthma therapy	Omalizumab	Effect of omalizumab on asthma control in patients with persistent allergic asthma inadequately controlled with NHLBI Step 4 or above asthma therapy
Bousquet, 2011	400, 32 weeks	Adults with severe allergic asthma	Omalizumab	Persistency of treatment responder classification in patients receiving omalizumab added to optimized asthma therapy

Study	N, Duration	Population	Comparison	Focus
Hanania, 2011	850, 48 weeks	Adults with inadequately controlled asthma despite treatment with high-dose ICS plus LABAs, with or without other controllers	Omalizumab	Efficacy and safety of omalizumab in patients with inadequately controlled severe asthma who are receiving high-dose ICS and LABAs with or without additional controller therapy
Rubin, 2012	unclear, 20 weeks	Brazilian adults with severe persistent allergic asthma inadequately controlled	Omalizumab	Impact of omalizumab as an add-on therapy to standard treatment with inhaled corticosteroids and long-acting beta-2 agonists on asthma-related quality of life in patients with severe allergic asthma
<i>Combination products</i>				
Sterling, 2012	75, NR	Adults with persistent asthma	Fluticasone furoate + vilanterol (Breo)	Efficacy of vilanterol used concurrently with inhaled corticosteroid in adult patients with persistent asthma
Frampton, 2012	NR, 26 weeks	Adults with persistent asthma uncontrolled on medium-dose inhaled corticosteroids	Formoterol fumarate + mometasone furoate	Effectiveness of mometasone/formoterol 200 mug/10 mug twice daily versus formoterol and placebo in patients with persistent asthma uncontrolled on medium-dose inhaled corticosteroids
<i>Long-acting anticholinergics</i>				
Kerstjens, 2011	107, 8 weeks	Patients with uncontrolled severe asthma	Tiotropium	Efficacy and safety of tiotropium administered through the Respimat inhaler as add-on therapy in patients with uncontrolled severe asthma despite maintenance treatment with at least a high-dose inhaled corticosteroid plus a long-acting beta(2)-agonist
Kerstjens, 2012	912, 48 weeks	Patients with asthma who were receiving inhaled glucocorticoids and LABAs	Tiotropium	Effect on lung function and exacerbations of adding tiotropium (a total dose of 5 mug) or placebo, both delivered by a soft-mist inhaler once daily for 48 weeks in patients with asthma who were receiving inhaled glucocorticoids and LABAs

Table 4. Secondary analyses of included primary trial publications

Study	N, Duration	Population	Comparison	Focus
Cohen, 2010	1041, 4 years	Children age 5 to 12 years with asthma	Budesonide vs placebo	To explore whether in utero smoke exposure is associated with increased airway responsiveness among children with asthma and whether IUS modifies the response to treatment with inhaled corticosteroids
Kelly, 2012	943, NR	Adults who has participated in the Childhood Asthma Management Program	Budesonide vs placebo	To determine whether the use of inhaled glucocorticoids causes a decrease in attained adult height.
Camargo, 2010	475, 52 weeks	African American patients with asthma	Fluticasone vs fluticasone propionate + salmeterol xinafoate	To explore whether obesity alters the risk, impairment and response to treatment in African Americans with asthma
Wang, 2011	unclear, 48 weeks	Children with mild-to-moderate persistent asthma	Fluticasone vs montelukast	Cost-effectiveness of 2 commonly used asthma controllers, fluticasone and montelukast, with data from the Pediatric Asthma Controller Trial
Vogelmeier, 2012	404, 1 year	Asian adults with asthma	Fluticasone propionate + salmeterol xinafoate vs budesonide + formoterol	Effectiveness of budesonide/formoterol maintenance and reliever therapy compared with salmeterol/fluticasone propionate plus as-needed salbutamol in patients enrolled across Asian countries, specifically China, Korea, Taiwan and Thailand.

Table 5. Breakdown of potentially relevant head-to-head comparisons:

	Budesonide	Ciclesonide	Fluticasone	Mometasone	Montelukast	Formoterol	Salmeterol	Tiotropium	Fluticasone/ Salmeterol	Budesonide/ Formoterol	Formoterol/ Mometasone
Budesonide					1					4	
Ciclesonide									2		
Fluticasone					1				2		
Mometasone						2					3
Montelukast	1		1				1				
Formoterol				2							2
Salmeterol					1			2			
Tiotropium							2				
Fluticasone/ Salmeterol		2	2							1	1
Budesonide/ Formoterol	4								1		
Formoterol/ Mometasone				3		2			1		

Summary and Recommendations

We identified 3 new medications and 43 new trials (18 head to head trials, 20 placebo controlled trials, and 5 subgroup or secondary analyses) published since the most recent update report. New head-to-head trials are available for 11 of the 20 included medications, including 4 studies comparing the new combination product Dulera® with mometasone or formoterol alone. New placebo controlled trials are available for 11 of the 20 included medications, including the new medications indacaterol (Arcapta®) and the two new combination products Breo® and Dulera®.

The most recent Controller Medications for Asthma update report used evidence from placebo controlled trials when head-to-head trials were not available and incorporated results of up-to-date good quality systematic reviews and meta-analyses when appropriate. Using a similar approach, a complete update at this time is likely to be large. An update that excluded studies of leukotriene modifiers (montelukast, zafirlukast, and zileuton), Anti IgE therapies (omalizumab), and long acting cholinergics (tiotropium) is also likely to be large because these medications represent only 13 of the total studies identified by the scan (5 head-to-head and 8 placebo controlled trials), and it is likely that other eligible studies exist for the medications that would remain included.

A streamlined approach that includes only new head-to-head trials and excludes placebo-controlled trials would likely be of medium size. We recommend that the Participants also consider a modified streamlined update that is limited to head-to-head trials for most of the included medications and placebo controlled trials of included medications that are being used off-label. Most of the head-to-head trials we identified were studies of combination products compared with single medications or other combinations, including the new Dulera® (but not including the new Breo®). With this scan, we identified three off-label placebo controlled trials (1 study of indacaterol and 2 studies of tiotropium). A modified streamlined update using this approach would likely be of medium size.

Appendix A. Abstracts of potentially relevant new trials of controller medications for asthma

Head-to-head trials

Bateman, E. D., O. Kornmann, et al. (2011). "Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma." *J Allergy Clin Immunol* 128(2): 315-22.

BACKGROUND: The efficacy and safety of inhaled long-acting beta(2)-adrenergic agonists in asthmatic patients with the B16-Arg/Arg genotype has been questioned, and the use of antimuscarinics has been proposed as an alternative in patients whose symptoms are not controlled by inhaled corticosteroids (ICSs). **OBJECTIVE:** We compared the efficacy and safety of the long-acting anticholinergic tiotropium with salmeterol and placebo added to an ICS in B16-Arg/Arg patients with asthma that was not controlled by ICSs alone. **METHODS:** In a double-blind, double-dummy, placebo-controlled trial, after a 4-week run-in period with 50 mug of twice-daily salmeterol administered through a metered-dose inhaler, 388 asthmatic patients were randomized 1:1:1 to 16 weeks of treatment with 5 mug of Respimat tiotropium administered daily in the evening, 50 mug of salmeterol administered twice daily through a metered-dose inhaler, or placebo. Patients aged 18 to 67 years demonstrated reversibility to bronchodilators, and their symptoms were uncontrolled by regular ICSs (400-1000 mug of budesonide/equivalent). ICS regimens were maintained throughout the trial. The mean weekly morning peak expiratory flow (PEF) before randomization was 358 +/- 115.7 L/min (range, 80.3-733.0 L/min). **RESULTS:** Changes in weekly PEF from the last week of the run-in period to the last week of treatment (primary end point: change in PEF) were -3.9 +/- 4.87 L/min (n = 128) for tiotropium and -3.2 +/- 4.64 L/min (n = 134) for salmeterol, and these were superior to placebo (-24.6 +/- 4.84 L/min, n = 125, P < .05). Tiotropium was noninferior to salmeterol (estimated difference, -0.78 L/min [95% CI, -13.096 to 11.53]; P = .002; alpha = .025, 1-sided; noninferiority, 20 L/min). Tiotropium and salmeterol were numerically superior to placebo in some patient-reported secondary outcomes. Adverse events were comparable across treatments. **CONCLUSION:** Tiotropium was more effective than placebo and as effective as salmeterol in maintaining improved lung function in B16-Arg/Arg patients with moderate persistent asthma. Safety profiles were comparable.

Brown, R. W., C. D. O'Brien, et al. (2012). "Long-term safety and asthma control measures with a budesonide/formoterol pressurized metered-dose inhaler in African American asthmatic patients: a randomized controlled trial." *J Allergy Clin Immunol* 130(2): 362-7 e9.

BACKGROUND: Information surrounding the long-term safety of combination inhaled corticosteroid/long-acting beta(2)-adrenergic agonist medications in African American asthmatic patients is limited. **OBJECTIVE:** We sought to assess safety and asthma control with a budesonide/formoterol pressurized metered-dose inhaler (pMDI) versus budesonide over 1 year in African American patients. **METHODS:** This 52-week, randomized, double-blind, parallel-group, multicenter, phase 3B safety study (NCT00419952) was conducted in 742 self-reported African American patients 12 years or older with moderate-to-severe asthma previously receiving medium- to high-dose

inhaled corticosteroids. After 2 weeks using a 320 mug twice-daily budesonide pMDI, patients were randomized 1:1 to 320/9 mug twice-daily budesonide/formoterol pMDI or 320 mug twice-daily budesonide pMDI. RESULTS: Both treatments were well tolerated. Asthma exacerbation incidence and rate (per patient-treatment year) were lower with budesonide/formoterol versus budesonide (incidence, 7.7% vs 14.0% [P= .006]; rate ratio, 0.615 [P= .002]). Time to first asthma exacerbation was longer (P= .018) with budesonide/formoterol versus budesonide. The most common adverse events, regardless of study drug relationship, were headache (9.5% and 7.7%), nasopharyngitis (6.9% and 8.0%), sinusitis (4.0% and 6.3%), and viral upper respiratory tract infection (5.8% and 4.4%) for budesonide/formoterol and budesonide, respectively. Serious adverse events occurred in 12 and 15 patients, respectively; none were considered drug related. No substantial or unexpected patterns of abnormalities were observed in laboratory, electrocardiographic, or Holter monitoring assessments. Hospitalization caused by asthma exacerbation occurred in 0 and 4 patients in the budesonide/formoterol and budesonide groups, respectively. Pulmonary function and asthma control measures generally favored budesonide/formoterol. CONCLUSIONS: In this population budesonide/formoterol pMDI was well tolerated over 12 months, with a safety profile similar to that of budesonide; the asthma exacerbation rate was reduced by 38.5% versus budesonide.

Djukanovic, R., S. J. Wilson, et al. (2010). "Montelukast added to fluticasone propionate does not alter inflammation or outcomes." *Respir Med* 104(10): 1425-35.

BACKGROUND: Airway inflammation is a key pathological feature of asthma which underlies its clinical presentation. **OBJECTIVES:** To examine whether adding a leukotriene modifier to an inhaled corticosteroid produces further clinical and/or anti-inflammatory benefits in patients symptomatic on short-acting beta(2)-agonists. **METHODS:** Patients uncontrolled on short-acting beta(2)-agonists were treated for 12 weeks with either fluticasone propionate (100mcg BD) or fluticasone propionate (100mcg BD) and montelukast (10mg QD) in a randomized, double-blind, parallel group study. Bronchoscopy with endobronchial biopsy and bronchoalveolar lavage (BAL) was performed before and after treatment to compare effects on airway inflammation. **RESULTS:** Of 103 subjects enrolled, 89 subjects completed treatment and 82 subjects had matched pair biopsy samples. Submucosal eosinophil counts, the primary endpoint, and asthma control improved to similar extents after both treatments ($p<\text{or}=0.008$). Both treatments significantly reduced submucosal mast cell, CD3+, CD4+, CD8+ and CD25+ cell counts. Submucosal mast cell reduction was greater in the fluticasone propionate plus montelukast group. There were no differences between treatments in BAL markers of inflammation or thickness of sub-epithelial collagen. **CONCLUSIONS:** Low-dose fluticasone propionate significantly improves clinical disease control and reduces airway inflammation in asthma patients uncontrolled with short-acting beta(2)-agonists without further improvement when montelukast is added to low-dose fluticasone propionate.

Hoshino, M.J. Ohtawa. (2012). "Effects of budesonide/formoterol combination therapy versus budesonide alone on airway dimensions in asthma." *Respirology* 17(4): 639-46.

BACKGROUND AND OBJECTIVE: Combination therapy with inhaled corticosteroids and long-acting beta(2)-agonists results in improved asthma symptom control compared

with the use of inhaled corticosteroids alone. However, the effects of combination therapy on structural changes and inflammation of the airways are still unknown. The aim of this study was to compare the effects of budesonide/formoterol with those of budesonide alone on airway dimensions and inflammation in individuals with asthma.

METHODS: Fifty asthmatic patients were randomized to treatment with budesonide/formoterol (200/6 microg, two inhalations bd) or budesonide (200 microg, two inhalations bd) for 24 weeks. Airway dimensions were assessed using a validated computed tomography technique, and airway wall area (WA) corrected for body surface area (BSA), percentage WA (WA%), wall thickness/square root BSA, and luminal area (Ai)/BSA at the right apical segmental bronchus, were measured. The percentage of eosinophils in induced sputum, pulmonary function, and Asthma Quality of Life Questionnaires (AQLQ) were also evaluated.

RESULTS: There were significantly greater decreases in WA/BSA ($P < 0.05$), WA% ($P < 0.001$) and wall thickness/square root BSA ($P < 0.05$), and increases in Ai/BSA ($P < 0.05$), in subjects treated with budesonide/formoterol compared with those treated with budesonide. The reduction in sputum eosinophils and increase in per cent of predicted forced expiratory volume in 1 s (FEV(1) %) were greater for subjects treated with budesonide/formoterol compared with those treated with budesonide alone. In the budesonide/formoterol group, the changes in WA% were significantly correlated with changes in sputum eosinophils and FEV(1%) ($r = 0.84$ and $r = 0.64$, respectively). There were improvements in the AQLQ scores after treatment with budesonide/formoterol.

CONCLUSIONS: Budesonide/formoterol combination therapy is more effective than budesonide alone for reducing airway wall thickness and inflammation in individuals with asthma.

Hozawa, S., M. Terada, et al. (2011). "Comparison of budesonide/formoterol Turbuhaler with fluticasone/salmeterol Diskus for treatment effects on small airway impairment and airway inflammation in patients with asthma." *Pulm Pharmacol Ther* 24(5): 571-6.

BACKGROUND: A course of combination therapy with an inhaled corticosteroid (ICS) and a long-acting beta₂ agonist (LABA) for asthma can improve lung function, asthma symptoms and reduce exacerbations. Because both medicinal substance and inhalation devices are associated with clinical efficacy, each ICS/LABA combination may have different features. This study aimed to compare the effects of two widely available formulations, budesonide/formoterol (BUD/FM) delivered by a Turbuhaler((R)), and fluticasone/salmeterol (FP/SM) delivered by a Diskus((R)), on small airway function and airway inflammation.

METHODS: Asthmatic patients ($n = 40$) treated twice daily with FP/SM 250/50 mug with forced expiratory volume in 1 s values controlled above 80% of the predicted normal but with suspected persistent airway inflammation and small airway impairment were enrolled in the study. Patients were randomized into two groups, receiving either twice daily BUD/FM 320/9 mug or FP/SM 250/50 mug, and treatment efficacy was compared after 4 weeks. Outcomes included impulse oscillometry (IOS), fractional exhaled nitric oxide (FeNO), spirometry and Asthma Control Questionnaire (ACQ) scores.

RESULTS: Patients in the BUD/FM group showed significant improvements in their IOS and spirometry parameters of small airway function, FeNO values and ACQ scores, compared with the FP/SM group. There were good correlations between IOS parameters, FeNO and ACQ score changes over the course of the treatment.

CONCLUSIONS: BUD/FM twice daily significantly improved small airway impairment

and airway inflammation in asthmatic patients, leading to a reduction in asthma symptoms and achievement of good asthma control. In addition, improvement of small airway function may improve airway inflammation and/or lead to better controlled asthma.

Katial, R. K., D. Bernstein, et al. (2011). "Long-term treatment with fluticasone propionate/salmeterol via Diskus improves asthma control versus fluticasone propionate alone." *Allergy Asthma Proc* 32(2): 127-36.

This 52-week study was designed to assess the safety and efficacy of fluticasone propionate/salmeterol combination (FSC) 250/50 micrograms versus fluticasone propionate (FP) 250 micrograms in subjects with persistent asthma symptomatic on open-label FP 100 micrograms. The primary objective of this study was to show that FSC 250/50 micrograms was superior to FP 250 micrograms at increasing pulmonary function as measured by forced expiratory volume in 1 second over a 52-week treatment period. A secondary objective was to compare the rate of asthma attacks defined as (1) a sustained 2-day decrease in morning peak expiratory flow or increase in albuterol use for 2 consecutive days, (2) an asthma exacerbation requiring systemic corticosteroids, or (3) an unscheduled clinic or hospital visit for acute asthma symptoms. Three hundred six subjects received FSC 250/50 micrograms and 315 subjects received FP 250 micrograms. Both treatments were administered twice daily. Treatment with FSC 250/50 micrograms resulted in a significant improvement in lung function compared with FP 250 micrograms ($p < 0.001$). Additionally, treatment with FSC 250/50 micrograms resulted in a reduction in the rate of exacerbations of asthma (i.e., requiring systemic corticosteroids or unscheduled urgent care intervention) compared with FP 250 micrograms (0.170 versus 0.273, respectively; $p = 0.017$). There was no differentiation between treatments for less severe attacks of asthma. FSC 250/50 micrograms showed consistently greater improvement in lung function, symptom control, and decreased albuterol use. In addition, FSC 250/50 micrograms-treated subjects experienced fewer severe asthma exacerbations than subjects treated with FP 250 micrograms.

Korn, S.R. Buhl. (2012). "Efficacy of a fixed combination of ciclesonide and formoterol: the EXCITED-study." *Respir Med* 106(1): 57-67.

Recommended treatment for moderate to severe asthma is the combination of an inhaled corticosteroid and a long-acting beta₂-agonist. The present study was designed to evaluate the efficacy of a newly developed fixed combination of ciclesonide and formoterol in comparison to the marketed fixed combination of fluticasone and salmeterol in patients with moderate asthma. This was a phase II, multi-centre, randomized, parallel-group, double-blind, double-dummy study. After a 2-week run-in period, 160 patients with moderate asthma were randomized to a 6-week treatment with ciclesonide/formoterol 320/9 mug bid (CIC/F) or fluticasone propionate/salmeterol 250/50 mug bid (FP/S), both delivered as powder formulations. The primary outcome FEV₁ increased during treatment by 0.356 L in the CIC/F group and by 0.288 L in the FP/S group ($p < 0.0001$). The increases were statistically significant and clinically relevant. The between-treatment analysis demonstrated non-inferiority of CIC/F to FP/S treatment ($p < 0.0001$). A significant improvement from baseline in lung function, symptom score and rescue medication use was observed in both groups at all time points.

No differences were observed between treatments in the frequency of adverse events and overnight urinary cortisol/creatinine ratio. The studied fixed combination of ciclesonide/formoterol is not inferior to the marketed fixed combination of fluticasone/salmeterol in terms of efficacy and tolerability.

Lipworth, B. J., K. Basu, et al. (2013). "Tailored second-line therapy in asthmatic children with the Arg(16) genotype." *Clin Sci (Lond)* 124(8): 521-8.

The Arg(16) beta(2) receptor genotype confers increased susceptibility to exacerbations in asthmatic children taking regular LABA (long-acting beta(2) agonists). We therefore evaluated using montelukast as an alternative to salmeterol as tailored second-line asthma controller therapy in children expressing this susceptible genotype. A total of 62 persistent asthmatic children with the homozygous Arg16 genotype were randomized to receive salmeterol (50 mug, b.i.d.) or montelukast (5 or 10 mg, once daily) as an add-on to inhaled fluticasone for 1 year. School absences (the primary outcome) were reduced with montelukast compared with salmeterol {difference in score=-0.40 [95% CI (confidence interval), -0.22 to -0.58]; P=0.005}. Salbutamol use was also reduced with montelukast compared with salmeterol [difference in score=-0.47 (95% CI, -0.16 to -0.79); P<0.0001]. Greater improvements occurred in both symptom and quality of life scores with montelukast against salmeterol, whereas there was no difference in FEV(1) (forced expiratory volume in 1 s). In conclusion, montelukast may be suitable as tailored second-line controller therapy instead of salmeterol in asthmatic children expressing the susceptible Arg(16) genotype, a move towards a personalized medicine approach to management.

Maspero, J. F., H. Nolte, et al. (2010). "Long-term safety of mometasone furoate/formoterol combination for treatment of patients with persistent asthma." *J Asthma* 47(10): 1106-15.

OBJECTIVE: The combination of inhaled corticosteroid (ICS) and long-acting beta(2)-agonist is recommended for treatment of patients with persistent asthma inadequately controlled on ICS monotherapy. This study was conducted to evaluate the long-term safety of mometasone furoate/formoterol (MF/F) administered through metered-dose inhaler (MDI) in patients with persistent asthma previously on medium- to high-dose ICS. **METHODS:** This was a 52-week, randomized, multicenter, parallel-group, open-label, evaluator-blinded study. At baseline, 404 patients (aged >/=12 years) were stratified according to their previous ICS dose (medium or high), then randomized 2:1 to receive twice-daily treatment of MF/F (200/10 or 400/10 mug) or fluticasone propionate/salmeterol (FP/S; 250/50 or 500/50 mug). The primary endpoint was the number and percentage of patients reporting any adverse event (AE). Additional safety evaluations included plasma cortisol 24-hour area under the curve (AUC(0-24 h)) and ocular changes. Pulmonary function, asthma symptoms, and use of rescue medication were monitored. **RESULTS:** The incidence of >/=1 treatment-emergent AE was similar across treatment groups (MF/F 200/10 mug, 77.3% [n= 109]; FP/S 250/50 mug, 82.4% [n= 56]; MF/F 400/10 mug, 79.2% [n= 103]; FP/S 500/50 mug, 76.9% [n= 50]). Rates of treatment-related AEs were also similar across treatment groups (MF/F 200/10 mug, 28.4%; FP/S 250/50 mug, 23.5%; MF/F 400/10 mug, 23.1%; FP/S 500/50 mug, 20.0%). Headache (3.7%) and dysphonia (2.7%) were the most common treatment-related AEs overall. The nature and frequency of AEs and the decreases in plasma cortisol AUC(0-24

h) observed with MF/F treatment were similar to those observed with FP/S treatment. Ocular events were rare (2-6% overall incidence among treatment groups); in particular, no posterior subcapsular cataracts were reported. Only three patients discontinued the study because of treatment-related ocular AEs (two for lens disorders in the MF/F 400/10 mug group; one for reduced visual acuity in the FP/S 250/50 mug group) and no asthma-related deaths occurred. Furthermore, MF/F showed numerical improvement in lung function and clinical benefits by reducing asthma symptoms and rescue medication use.

CONCLUSIONS: One-year treatment with the new combination therapies - twice-daily MF/F-MDI 200/10 and 400/10 mug - is safe and well tolerated in patients with persistent asthma.

Meltzer, E. O., P. Kuna, et al. (2012). "Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function." *Eur Respir J* 39(2): 279-89.

This study evaluated the effect of mometasone furoate (MF)/formoterol (F) versus its monocomponents, each administered via metered-dose inhaler, on asthma deteriorations and lung function. This 26-week, multicentre, double-blind, placebo-controlled study included subjects aged ≥ 12 yrs with not well-controlled asthma on low-dose inhaled corticosteroids. After a 2-3-week open-label run-in (MF 100 mug b.i.d.), 746 subjects were randomised to receive placebo, F 10 mug, MF 100 mug or MF/F 100/10 mug b.i.d. Co-primary end-points were time to first asthma deterioration (MF/F versus F to assess effect of MF) and change in forced expiratory volume in 1 s (FEV(1)) area under the curve of serial spirometry measurements over the 12-h period following the morning dose (AUC(0-12h)) (baseline to week 12; MF/F versus MF to assess effect of F). The therapeutic effect of MF in the combination was demonstrated by a reduction in asthma deterioration incidence with MF/F versus F and a delayed time to first asthma deterioration ($p < 0.001$). Asthma deterioration incidence was also reduced with MF/F versus MF ($p = 0.006$). The therapeutic effect of F in the combination was demonstrated by MF/F versus MF in FEV(1) AUC(0-12h) change (4.00 versus 2.53 L.h, respectively; $p = 0.001$). MF/F treatment also resulted in a marked improvement in health-related quality of life. MF/F 100/10 mug b.i.d. treatment showed greater clinical efficacy than its individual components or placebo; both components contributed to the efficacy of MF/F.

Nathan, R. A., H. Nolte, et al. (2010). "Twenty-six-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg combination treatment in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids." *Allergy Asthma Proc* 31(4): 269-79.

Asthma is a heterogeneous condition characterized by reduced lung function, chronic inflammation, and periodic asthma deteriorations. This study was performed to evaluate the effect of mometasone furoate (MF)/formoterol (F) combination, 200/10 microg, administered twice daily (b.i.d.) on asthma deteriorations and pulmonary function in patients with asthma uncontrolled on medium-dose inhaled corticosteroid (ICS). After 2- to 3-week open-label run-in with MF 200 microg b.i.d., patients ($>\text{or}=\text{12}$ years) were randomized to 26 weeks of treatment with MF/F 200/10 microg, MF 200 microg, F 10 microg, or placebo b.i.d. Coprimary end points were time to first asthma deterioration (MF/F versus F) and bronchodilation, assessed by the area under the curve of the change in forced expiratory volume in 1 second 0-12 hours (FEV(1) AUC(0-12h); MF/F versus

MF). A total of 781 patients were randomized. Treatment with MF/F 200/10 microg reduced asthma deteriorations and clinically judged deteriorations (i.e., deterioration resulting in emergency treatment, hospitalization, or treatment with additional excluded asthma medication [i.e., systemic corticosteroids]). The proportion of patients experiencing asthma deteriorations was MF/F, 30.4%; MF, 33.9%; F, 54.0%; placebo, 55.6% ($p < 0.001$, MF/F versus F and placebo). There was a sixfold reduction in clinically judged deteriorations with MF/F versus F and placebo ($p < 0.001$). Lung function improved more rapidly with MF/F than MF and placebo. Mean change from baseline FEV(1) AUC(0-12h) at week 12 was MF/F, 11.7% versus MF, 5.7%; F, 8.5%; and placebo, 3.9% ($p < 0.001$). Treatment-related AEs were rare and similar across groups. Treatment with MF/F 200/10 microg was effective in reducing the risk of asthma deteriorations. MF/F was safe and provided rapid and sustained bronchodilation in patients with asthma.

Peters, S. P., S. J. Kinselman, et al. (2010). "Tiotropium bromide step-up therapy for adults with uncontrolled asthma." *N Engl J Med* 363(18): 1715-26.

BACKGROUND: Long-acting beta-agonist (LABA) therapy improves symptoms in patients whose asthma is poorly controlled by an inhaled glucocorticoid alone. Alternative treatments for adults with uncontrolled asthma are needed. **METHODS:** In a three-way, double-blind, triple-dummy crossover trial involving 210 patients with asthma, we evaluated the addition of tiotropium bromide (a long-acting anticholinergic agent approved for the treatment of chronic obstructive pulmonary disease but not asthma) to an inhaled glucocorticoid, as compared with a doubling of the dose of the inhaled glucocorticoid (primary superiority comparison) or the addition of the LABA salmeterol (secondary noninferiority comparison). **RESULTS:** The use of tiotropium resulted in a superior primary outcome, as compared with a doubling of the dose of an inhaled glucocorticoid, as assessed by measuring the morning peak expiratory flow (PEF), with a mean difference of 25.8 liters per minute ($P < 0.001$) and superiority in most secondary outcomes, including evening PEF, with a difference of 35.3 liters per minute ($P < 0.001$); the proportion of asthma-control days, with a difference of 0.079 ($P = 0.01$); the forced expiratory volume in 1 second (FEV1) before bronchodilation, with a difference of 0.10 liters ($P = 0.004$); and daily symptom scores, with a difference of -0.11 points ($P < 0.001$). The addition of tiotropium was also noninferior to the addition of salmeterol for all assessed outcomes and increased the prebronchodilator FEV1 more than did salmeterol, with a difference of 0.11 liters ($P = 0.003$). **CONCLUSIONS:** When added to an inhaled glucocorticoid, tiotropium improved symptoms and lung function in patients with inadequately controlled asthma. Its effects appeared to be equivalent to those with the addition of salmeterol. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00565266.).

Postma, D. S., P. M. O'Byrne, et al. (2011). "Comparison of the effect of low-dose ciclesonide and fixed-dose fluticasone propionate and salmeterol combination on long-term asthma control." *Chest* 139(2): 311-8.

BACKGROUND: Patients with mild persistent asthma constitute about 70% of the asthma population; thus, it is important to know which first-line treatment is best for the management of mild asthma. We compared benefits of first-line treatment with

ciclesonide and a combination of fluticasone and salmeterol in patients with mild asthma. METHODS: Patients aged 12 to 75 years with mild persistent asthma were enrolled in a randomized, double-blind, placebo-controlled study. After run-in, patients were randomized to ciclesonide 160 mug once daily (CIC160), fluticasone propionate/salmeterol 100/50 mug bid (FP200/S100), or placebo for 52 weeks. The primary variable was time to first severe asthma exacerbation; the coprimary variable was the percentage of poorly controlled asthma days. Patients recorded asthma symptoms and salbutamol use in electronic diaries and completed a standardized version of the Asthma Quality of Life Questionnaire. RESULTS: Compared with placebo, the time to first severe asthma exacerbation was prolonged, and lung function was improved with FP200/S100 treatment ($P = .0002$) but not with CIC160. Both CIC160 and FP200/S100 provided significantly fewer poorly controlled asthma days than placebo ($P \leq .0016$ for both active treatments). Moreover, both active treatments provided significantly more asthma symptom-free days ($P \leq .0001$), rescue medication-free days ($P = .0005$, one-sided), and days with asthma control ($P \leq .0033$). Overall Asthma Quality of Life Questionnaire scores were significantly higher in both active treatment groups than placebo ($P \leq .0017$). CONCLUSIONS: In mild asthma, FP200/S100 prolonged time to first severe asthma exacerbation, and CIC160 and FP200/S100 were clinically equieffective for most measures of asthma control. Trial registry: ClinicalTrials.gov; No.: NCT00163358; URL: www.clinicaltrials.gov.

Spector, S. L., U. J. Martin, et al. (2012). "Budesonide/formoterol pressurized metered-dose inhaler versus budesonide: a randomized controlled trial in black patients with asthma." *J Asthma* 49(1): 70-7.

OBJECTIVE: Concerns exist that responses to long-acting beta(2)-adrenergic agonists in black patients may differ from the general population. The efficacy and safety of budesonide/formoterol (BUD/FM) pressurized metered-dose inhaler (pMDI) versus budesonide dry powder inhaler (BUD DPI) were evaluated in adolescent and adult black asthma patients. METHODS: This 12-week, randomized, double-blind, multicenter, phase IV US study was conducted in 311 self-reported black patients aged ≥ 12 years with moderate to severe persistent asthma, previously receiving medium- to high-dose inhaled corticosteroid. After 2 weeks on BUD 90 mug x 2 inhalations twice daily (bid), symptomatic patients were randomized to BUD/FM 160/4.5 mug x 2 inhalations bid or BUD 180 mug x 2 inhalations bid. RESULTS: Improvement in predose forced expiratory volume in 1 second from baseline to the treatment mean (primary variable) was greater with BUD/FM versus BUD (0.16 vs. 0.07 L; $p = .008$); this effect was also observed at weeks 2, 6, and end of treatment ($p \leq .032$). Greater improvements ($p < .001$) in peak expiratory flow with BUD/FM versus BUD were seen at first measurement and maintained during 12 weeks (morning: 25.34 vs. 7.53 L/minute, respectively; evening: 21.61 vs. 7.67 L/minute, respectively); greater improvements in daily asthma symptom score and rescue medication use were also observed ($p \leq .039$). Both treatments were well tolerated, with similar safety profiles. CONCLUSIONS: In this population of black asthma patients, BUD/FM pMDI resulted in greater improvements in pulmonary function and asthma control versus BUD DPI, with similar safety profiles.

Stelmach, I., M. Olszowiec-Chlebna, et al. (2011). "Inhaled corticosteroids may have a beneficial effect on bone metabolism in newly diagnosed asthmatic children." *Pulm Pharmacol Ther* 24(4): 414-20.

BACKGROUND: The adverse effect of inhaled corticosteroids (ICS) treatment on bone metabolism in children with asthma is still controversial, and a possible beneficial effect of vitamin D added to ICS on bone turnover is uncertain. **OBJECTIVE:** We conducted a randomized, double-blind, parallel-group, 6-month trial to assess the effects of a medium and high dose of ICS and a high-dose ICS with vitamin D on bone metabolism in children with newly diagnosed atopic asthma. **METHODS:** 96 children were equally randomized to 4 groups receiving the following doses of inhaled budesonide [μg/day]: 400 (ICS 400 group), 800 (ICS 800 group), 800 with oral vitamin D (ICS 800 with vit D group), and montelukast as a control (control group). Markers of bone production (osteocalcin, alkaline phosphatase) and bone degradation (amino-terminal cross-linked telopeptide of type I collagen-NTx, carboxy-terminal telopeptides of type I collagen), and also concentration of 25-hydroxycholecalciferol (25OH D) and calcium-phosphorus balance (calcium, phosphorus, parathormone-PTH) in serum and/or urine were assessed twice: before and after 6 months of treatment. **RESULTS:** We obtained a significant decrease in phosphorus and PTH serum levels in ICS 400 and ICS 800 with vit D groups compared to control group, and a significant decrease of NTx urine level in ICS 800 with vit D group. **CONCLUSIONS:** Medium doses of inhaled corticosteroids exert an advantageous effect on bone metabolism in newly diagnosed asthmatic children. Vitamin D together with a high dose of inhaled corticosteroids has a beneficial effect on both calcium-phosphorus balance and collagen turnover.

Vaessen-Verberne, A. A., N. J. van den Berg, et al. (2010). "Combination therapy salmeterol/fluticasone versus doubling dose of fluticasone in children with asthma." *Am J Respir Crit Care Med* 182(10): 1221-7.

RATIONALE: For children with symptomatic asthma despite low to moderate doses of inhaled corticosteroids, evidence is still lacking whether to add a long-acting bronchodilator or to increase the dose of inhaled corticosteroids. **OBJECTIVE:** To evaluate whether salmeterol/fluticasone propionate (SFP), 50/100 μg twice a day, is noninferior regarding symptom control compared with fluticasone propionate (FP), 200 μg twice a day Diskus in children with symptomatic asthma. **METHODS:** A multicenter, randomized, parallel-group, double-blind study was performed comparing SFP and FP treatment during 26 weeks on asthma control and lung function. **MEASUREMENTS AND MAIN RESULTS:** A total of 158 children, 6-16 years old, still symptomatic on FP, 100 μg twice a day, during a 4-week run-in period, were included. Percentage of symptom-free days during the last 10 weeks of the treatment period did not differ between treatment groups (per protocol analysis: adjusted mean difference [FP minus SFP] 2.6%; 95% confidence interval, -8.1 to 13.4). Both groups showed substantial improvements of about 25 percent points in symptom-free days (both $P < 0.001$ from baseline). Lung function measurements (FEV(1), FVC, PEF rate, and maximal expiratory flow) did not differ between groups except for a slight advantage in maximal expiratory flow in the SFP group at 1 week. No differences were found between FP and SFP regarding exacerbation rates, adverse events, or growth. **CONCLUSIONS:** In our study the efficacy on symptom control and lung function of the combination of a

long-acting bronchodilator with inhaled corticosteroid is equal to doubling the dose of the inhaled corticosteroid in children still symptomatic on a moderate dose of inhaled corticosteroid.

Weinstein, S. F., J. Corren, et al. (2010). "Twelve-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg and 400/10 microg combination treatments in patients with persistent asthma previously receiving high-dose inhaled corticosteroids." *Allergy Asthma Proc* 31(4): 280-9.

A significant unmet medical need exists in patients with uncontrolled asthma. The purpose of this study was to evaluate the efficacy and safety of mometasone furoate/formoterol (MF/F) 400/10 microg versus MF 400 microg administered twice-daily (b.i.d.) via metered-dose inhaler in patients with asthma uncontrolled on high-dose inhaled corticosteroids (ICS). In a 12-week, randomized, multicenter, double-blind, parallel-group study, patients (>or=12 years of age) were randomized to MF/F 200/10 microg, MF/F 400/10 microg, or MF 400 microg, b.i.d. after a 2- to 3-week open-label run in with MF 400 microg b.i.d. The primary end point was mean change in area under the curve from 0 to 12 hours in forced expiratory volume in 1 second (FEV(1) AUC(0-12h)) from baseline to week 12 for MF/F 400/10 microg versus MF 400 microg. Effects of MF/F on asthma control and symptoms were evaluated and adverse events recorded. Seven hundred twenty-eight patients were randomized. Significant improvement from baseline to week 12 occurred for mean change in FEV(1) AUC(0-12h) with MF/F 400/10 microg (4.19 L x hour) versus MF 400 microg (2.04 L x hour; p < 0.001). Both MF/F doses resulted in rapid (5 minutes) and sustained improvement in lung function throughout 12 weeks. Both MF/F doses were superior to MF in improving asthma control and reducing nocturnal awakenings due to asthma requiring short-acting beta(2)-agonist use. All treatments were well tolerated. Asthma patients who were poorly controlled on high-dose ICS experienced significant improvement in asthma control, lung function, and symptoms when treated with MF/F compared with MF.

Zangrilli, J., L. E. Mansfield, et al. (2011). "Efficacy of budesonide/formoterol pressurized metered-dose inhaler versus budesonide pressurized metered-dose inhaler alone in Hispanic adults and adolescents with asthma: a randomized, controlled trial." *Ann Allergy Asthma Immunol* 107(3): 258-65 e2.

BACKGROUND: Few clinical trials in asthma have focused on Hispanic populations. **OBJECTIVE:** To compare the efficacy and safety of budesonide/formoterol (BUD/FM) with BUD in an ethnically diverse group of Hispanic participants with asthma previously treated with inhaled corticosteroids (ICS). **METHODS:** This 12-week, randomized, double-blind, active-controlled study (NCT00419757) was designed to enroll Hispanic participants (self-reported) (>=12 years of age) with moderate to severe asthma requiring medium- to high-dose ICS. After a 2-week run-in period (low-dose BUD pressurized metered-dose inhaler [pMDI] 80 mug x 2 inhalations [160 mug] twice daily), participants with a symptom score greater than 0 (scale: 0-3) on 3 or more of 7 run-in days and forced expiratory volume in 1 second (FEV(1)) 45%-85% predicted were randomized to BUD/FM pMDI 160/4.5 mug x 2 inhalations (320/9 mug) twice daily or BUD pMDI 160 mug x 2 inhalations (320 mug) twice daily. **RESULTS:** Randomized participants (n = 127 BUD/FM; n = 123 BUD) were predominately Mexican (51%) or Puerto Rican

(21%). During low-dose ICS run-in, the mean symptom score was 1.0; however, mean predose FEV(1) improved (2.10-2.21 L). During randomized treatment, small, but not statistically significant, improvements favored BUD/FM vs BUD (am peak expiratory flow [PEF; primary efficacy variable] 25.4 vs 19.9 L/min; pm PEF 20.6 vs 15.8 L/min; predose FEV(1) 0.16 vs 0.11 L; rescue medication use -0.7 vs -0.6 inhalations/d). Most adverse events were mild or moderate in intensity. CONCLUSIONS: Improvement in clinically relevant control end points occurred in both BUD/FM and BUD groups; both treatments were well tolerated in this Hispanic asthma population but were not significantly differentiated.

Placebo-controlled trials

Bardelas, J., M. Figliomeni, et al. (2012). "A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma." *J Asthma* 49(2): 144-52.

OBJECTIVE: The 2007 National Heart, Lung, and Blood Institute (NHLBI) asthma guidelines shifted the focus of care from asthma severity to ongoing assessment of asthma control using the components of impairment and risk. We evaluated the effect of omalizumab on asthma control in patients with persistent allergic asthma inadequately controlled with NHLBI Step 4 or above asthma therapy. **METHODS:** In this double-blind, placebo-controlled study, patients ≥ 12 years ($n = 271$) received omalizumab ($n = 136$) or placebo ($n = 135$) every 2 or 4 weeks for 24 weeks. The primary efficacy variable, change from baseline in Asthma Control Test (ACT) total score, and Investigator's Global Evaluation of Treatment Effectiveness (IGETE, secondary efficacy variable) were evaluated at week 24. **RESULTS:** ACT score improved more with omalizumab compared with placebo (least squares means [LSMs]: 5.01, 4.36); however, the difference was not significant ($p = .1779$). Similarly, IGETE was not significantly different ($p = .1177$), but more patients treated with omalizumab (26/127, 20%) compared with placebo (19/131, 15%) had IGETE rated as "Excellent." Significant benefits were observed for omalizumab compared with placebo for change in ACT score (LSMs: 6.66, 5.27; $p = .0334$) and IGETE ($p = .0321$) at week 24 in a subgroup of patients with very poorly controlled asthma (ACT ≤ 15) at baseline. There were no significant differences for the subgroup of patients with forced expiratory volume in 1 second $\leq 80\%$ predicted at baseline. Adverse events (AEs) were similar between groups with no drug-related serious AEs or deaths. **CONCLUSIONS:** For allergic asthma patients with NHLBI Step 4 or above asthma therapy, omalizumab consistently improved asthma control; however, compared with placebo, differences were not significant. Placebo-treated patients had substantial improvement in their ACT score, which may have limited the ability to detect differences between treatment groups. Subgroup analyses showed significant improvements with omalizumab versus placebo in patients with very poorly controlled asthma.

Bateman, E. D., E. R. Bleecker, et al. (2012). "Dose effect of once-daily fluticasone furoate in persistent asthma: a randomized trial." *Respir Med* 106(5): 642-50.

BACKGROUND: This randomized, double-blind, multicenter study was designed to evaluate the efficacy of inhaled once-daily fluticasone furoate (FF) administered in the

evening in patients with persistent asthma not controlled by short-acting beta(2) agonists, and to determine the dose(s) suitable for further development. METHODS: Of 1459 patients screened, 598 received one of six treatments: placebo, FF (25 mug, 50 mug, 100 mug or 200 mug) once daily each evening, or fluticasone propionate (FP) 100 mug twice daily for 8 weeks. The primary endpoint was change from baseline in pre-dose evening forced expiratory volume in 1 s (FEV(1)). RESULTS: A dose-response effect was observed for once-daily FF 25-200 mug including ($p < 0.001$) and excluding placebo ($p = 0.03$). FF 50-200 mug once daily significantly increased FEV(1) from baseline ($p < 0.05$ vs placebo), by >200 mL for FF 100 mug and 200 mug. Significant improvements were also achieved for peak expiratory flow, and percentage symptom-free and rescue-free 24 h periods. The magnitude of effect was at least as good as twice-daily FP. Overall, once-daily FF was well tolerated with no systemic corticosteroid effects. CONCLUSION: FF 50-200 mug/day once daily in the evening demonstrated dose-related efficacy in asthma with 100-200 mug appearing to be the optimal doses for further evaluation.

ClinicalTrials.gov: NCT00603382.

Bensch, G. W., L. S. Greos, et al. (2011). "Linear growth and bone maturation are unaffected by 1 year of therapy with inhaled flunisolide hydrofluoroalkane in prepubescent children with mild persistent asthma: a randomized, double-blind, placebo-controlled trial." Ann Allergy Asthma Immunol 107(4): 323-9.

BACKGROUND: Inhaled corticosteroids (ICS) are the preferred long-term therapy for subjects with persistent asthma. However, concerns remain about potential effects of long-term ICS use on growth in children. OBJECTIVE: To determine the effect of 1 year of inhalation therapy with flunisolide hydrofluoroalkane (HFA) on growth velocity and bone maturation in children with mild persistent asthma. METHODS: In this double-blind, placebo-controlled study, 218 prepubescent (Tanner Stage 1) children with mild persistent asthma ranging in age from 4 to 10 years were evaluated. After a 2-week run-in period, subjects were randomized (1:1) to 2 puffs flunisolide HFA twice daily (85 mug/puff) or placebo for 52 weeks. Height was assessed by stadiometry at each visit. Growth velocity (cm/52 weeks) was estimated by the slope of the linear regression of height over time. An independent assessor scored hand and wrist radiographs for bone development pretreatment and at week 52. Analysis of covariance was used for all efficacy endpoints. RESULTS: The 2 treatment groups were similar at baseline for sex, race, age, weight, and height. At the end of double-blind treatment, mean growth velocity was 6.01 ± 1.84 cm/52 weeks for flunisolide HFA ($n = 106$) and 6.19 ± 1.30 cm/52 weeks for placebo ($n = 112$) ($P = .425$). Mean advancement in bone age during the 1-year study was similar for the 2 groups: 0.93 ± 0.46 years for flunisolide HFA ($n = 70$) and 1.01 ± 0.41 years for placebo ($n = 75$) ($P = .128$). CONCLUSIONS: In this study, flunisolide HFA did not suppress growth or bone maturation at the highest approved dose for children with persistent asthma.

Bleecker, E. R., E. D. Bateman, et al. (2012). "Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids." Ann Allergy Asthma Immunol 109(5): 353-8 e4.

BACKGROUND: Fluticasone furoate (FF) is an inhaled corticosteroid (ICS) with 24-hour activity in development as a once-daily treatment for the long-term management of

asthma. OBJECTIVE: To assess the efficacy and safety of 4 doses of once-daily FF administered using a dry powder inhaler in patients ($>/=12$ years) with moderate asthma, uncontrolled on low-dose ICS (fluticasone propionate [FP] 200 mug/day or equivalent). METHODS: This double-blind, placebo-controlled, dose-ranging study randomized 622 patients to 1 of 6 treatments: FF (100, 200, 300, or 400 mug) once daily in the evening, FP 250 mug twice daily (active control), or placebo for 8 weeks. The primary endpoint was the change from baseline in predose evening forced expiratory volume in 1 second (FEV1) at week 8. RESULTS: At week 8, relative to placebo, all doses of FF once daily and FP twice daily demonstrated significantly ($P < .001$) greater increases from baseline and greater than 200-mL increases in predose FEV1. There was no evidence of a dose-response relationship between FF doses. Improvement with once-daily FF was similar to or greater than that for twice-daily FP. Secondary efficacy endpoint findings generally supported the efficacy of FF 100 to 400 mug once daily, although statistically significant improvements versus placebo in symptom-free 24-hour periods were only reported for FF 400 mug. There were few withdrawals due to lack of efficacy. Oral candidiasis was reported in 0 to 4% of patients; 24-hour urinary cortisol excretion ratios were similar across active treatment groups and not significantly different from placebo. CONCLUSION: FF 100 to 400 mug once daily in the evening is effective and well tolerated in patients with asthma uncontrolled on low-dose ICS, with 100 mug and 200 mug, considered the most applicable doses in this asthma population. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00603278.

Bousquet, J., Z. Siergiejko, et al. (2011). "Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma." Allergy 66(5): 671-8.

BACKGROUND: The physician's global evaluation of treatment effectiveness (GETE) at 16 weeks has been shown to be the most effective assessment of response to omalizumab (XOLAIR(R)). This randomized, open-label, parallel-group study evaluated the persistency of treatment responder classification in patients receiving omalizumab added to optimized asthma therapy (OAT). METHODS: Patients (12-75 years, n = 400) with severe allergic asthma, uncontrolled despite Global Initiative for Asthma 2004 Step 4 therapy, received OAT and omalizumab (n = 272) or OAT (n = 128) for 32 weeks. Response or nonresponse was evaluated at Weeks 16 and 32. Response was defined as an investigator's (physician's) GETE rating of excellent or good; nonresponse was defined as a rating of moderate, poor or worsening. RESULTS: Three hundred and forty-nine patients had GETE ratings available at Weeks 16 and 32 (omalizumab n = 258, OAT n = 91). Omalizumab responders of about 171/187 (91.4%) and 44/71 (62.0%) omalizumab nonresponders at Week 16 persisted as responders or nonresponders at Week 32. The investigator's GETE at Week 16 predicted persistency of response or nonresponse to omalizumab at Week 32 for 83.3% (215/258) of patients. OAT patients showed a lower persistency of response (18/28 [64.3%]) and a higher persistency of nonresponse (57/63 [90.5%]) than omalizumab patients. Excellent and good GETE ratings in omalizumab-treated patients were reflected by improvements in exacerbation rates ($P < 0.001$), severe exacerbation rates ($P = 0.023$), hospitalizations ($P = 0.003$), total emergency visits ($P = 0.026$) and Asthma Control Questionnaire overall score ($P < 0.001$). CONCLUSION: Response to omalizumab, as assessed by a physician's GETE at 16 weeks, is an effective predictor of continuing persistent response to omalizumab for the majority of patients.

Busse, W. W., E. R. Bleecker, et al. (2012). "Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial." *Thorax* 67(1): 35-41.

BACKGROUND: Fluticasone furoate (FF) is a novel inhaled corticosteroid with 24 h activity. FF is being developed as a once-daily treatment in combination with the long-acting beta(2) agonist vilanterol trifenatate for asthma and chronic obstructive pulmonary disease. **OBJECTIVES:** To determine the optimal dose(s) of FF for treating patients with asthma. **METHODS:** An 8-week multicentre, randomised, double-blind study. 627 patients with persistent moderate-to-severe asthma, symptomatic on medium-dose inhaled corticosteroid therapy, were randomised to placebo, FF 200, 400, 600 or 800 mug (once daily in the evening using a novel dry powder inhaler), or fluticasone propionate 500 mug twice daily (via Diskus/Accuhaler). The primary efficacy measure was mean change from baseline in pre-dose evening forced expiratory volume in one second (FEV(1)). Other endpoints included morning and evening peak expiratory flow, and rescue/symptom-free 24 h periods. **RESULTS:** Each dose was significantly superior to placebo for the primary endpoint ($p<0.001$) with efficacy at least similar to that reported with fluticasone propionate. There was no dose-response relationship across the FF doses studied. Peak expiratory flow improved in all groups ($p<0.001$ vs placebo), and there were significant treatment effects on rescue/symptom-free 24 h periods with all active treatments. FF was generally well tolerated. The incidence of oral candidiasis was higher with FF 800 mug than placebo; pharmacokinetic and 24 h urinary cortisol analyses confirmed a higher systemic exposure of FF at this highest dose level. **CONCLUSIONS:** FF doses <800 mug have a favourable therapeutic index. The absence of an efficacy dose response suggests that 200 mug is an appropriate dose in patients with moderate persistent asthma. **CLINICALTRIALS.GOV IDENTIFIER:** NCT00603746.

Chuchalin, A. G., A. N. Tsoi, et al. (2007). "Safety and tolerability of indacaterol in asthma: a randomized, placebo-controlled 28-day study." *Respir Med* 101(10): 2065-75.

The safety and tolerability of indacaterol, a novel once-daily beta(2)-agonist bronchodilator with a fast onset of action, were assessed in 156 asthma patients in a multicentre, randomized, double-blind, placebo-controlled study. Patients received indacaterol 200, 400 or 600 microg or placebo once daily for 28 days. Adverse events (AEs), laboratory assessments, vital signs, electrocardiograms, spirometry and physical examinations were monitored. Indacaterol pharmacokinetics were assessed. There was no evidence of dose-related increases in AE incidence or clinically significant hypokalaemia or hyperglycaemia in indacaterol-treated patients. Mean pulse rate changes were minor in any group, with maximum 1-h post-dose changes from baseline of -3.7, -3.3 and -2.2 bpm for indacaterol 200, 400 and 600 microg, respectively, and -2.9 bpm for placebo. Mean QTc interval was similar between groups; change from baseline >60 ms occurred in only two patients. Mean FEV(1) increased after the first indacaterol dose; baseline-adjusted pre-dose (trough) values remained >or=166 mL higher than placebo at all subsequent visits, supporting a 24-h bronchodilator effect. Pre-dose (but not post-dose) serum indacaterol concentrations indicated a slight trend for accumulation. Once-daily indacaterol 200-600 microg has a favourable therapeutic index. It is well tolerated, and is

not associated with any adverse cardiac or metabolic effects, while providing effective 24-h bronchodilation.

Frampton, J. E. (2012). "Mometasone/formoterol inhalation aerosol: in asthma uncontrolled on medium- or high-dose inhaled corticosteroids." *Drugs* 72(9): 1229-41.

The corticosteroid mometasone and the long-acting beta(2)-selective adrenoreceptor agonist formoterol have been combined in a single pressurized metered-dose inhaler for use in patients aged ≥ 12 years with asthma. In a 26-week well designed trial in patients with persistent asthma uncontrolled on medium-dose inhaled corticosteroids (ICS), mometasone/formoterol 200 mug/10 mug twice daily (bid) was more effective than placebo or the same nominal dosage of formoterol alone in reducing the incidence of asthma deteriorations, as well as in improving lung function, asthma control, asthma symptoms and asthma-related quality-of-life outcomes. The combination was also more effective than the same nominal dosage of mometasone alone in improving lung function and asthma control. Similarly, in a 12-week well designed trial in patients with persistent asthma uncontrolled on high-dose ICS, mometasone/formoterol 400 mug/10 mug bid was more effective than the same nominal dosage of mometasone alone in improving lung function, asthma control and asthma symptoms. Treatment with a lower dosage of the combination (200 mug/10 mug bid) yielded similar results and, moreover, significantly reduced the incidence of asthma deteriorations compared with mometasone alone. Mometasone/formoterol was generally well tolerated in clinical trials of 12-52 weeks' duration. The adverse event profile of the combination was consistent with that of its individual components; no new or unexpected safety signals were detected.

Guilbert, T. W., D. T. Mauger, et al. (2011). "Growth of preschool children at high risk for asthma 2 years after discontinuation of fluticasone." *J Allergy Clin Immunol* 128(5): 956-63 e1-7.

BACKGROUND: The effect on linear growth of daily long-term inhaled corticosteroid therapy in preschool-aged children with recurrent wheezing is controversial. **OBJECTIVE:** We sought to determine the effect of daily inhaled corticosteroid given for 2 years on linear growth in preschool children with recurrent wheezing. **METHODS:** Children aged 2 and 3 years with recurrent wheezing and positive modified Asthma Predictive Index scores were randomized to a 2-year treatment period of chlorofluorocarbon-delivered fluticasone propionate (176 mug/d) or masked placebo delivered through a valved chamber with a mask and then followed for 2 years off study medication. Height growth determined by means of stadiometry was compared between treatment groups. **RESULTS:** In the study cohort as a whole, the fluticasone group did not have significantly less linear growth than the placebo group (change in height from baseline difference, -0.2 cm; 95% CI, -1.1 to 0.6) 2 years after discontinuation of study treatment. In post hoc analyses children 2 years old who weighed less than 15 kg at enrollment and were treated with fluticasone had less linear growth compared with those treated with placebo (change in height from baseline difference, -1.6 cm; 95% CI, -2.8 to -0.4; $P = .009$). **CONCLUSION:** Linear growth was not significantly different in high-risk preschool-aged children with recurrent wheezing treated with 176 mug/d chlorofluorocarbon-delivered fluticasone compared with placebo 2 years after fluticasone is discontinued. However, post hoc subgroup analyses revealed that children who are

younger in age and of lesser weight relative to the entire study cohort had significantly less linear growth, possibly because of a higher relative fluticasone exposure.

Hanania, N. A., O. Alpan, et al. (2011). "Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial." Ann Intern Med 154(9): 573-82.

BACKGROUND: Inhaled corticosteroids (ICS) and long-acting beta(2)-agonists (LABAs) are recommended in patients with asthma that is not well-controlled; however, many patients continue to have inadequately controlled asthma despite this therapy.

OBJECTIVE: To evaluate the efficacy and safety of omalizumab in patients with inadequately controlled severe asthma who are receiving high-dose ICS and LABAs, with or without additional controller therapy. **DESIGN:** Prospective, multicenter, randomized, parallel-group, double-blind, placebo-controlled trial. (ClinicalTrials.gov registration number: NCT00314575). **SETTING:** 193 investigational sites in the United States and 4 sites in Canada. **PATIENTS:** 850 patients aged 12 to 75 years who had inadequately controlled asthma despite treatment with high-dose ICS plus LABAs, with or without other controllers. **Intervention:** Omalizumab (n = 427) or placebo (n = 423) was added to existing medication regimens for 48 weeks. **MEASUREMENTS:** The primary end point was the rate of protocol-defined exacerbations over the study period. Secondary efficacy end points included the change from baseline to week 48 in mean daily number of puffs of albuterol, mean total asthma symptom score, and mean overall score on the standardized version of the Asthma Quality of Life Questionnaire (AQLQ[S]). Safety end points included the frequency and severity of treatment-emergent adverse events. **RESULTS:** During 48 weeks, the rate of protocol-defined asthma exacerbations was significantly reduced for omalizumab compared with placebo (0.66 vs. 0.88 per patient; P = 0.006), representing a 25% relative reduction (incidence rate ratio, 0.75 [95% CI, 0.61 to 0.92]). Omalizumab improved mean AQLQ(S) scores (0.29 point [CI, 0.15 to 0.43]), reduced mean daily albuterol puffs (-0.27 puff/d [CI, -0.49 to -0.04 puff/d]), and decreased mean asthma symptom score (-0.26 [CI, -0.42 to -0.10])

compared with placebo during the 48-week study period. The incidence of adverse events (80.4% vs. 79.5%) and serious adverse events (9.3% vs. 10.5%) were similar in the omalizumab and placebo groups, respectively. **LIMITATIONS:** The results are limited by early patient discontinuation (20.8%). The study was not powered to detect rare safety events or the treatment effect in the oral corticosteroid subgroup. **CONCLUSION:** In this study, omalizumab provided additional clinical benefit for patients with severe allergic asthma that is inadequately controlled with high-dose ICS and LABA therapy. Primary Funding Source: Genentech and Novartis Pharmaceuticals.

Kerstjens, H. A., M. Engel, et al. (2012). "Tiotropium in asthma poorly controlled with standard combination therapy." N Engl J Med 367(13): 1198-207.

BACKGROUND: Some patients with asthma have frequent exacerbations and persistent airflow obstruction despite treatment with inhaled glucocorticoids and long-acting beta-agonists (LABAs). **METHODS:** In two replicate, randomized, controlled trials involving 912 patients with asthma who were receiving inhaled glucocorticoids and LABAs, we compared the effect on lung function and exacerbations of adding tiotropium (a total dose of 5 mug) or placebo, both delivered by a soft-mist inhaler once daily for 48 weeks. All the patients were symptomatic, had a post-bronchodilator forced expiratory volume in 1

second (FEV(1)) of 80% or less of the predicted value, and had a history of at least one severe exacerbation in the previous year. RESULTS: The patients had a mean baseline FEV(1) of 62% of the predicted value; the mean age was 53 years. At 24 weeks, the mean (+/-SE) change in the peak FEV(1) from baseline was greater with tiotropium than with placebo in the two trials: a difference of 86+/-34 ml in trial 1 ($P=0.01$) and 154+/-32 ml in trial 2 ($P<0.001$). The predose (trough) FEV(1) also improved in trials 1 and 2 with tiotropium, as compared with placebo: a difference of 88+/-31 ml ($P=0.01$) and 111+/-30 ml ($P<0.001$), respectively. The addition of tiotropium increased the time to the first severe exacerbation (282 days vs. 226 days), with an overall reduction of 21% in the risk of a severe exacerbation (hazard ratio, 0.79; $P=0.03$). No deaths occurred; adverse events were similar in the two groups. CONCLUSIONS: In patients with poorly controlled asthma despite the use of inhaled glucocorticoids and LABAs, the addition of tiotropium significantly increased the time to the first severe exacerbation and provided modest sustained bronchodilation. (Funded by Boehringer Ingelheim and Pfizer; ClinicalTrials.gov numbers, NCT00772538 and NCT00776984.).

Kerstjens, H. A., B. Disse, et al. (2011). "Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial." *J Allergy Clin Immunol* 128(2): 308-14.

BACKGROUND: Some patients with severe asthma remain symptomatic and obstructed despite maximal recommended treatment. Tiotropium, a long-acting inhaled anticholinergic agent, might be an effective bronchodilator in such patients.

OBJECTIVE: We sought to compare the efficacy and safety of 2 doses of tiotropium (5 and 10 mug daily) administered through the Respimat inhaler with placebo as add-on therapy in patients with uncontrolled severe asthma (Asthma Control Questionnaire score, ≥ 1.5 ; postbronchodilator FEV(1), $\leq 80\%$ of predicted value) despite maintenance treatment with at least a high-dose inhaled corticosteroid plus a long-acting beta(2)-agonist.

METHODS: This was a randomized, double-blind, crossover study with three 8-week treatment periods. The primary end point was peak FEV(1) at the end of each treatment period.

RESULTS: Of 107 randomized patients (54% female patients; mean, 55 years of age; postbronchodilator FEV(1), 65% of predicted value), 100 completed all periods. Peak FEV(1) was significantly higher with 5 mug (difference, 139 mL; 95% CI, 96-181 mL) and 10 mug (difference, 170 mL; 95% CI, 128-213 mL) of tiotropium than with placebo (both $P < .0001$). There was no significant difference between the active doses. Trough FEV(1) at the end of the dosing interval was higher with tiotropium (5 mug: 86 mL [95% CI, 41-132 mL]; 10 mug: 113 mL [95% CI, 67-159 mL]; both $P < .0004$). Daily home peak expiratory flow measurements were higher with both tiotropium doses. There were no significant differences in asthma-related health status or symptoms. Adverse events were balanced across groups except for dry mouth, which was more common on 10 mug of tiotropium.

CONCLUSION: The addition of once-daily tiotropium to asthma treatment, including a high-dose inhaled corticosteroid plus a long-acting beta(2)-agonist, significantly improves lung function over 24 hours in patients with inadequately controlled, severe, persistent asthma.

Krishnan, J. A., B. G. Bender, et al. (2012). "Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial." *J Allergy Clin Immunol* 129(1): 112-8.

BACKGROUND: Information comparing subjective and objective measurements of adherence to study medications and the effects of adherence on treatment-related differences in asthma clinical trials are limited. **OBJECTIVE:** We sought to compare subjective and objective measurements of children's adherence to inhaled corticosteroids or placebo and to determine whether adherence to study medications modified treatment-related differences in outcomes. **METHODS:** In an ancillary study conducted in 3 of 8 Childhood Asthma Management Program Clinical Centers, adherence was assessed by using self-reported and objective data in 5- to 12-year-old children with mild or moderate asthma who were randomly assigned to 200 mug of inhaled budesonide twice per day ($n = 84$) or placebo ($n = 56$) for 4 years. The kappa statistic was used to evaluate agreement between self-reported adherence (daily diary cards) and objectively measured adherence (number of doses left in study inhalers). Multivariable analyses were used to determine whether adherence to study treatment modified treatment-related differences in outcomes. **RESULTS:** Adherence of less than 80% was seen in 75% of 140 children when adherence was measured objectively but only in 6% of children when measured by means of self-report. There was poor agreement between objective and subjective measurements of adherence of at least 80% ($\kappa = 0.00$; 95% CI, -0.05 to 0.04); self-reported adherence over the 4-year period generally overestimated objectively measured adherence (93.6% vs 60.8%, $P < .0001$). There was little evidence to indicate that adherence modified treatment-related differences in outcomes. **CONCLUSION:** Researchers should use objective rather than self-reported adherence data to identify clinical trial participants with low levels of adherence to study treatment.

Pedersen, S., P. Potter, et al. (2010). "Efficacy and safety of three ciclesonide doses vs placebo in children with asthma: the RAINBOW study." *Respir Med* 104(11): 1618-28.

OBJECTIVE: To evaluate the efficacy and safety of three doses of ciclesonide (with or without spacer) in children with persistent asthma. **PATIENTS AND METHODS:** This was a multicentre, double-blind, placebo-controlled, 12-week study of ciclesonide 40, 80 or 160 mug (once daily pm). Children (6-11 years) were randomised 1:1 to treatment via a metered dose inhaler (MDI) or MDI plus spacer. The primary variable was change from baseline in mean morning peak expiratory flow (PEF). Secondary variables included: time to first lack of efficacy (LOE), asthma control, forced expiratory volume in 1 s (FEV(1)), asthma symptom score and quality of life (QoL). Safety assessments included: adverse events (AEs), urinary cortisol excretion and body height. **RESULTS:** In total, 1073 children received treatment. At endpoint, mean morning PEF significantly improved with all doses of ciclesonide vs. placebo. There was no difference over placebo in time to first LOE, but ciclesonide was superior to placebo on asthma control, symptom score, FEV(1) and QoL. There were no differences between the spacer or non-spacer subgroups. The incidences of AEs were comparable between treatment groups (approximately 35%) and there were no between-group differences in body height or urinary cortisol. **CONCLUSIONS:** Ciclesonide 40-160 mug once daily is effective and well tolerated in children with persistent asthma; its efficacy and safety are unaffected by the use of a spacer. clinicaltrials.gov registration number: NCT00384189.

Philip, G., C. Villaran, et al. (2011). "The efficacy and tolerability of inhaled montelukast plus inhaled mometasone compared with mometasone alone in patients with chronic asthma." *J Asthma* 48(5): 495-502.

BACKGROUND: The efficacy of oral montelukast in chronic asthma is well established. Montelukast is also an effective adjunctive therapy to inhaled corticosteroids (ICS) in asthma uncontrolled on ICS alone. Inhaled montelukast was recently shown to provide significant bronchodilation compared with placebo in patients with chronic asthma. The purpose of this study was to evaluate the efficacy of inhaled montelukast added to inhaled mometasone. **METHODS:** This was an 8-week, multicenter, randomized, double-blind, placebo-controlled study comparing once-daily inhaled montelukast 1 mg plus inhaled mometasone 220 mug (delivered by separate dry powder inhalers) with placebo plus inhaled mometasone 220 mug. Men and women aged 15-85 years with chronic asthma, forced expiratory volume in 1 second (FEV(1)) 50-80% of the predicted value, and beta-agonist reversibility $\geq 12\%$ were eligible. Patients were required to meet a minimum symptom threshold while receiving open-label inhaled mometasone during a 3-week prestudy/run-in period. Patients received blinded (montelukast vs. placebo) treatment for 2 weeks, entered a 1-week washout period, then crossed over to the other treatment for 2 weeks. The primary endpoint was the average change from baseline in FEV(1) over the 2-week treatment period. Secondary endpoints included daytime and nighttime symptom scores. Other endpoints included short-acting beta-agonist (SABA) use, asthma exacerbations, asthma control, peak expiratory flow (PEF), and blood eosinophil count. **RESULTS:** A total of 134 patients were randomized. For the primary endpoint, change from baseline in FEV(1), inhaled montelukast plus inhaled mometasone was significantly more effective than placebo plus inhaled mometasone (least squares mean 0.22 L vs. 0.17 L; $p = .033$ [two-sided at alpha = 0.05]). Inhaled montelukast plus inhaled mometasone was also significantly more effective than placebo plus inhaled mometasone in improving daytime asthma symptom scores ($p = .005$) and nighttime asthma symptom scores ($p = .015$), increasing the percentage of days with asthma control ($p = .004$), decreasing the percentage of days with asthma exacerbations ($p \leq .001$), and decreasing the blood eosinophil count ($p = .013$). Differences were not significant on AM or PM PEF or SABA use, although the latter approached significance ($p = .073$). Both treatments were well tolerated. **CONCLUSION:** Inhaled montelukast plus inhaled mometasone was significantly more effective than placebo plus inhaled mometasone in improving FEV(1), symptoms, asthma control, and blood eosinophil count.

Rubin, A. S., A. Souza-Machado, et al. (2012). "Effect of omalizumab as add-on therapy on asthma-related quality of life in severe allergic asthma: a Brazilian study (QUALITX)." *J Asthma* 49(3): 288-93.

OBJECTIVE: To assess the impact of omalizumab as an add-on therapy to standard treatment with inhaled corticosteroids (ICS) and long-acting beta-2 agonists (LABA) on asthma-related quality of life (QoL) in patients with severe allergic asthma. **METHODS:** This was a 20-week, randomized, open-label, study involving Brazilian patients (>12 years) with severe persistent allergic asthma inadequately controlled despite regular treatment with, at least, ICS (≥ 500 mug/day fluticasone or equivalent) + LABA. The primary objective was to assess the mean change from baseline in overall Asthma-related

Quality of Life Questionnaire (AQLQ) score in omalizumab-treated patients compared with the control group. Secondary outcome measures included rescue medication use, incidence of asthma exacerbations, perception of treatment efficacy among patients, mean change from baseline in AQLQ score, and >1.5-point increase in overall AQLQ score. RESULTS: In the omalizumab group, overall AQLQ score was 3.2 (0.9) (mean [SD]) at baseline and 4.4 (1.3) at week 20 versus 3.0 (1.0) at baseline and 3.0 (1.1) at week 20 in the control group. Mean change from baseline on overall AQLQ score at week 20 in the omalizumab group was 1.2 (0.2) versus 0 (0.1) in the control group, showing a significant increase in scores from baseline in the omalizumab group ($p < .001$). There was also a statistically significant difference ($p < .001$) in the number of patients who showed a >1.5-point increase from baseline in overall AQLQ score after 20 weeks, thus indicating a better QoL in the omalizumab group. There was no significant difference with respect to the use of rescue medication, incidence of asthma exacerbation, and adverse events between treatment groups. The global evaluation of treatment effectiveness was significantly better for omalizumab ($p < .001$). CONCLUSION: Omalizumab was well tolerated and significantly improved the overall AQLQ score. Hence, it is a potential add-on therapy for severe persistent allergic asthma not controlled by standard prescribed treatment in Brazilian patients.

Skoner, D. P., E. O. Meltzer, et al. (2011). "Effects of inhaled mometasone furoate on growth velocity and adrenal function: a placebo-controlled trial in children 4-9 years old with mild persistent asthma." *J Asthma* 48(8): 848-59.

OBJECTIVE: To assess the effects of long-term mometasone furoate delivered via a dry powder inhaler (MF-DPI) on growth velocity and hypothalamic-pituitary-adrenal axis function in children with asthma. STUDY DESIGN: Children aged 4-9 years with asthma ($n = 187$) were randomized to MF-DPI 100 mug (delivered dose; actuated dose is 110 mug) once daily in the morning (QD AM), 100 mug twice daily (BID), 200 mug QD AM, or placebo for 52 weeks followed by a 3-month follow-up period. The primary outcome was growth velocity calculated from stadiometric heights recorded at each visit. Secondary outcomes included serum and 12-h urinary cortisol, serum osteocalcin, and urinary N-telopeptide. RESULTS: MF-DPI 100 mug QD AM treatment did not significantly affect growth velocity compared with placebo (-0.10 ± 0.31 cm/y, $p = 0.76$). When the effect of a total daily dose of 200 mug MF-DPI on growth velocity was examined, no significant effect was demonstrated for MF-DPI 100 mug BID compared with placebo (-0.64 ± 0.39 cm/y, $p = 0.10$), although the change in mean growth velocity with MF-DPI 200 mug QD AM reached statistical significance (-0.70 ± 0.29 cm/y, $p = 0.02$). The effects of all examined doses of MF-DPI on mean plasma cortisol levels were similar to cortisol changes seen in the placebo group, suggesting an absence of drug-related effects. No differences in 12-h urinary cortisol or other outcomes were observed between groups. CONCLUSIONS: One year of treatment with a total daily dose of 100 mug of MF-DPI in the morning resulted in no significant difference, whereas a total daily dose of 200 mug of MF-DPI was associated with some changes in growth velocity when compared with placebo. The differences in growth velocity, and the absence of drug-related cortisol effects, support the use of a total daily dose of 100 mug of MF-DPI in children aged 4-9 years with mild persistent asthma.

Sterling, R., J. Lim, et al. (2012). "Efficacy and optimal dosing interval of the long-acting beta(2) agonist, vilanterol, in persistent asthma: a randomised trial." *Respir Med* 106(8): 1110-5.

BACKGROUND: Vilanterol (VI) is a novel once-daily long-acting beta(2) agonist with inherent 24-h activity. The aim of this study was to evaluate the efficacy of three once-daily doses and one twice-daily dose of VI used concurrently with ICS in adult patients ($>/=18$ years) with persistent asthma. Safety was also assessed. **METHODS:** Multicentre, randomised, double-blind, placebo-controlled, five-period crossover study consisting of 7-day treatment periods separated by 7-day wash-out periods. Seventy-five patients, maintained on ICS, received VI 6.25, 12.5 and 25 mcg once-daily (evening), VI 6.25 mcg twice-daily (morning/evening), and placebo. The primary endpoint was trough forced expiratory volume in 1 s (FEV(1)) (mean of 23 h and 24 h post evening dose) on Day 7; secondary endpoint was weighted mean 24-h serial FEV(1) on Day 7. **RESULTS:** All VI groups demonstrated statistically significant increases in trough FEV(1) versus placebo ($p < 0.001$). There was a statistically significant increase in weighted mean 24-h FEV(1) for each VI group versus placebo ($p < 0.001$). The effects of once-daily VI on trough FEV(1) and weighted mean 24-h FEV(1) were dose dependent. The incidence of adverse events (AEs) was low in each VI treatment group and was not dose dependent (5-9%; placebo = 18%); no drug-related AEs or serious AEs were reported. **CONCLUSION:** Once-daily treatment with VI was well tolerated and associated with improvements in lung function. The VI 6.25 mcg twice-daily dose showed the greatest change in trough FEV(1), however, similar changes in weighted mean 24-h FEV(1) with VI 12.5 mcg once-daily were observed. Although our study was not powered to demonstrate non-inferiority of once- versus twice-daily dosing of VI, the data suggest no advantage over a 24-h period of twice-daily over once-daily dosing for the same total daily dose. ClinicalTrials.gov: NCT00980200.

Valovirta, E., M. L. Boza, et al. (2011). "Intermittent or daily montelukast versus placebo for episodic asthma in children." *Ann Allergy Asthma Immunol* 106(6): 518-26.

BACKGROUND: No standard, optimal treatment exists for severe intermittent (ie, episodic) asthma in children. However, evidence suggests that both daily and episode-driven montelukast are effective for this phenotype. **OBJECTIVE:** To assess the regimen-related efficacy of montelukast in treating pediatric episodic asthma. **METHODS:** A multicenter, randomized, double-blind, double-dummy, parallel-group, 52-week study was performed in children 6 months to 5 years of age comparing placebo with two regimens of montelukast 4 mg: (1) daily; or (2) episode-driven for 12 days beginning with signs/symptoms consistent with imminent cold or breathing problem. The main outcome measure was the number of asthma episodes (symptoms requiring treatment) culminating in an asthma attack (symptoms requiring physician visit, emergency room visit, corticosteroids, or hospitalization). **RESULTS:** Five hundred eighty-nine patients were randomized to daily montelukast, 591 to intermittent montelukast, and 591 to placebo. Compared with placebo, no significant difference was seen between daily montelukast ($P = .510$) or intermittent montelukast ($P = .884$) in the number of asthma episodes culminating in an asthma attack over 1 year. Daily montelukast reduced symptoms over the 12-day treatment period of asthma episodes compared with placebo ($P = .045$). Beta-agonist use was reduced with both daily ($P = .048$) and intermittent montelukast ($P = .028$) compared with placebo. However, because of prespecified rules

for multiplicity adjustments (requiring a positive primary endpoint), statistical significance for secondary endpoints cannot be concluded. All treatments were well tolerated. CONCLUSIONS: Montelukast did not reduce the number of asthma episodes culminating in an asthma attack over 1 year in children 6 months to 5 years of age, although numerical improvements occurred in some endpoints.

Woodcock, A., E. D. Bateman, et al. (2011). "Efficacy in asthma of once-daily treatment with fluticasone furoate: a randomized, placebo-controlled trial." *Respir Res* 12(132).

BACKGROUND: Fluticasone furoate (FF) is a novel long-acting inhaled corticosteroid (ICS). This double-blind, placebo-controlled randomized study evaluated the efficacy and safety of FF 200 mcg or 400 mcg once daily, either in the morning or in the evening, and FF 200 mcg twice daily (morning and evening), for 8 weeks in patients with persistent asthma. **METHODS:** Asthma patients maintained on ICS for ≥ 3 months with baseline morning forced expiratory volume in one second (FEV(1)) 50-80% of predicted normal value and FEV(1) reversibility of $\geq 12\%$ and ≥ 200 ml were eligible. The primary endpoint was mean change from baseline FEV(1) at week 8 in pre-dose (morning or evening [depending on regimen], pre-rescue bronchodilator) FEV(1). **RESULTS:** A total of 545 patients received one of five FF treatment groups and 101 patients received placebo (intent-to-treat population). Each of the five FF treatment groups produced a statistically significant improvement in pre-dose FEV(1) compared with placebo ($p < 0.05$). FF 400 mcg once daily in the evening and FF 200 mcg twice daily produced similar placebo-adjusted improvements in evening pre-dose FEV(1) at week 8 (240 ml vs. 235 ml). FF 400 mcg once daily in the morning, although effective, resulted in a smaller improvement in morning pre-dose FEV(1) than FF 200 mcg twice daily at week 8 (315 ml vs. 202 ml). The incidence of oral candidiasis was low (0-4%) and UC excretion was comparable with placebo for all FF groups. **CONCLUSIONS:** FF at total daily doses of 200 mcg or 400 mcg was significantly more effective than placebo. FF 400 mcg once daily in the evening had similar efficacy to FF 200 mcg twice daily and all FF regimens had a safety tolerability profile generally similar to placebo. This indicates that inhaled FF is an effective and well tolerated once-daily treatment for mild-to-moderate asthma.

TRIAL REGISTRATION: NCT00398645.

Secondary analyses of included primary trial publications

Camargo, C. A., Jr., E. R. Sutherland, et al. (2010). "Effect of increased body mass index on asthma risk, impairment and response to asthma controller therapy in African Americans." *Curr Med Res Opin* 26(7): 1629-35.

OBJECTIVE: To explore whether obesity alters the risk, impairment and response to treatment in African Americans with asthma. **METHODS:** The data used for this secondary analysis are from a 1-year study in African American subjects comparing fluticasone propionate/salmeterol 100/50 microg combination (FSC) and fluticasone propionate 100 microg (FP). Subjects were retrospectively stratified by body mass index (BMI) <20 [underweight], 20-24.9 [normal weight], 25-29.9 [overweight], 30-34.9 [obese I], 35-39.9 [obese II], and $>=40$ [obese III] kg/m². Outcomes studied included impairment domains: FEV(1), morning and evening peak expiratory flow (AM and PM PEF), daily albuterol use, daily symptom scores and future risk domain: exacerbations.

CLINICAL TRIAL REGISTRATION: www.clinicaltrials.gov; NCT00102765.

RESULTS: There were 475 subjects evenly distributed between FSC and FP by baseline parameters. There were 207 subjects with a BMI $>\text{or}=30$, including 70 subjects with a BMI $>\text{or}=40$. Baseline BMI $>\text{or}=40$ was associated with numerically lower baseline AM and PM PEF. There was an attenuation of response to both treatments for only PM PEF ($p < 0.05$). By contrast, subjects with lower degrees of obesity or overweight did not differ from those with normal weight. The total population exacerbation rate was 2-fold greater in obese III subjects (39%) compared with subjects in other BMI categories (16-21%) ($p < 0.05$). A potential study limitation is the retrospective analysis of existing data.

DISCUSSION: Response to treatment was attenuated for PM PEF for subjects with BMI $>\text{or}=40$ and was also associated with an increased rate of asthma exacerbations.

Cohen, R. T., B. A. Raby, et al. (2010). "In utero smoke exposure and impaired response to inhaled corticosteroids in children with asthma." *J Allergy Clin Immunol* 126(3): 491-7.

BACKGROUND: Few studies have examined the effects of in utero smoke exposure (IUS) on lung function in children with asthma, and there are no published data on the impact of IUS on treatment outcomes in children with asthma. **OBJECTIVES:** To explore whether IUS exposure is associated with increased airway responsiveness among children with asthma and whether IUS modifies the response to treatment with inhaled corticosteroids (ICSs). **METHODS:** To assess the impact of parent-reported IUS exposure on airway responsiveness in childhood asthma, we performed a repeated-measures analysis of methacholine PC(20) data from the Childhood Asthma Management Program, a 4-year, multicenter, randomized, double-masked, placebo-controlled trial of 1041 children age 5 to 12 years comparing the long-term efficacy of ICS with mast cell stabilizing agents or placebo. **RESULTS:** Although improvement was seen in both groups, children with asthma and IUS exposure had on average 26% less of an improvement in airway responsiveness over time compared with unexposed children ($P = .01$). Moreover, while children who were not exposed to IUS who received budesonide experienced substantial improvement in PC(20) compared with untreated children (1.25-fold increase; 95% CI, 1.03-1.50; $P = .02$), the beneficial effects of budesonide were attenuated among children with a history of IUS exposure (1.04-fold increase, 95% CI, 0.65-1.68; $P = .88$). **CONCLUSION:** In utero smoke exposure reduces age-related improvements in airway responsiveness among children with asthma. Moreover, IUS appears to blunt the beneficial effects of ICS use on airways responsiveness. These results emphasize the importance of preventing this exposure through smoking cessation counseling efforts with pregnant women.

Kelly, H. W., A. L. Sternberg, et al. (2012). "Effect of inhaled glucocorticoids in childhood on adult height." *N Engl J Med* 367(10): 904-12.

BACKGROUND: The use of inhaled glucocorticoids for persistent asthma causes a temporary reduction in growth velocity in prepubertal children. The resulting decrease in attained height 1 to 4 years after the initiation of inhaled glucocorticoids is thought not to decrease attained adult height. **METHODS:** We measured adult height in 943 of 1041 participants (90.6%) in the Childhood Asthma Management Program; adult height was determined at a mean (+/-SD) age of 24.9+/-2.7 years. Starting at the age of 5 to 13 years, the participants had been randomly assigned to receive 400 mug of budesonide, 16 mg of

nedocromil, or placebo daily for 4 to 6 years. We calculated differences in adult height for each active treatment group, as compared with placebo, using multiple linear regression with adjustment for demographic characteristics, asthma features, and height at trial entry. RESULTS: Mean adult height was 1.2 cm lower (95% confidence interval [CI], -1.9 to -0.5) in the budesonide group than in the placebo group ($P=0.001$) and was 0.2 cm lower (95% CI, -0.9 to 0.5) in the nedocromil group than in the placebo group ($P=0.61$). A larger daily dose of inhaled glucocorticoid in the first 2 years was associated with a lower adult height (-0.1 cm for each microgram per kilogram of body weight) ($P=0.007$). The reduction in adult height in the budesonide group as compared with the placebo group was similar to that seen after 2 years of treatment (-1.3 cm; 95% CI, -1.7 to -0.9). During the first 2 years, decreased growth velocity in the budesonide group occurred primarily in prepubertal participants. CONCLUSIONS: The initial decrease in attained height associated with the use of inhaled glucocorticoids in prepubertal children persisted as a reduction in adult height, although the decrease was not progressive or cumulative. (Funded by the National Heart, Lung, and Blood Institute and the National Center for Research Resources; CAMP ClinicalTrials.gov number, NCT00000575.).

Vogelmeier, C., I. Naya, et al. (2012). "Budesonide/formoterol maintenance and reliever therapy in Asian patients (aged ≥ 16 years) with asthma: a sub-analysis of the COSMOS study." Clin Drug Investig 32(7): 439-49.

BACKGROUND: The combination of an inhaled corticosteroid (ICS), budesonide, and a rapid long-acting beta(2)-agonist (LABA), formoterol, in a single inhaler for use as maintenance and reliever therapy (Symbicort Turbuhaler SMART) effectively achieves a high level of asthma control and reduces exacerbations and asthma-related hospitalizations. The COSMOS study, a multinational, 12-month study ($N = 2143$), compared budesonide/formoterol maintenance and reliever therapy with salmeterol/fluticasone propionate plus as-needed salbutamol, allowing physicians to modify maintenance doses of both combinations according to routine clinical practice. **OBJECTIVE:** The aim of this post hoc sub-group analysis of the COSMOS study is to provide focused data on budesonide/formoterol maintenance and reliever therapy compared with salmeterol/fluticasone propionate plus as-needed salbutamol in patients (aged ≥ 16 years) enrolled across Asian countries, specifically China, Korea, Taiwan and Thailand. **METHODS:** This sub-analysis of the COSMOS study concerns all 404 randomized patients ≥ 16 years of age (mean forced expiratory volume in 1 second [FEV(1)] 69.1%) who were recruited from Asian countries. Patients received either budesonide/formoterol (Symbicort Turbuhaler SMART, $n = 198$), starting dose 160 mg/4.5 mg two inhalations twice daily (bid) [plus additional as-needed inhalations], or salmeterol/fluticasone propionate (Seretide((R)) Diskus((R)), $n = 206$), starting dose 50 mg/250 mg bid (plus salbutamol [Ventolin((R))] as needed). Maintenance doses could be titrated by clinicians after the first 4 weeks (budesonide/formoterol maintenance plus as needed, $n = 198$; salmeterol/fluticasone propionate plus salbutamol, $n = 206$). To allow for free adjustment in maintenance doses in both arms, the trial was performed open-label; maintenance doses could be titrated by clinicians after the first 4 weeks. The time to first severe exacerbation (defined as deterioration in asthma resulting in hospitalization/emergency room treatment, oral corticosteroids for ≥ 3 days or unscheduled visit leading to treatment change) was the primary variable. **RESULTS:** The

time to first severe exacerbation was prolonged in patients using maintenance plus as-needed budesonide/formoterol compared with salmeterol/fluticasone propionate plus salbutamol ($\log\text{-rank } p = 0.024$). The risk of a first exacerbation was reduced by 44% (hazard ratio 0.56; 95% confidence interval [CI] 0.32, 0.95; $p = 0.033$) in patients using the adjusted budesonide/formoterol regimen versus titrated salmeterol/fluticasone propionate. The overall exacerbation rates were 0.16 versus 0.26 events/patient-year, respectively, with a 38% reduction (rate ratio 0.62/patient/year; 95% CI 0.41, 0.94; $p = 0.024$) in favour of the budesonide/formoterol regimen. Compared with baseline, both regimens provided clinically relevant improvements in asthma control, quality of life and FEV(1); no statistically significant differences between the treatment groups were observed. Mean adjusted (standard deviation) ICS dose (expressed as beclomethasone dose equivalents) during treatment, including as-needed budesonide doses, was 944 (281) and 1034 (394) mug/day, respectively, in patients using maintenance plus as-needed budesonide/formoterol compared with salmeterol/fluticasone propionate.

CONCLUSION: In patients (aged $>/= 16$ years) enrolled from Asian countries as part of the COSMOS study, the budesonide/formoterol maintenance and reliever regimen was associated with a lower future risk of exacerbations versus the physicians' free choice of salmeterol/fluticasone propionate dose plus salbutamol. Single inhaler combination treatment with maintenance plus as-needed budesonide/formoterol was also at least as efficacious as salmeterol/fluticasone propionate dose plus salbutamol in improving current asthma control.

Wang, L., C. S. Hollenbeak, et al. (2011). "Cost-effectiveness analysis of fluticasone versus montelukast in children with mild-to-moderate persistent asthma in the Pediatric Asthma Controller Trial." *J Allergy Clin Immunol* 127(1): 161-6, 6 e1.

BACKGROUND: Cost-effectiveness analyses of asthma controller regimens for adults exist, but similar evaluations exclusively for children are few. **OBJECTIVE:** We sought to compare the cost-effectiveness of 2 commonly used asthma controllers, fluticasone and montelukast, with data from the Pediatric Asthma Controller Trial. **METHODS:** We compared the cost-effectiveness of low-dose fluticasone with that of montelukast in a randomized, controlled, multicenter clinical trial in children with mild-to-moderate persistent asthma. Analyses were also conducted on subgroups based on phenotypic factors. Effectiveness measures included (1) the number of asthma-control days, (2) the percentage of participants with an increase over baseline of FEV(1) of 12% or greater, and (3) the number of exacerbations avoided. Costs were analyzed from both a US health care payer's perspective and a societal perspective. **RESULTS:** For all cost-effectiveness measures studied, fluticasone cost less and was more effective than montelukast. For example, fluticasone treatment cost \$430 less in mean direct cost ($P < .01$) and resulted in 40 more asthma-control days ($P < .01$) during the 48-week study period. Considering sampling uncertainty, fluticasone cost less and was more effective at least 95% of the time. For the high exhaled nitric oxide (eNO) phenotypic subgroup ($eNO >/= 25$ ppb) and more responsive PC(20) subgroup ($PC(20) < 2$ mg/mL), fluticasone was cost-effective compared with montelukast for all cost-effectiveness measures, whereas not all the effectiveness measures were statistically different for the other 2 phenotypic subgroups. **CONCLUSION:** For children with mild-to-moderate persistent asthma, low-dose fluticasone had lower cost and higher effectiveness compared with montelukast,

especially in those with more airway inflammation, as indicated by increased levels of eNO and more responsivity to methacholine.

Drug Class Review

Triptans

Preliminary Scan Report #2

April 2013

Last Report: Update #4 (June 2009)

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

Scan conducted by:
Susan Carson, MPH

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

Copyright © 2013 by Oregon Health & Science University
Portland, Oregon 97239. All rights reserved.



OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Update #4, June 2009 (searches through January 2009)

Date of Last Preliminary Update Scan Report

April 2010

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. How do effectiveness and efficacy outcomes (reduced severity and duration of symptoms, functional outcomes, quality of life, etc) differ for adult patients with migraine within the following treatment comparisons:
 - 1a. Monotherapy compared with monotherapy
 - 1b. Fixed-dose tablets containing a triptan compared with triptan monotherapy
 - 1c. Fixed-dose tablets containing a triptan compared with co-administration of its individual triptan and analgesic components
2. How do the incidence and nature of adverse effects (serious or life-threatening or those that may adversely effect compliance) differ for adult patients with migraine within the following triptan treatment comparisons:
 - 2a. Monotherapy compared with monotherapy
 - 2b. Fixed-dose tablets containing a triptan compared with triptan monotherapy
 - 2c. Fixed-dose tablets containing a triptan compared with co-administration of its individual triptan and analgesic components

3. Are there subgroups of patients based on demographics, other medications, or comorbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

Adult patients with any level of migraine (mild, moderate, severe), with or without aura. Definition of migraine must be explicit, to exclude other types of headache (for example, tension headache).

Interventions

Table 1. Included drugs

Active ingredient	Form(s)	Brand name(s)
Almotriptan	Oral tablet	Axert®
Eletriptan	Oral tablet	Relpax®
Frovatriptan	Oral tablet	Frova®
Naratriptan	Oral tablet	Amerge®
Rizatriptan	Oral tablet, orally disintegrating tablet	Maxalt®, Maxalt-MLT®
Sumatriptan	Oral tablet, nasal spray, subcutaneous injection	Imitrex®, Imitrex® StatDose®, Sumavel DosePro®, Alsuma®
Sumatriptan	Iontophoretic transdermal system	Zecuity®
Sumatriptan-naproxen sodium fixed dose combination product	Oral tablet	Treximet®
Zolmitriptan	Oral tablet, nasal spray, orally disintegrating tablet	Zomig®, Zomig-ZMT®

*Not in most recent DERP report; FDA approved 1/17/2013

Study designs

- For effectiveness/efficacy, study is a controlled clinical trial in an outpatient setting or a good-quality systematic review.
- For harms, the study is a controlled clinical trial or observational study.

Comparators

- Another triptan
- Placebo

Effectiveness outcomes

- Reduction or resolution of symptoms (pain, nausea, vomiting, photophobia, phonophobia), reduction of duration of symptoms, duration of improvement, consistency of effectiveness (proportion of headaches successfully treated per patient), functional outcome (for example, change in days of work lost), quality of life, or adverse effect (including drug interactions).
- Measures: Response, time to response, pain-free, sustained response, sustained pain-free, rescue (use of rescue medications), recurrence (reappearance of any degree of symptoms

within 24 or 48 hours) after response or becoming pain-free, time to relief, relief of associated symptoms, tablets per attack, and patient satisfaction.

Harms outcomes

- Overall withdrawals
- Withdrawals due to any adverse events
- Withdrawals due to specific adverse events (central nervous system effects, chest tightness)

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from April 2010 through March 26, 2013 using terms for included drugs. We also searched the FDA website (<http://www.fda.gov/medwatch/safety.htm>) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (<http://www.ahrq.gov/>) and the Canadian Agency for Drugs and Technology in Health (<http://www.cadth.ca/>). All citations were imported into an electronic database (EndNote X1) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan

Zecuity (sumatriptan iontophoretic transdermal system): Approved to treat acute migraine in adults with or without aura (1/17/2013).

Identified in previous Preliminary Update Scans

None.

New Indications

Identified in this Preliminary Update Scan

None.

Identified in previous Preliminary Update Scans

Almotriptan: Acute treatment of migraine in adolescents, aged 12 to 17 years (5/2009).

New Safety Alerts***Identified in this Preliminary Update Scan***

None.

Identified in previous Preliminary Update Scans

None.

Comparative Effectiveness Reviews***Reviews identified in this Preliminary Update Scan***

We identified 2 new comparative effectiveness reviews. One compares acute migraine treatments in emergency settings, and the other is a rapid review of clinical evidence on safety of the triptans. Abstracts of these reviews are attached in Appendix A, and links to the full reports are listed below.

From the AHRQ Effective Healthcare Program:

Acute Migraine Treatment in Emergency Settings. Sumamo Schellenberg E, Dryden DM, Pasichnyk D, Ha C, Vandermeer B, Friedman BW, Colman I, Rowe BH.

Comparative Effectiveness Review No. 84. (Prepared by the University of Alberta Evidence based Practice Center under Contract No. 290-2007-10021-I.) AHRQ Publication No. 12(13)-EHC142-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012.

Available at:

http://effectivehealthcare.ahrq.gov/ehc/products/289/1323/CER84_Migraine_FinalReport_2012119.pdf

From CADTH:

Triptans for Migraine Headaches: A Review of Clinical Evidence on Safety. Rapid Response Report, Summary with Critical Appraisal. March 2012. Available at:

<http://www.cadth.ca/media/pdf/htis/mar-2012/RC0333%20Triptans%20Final.pdf>

Reviews identified in previous Preliminary Update Scans

None.

Randomized Controlled Trials***Trials identified since the most recent Full Report***

Medline searches this scan resulted in 47 citations. Of those, there were 19 potentially relevant new publications. Abstracts of these trials are attached in Appendix B. Since the most recent Update Report, we have identified 6 head-to-head trials (in 8 publications) and 16 placebo-controlled trials (Tables 2 and 3). We identified one placebo controlled trial of the newly approved product sumatriptan iontophoretic transdermal system.

Table 2. New head to head trials*

Author Year	Comparison	Focus
Ng-Mak 2009	Almotriptan vs rizatriptan	Time to response
Bartolini 2011	Almotriptan vs frovatriptan	Pain relief, recurrence
Bartolini 2012		Menstrual migraine (subgroup analysis)
Savi 2011a	Frovatriptan vs rizatriptan	Pain relief, patient satisfaction
Savi 2011b		Menstrual migraine (subgroup analysis)
Allais 2011	Frovatriptan vs zolmitriptan	Menstrual migraine
Tulio 2010	Frovatriptan vs zolmitriptan	Pain relief, recurrence, tolerability
Müller 2011	Rizatriptan orally disintegrating tablet vs sumatriptan vs parecoxib	Acute migraine

*Shading indicates trials identified in this scan; others were identified in previous scan.

Table 2. New placebo controlled trials*

Author Year	Treatment	Focus
Allais 2011a	Almotriptan	Menstrual migraine
Merelle 2009	Eletriptan	Response, quality of life, absence from work
Diener 2011	Eletriptan vs placebo vs an oral CGRP antagonist	Phase II study
Spierings 2009	Frovatriptan	Time to response, recurrence
Latsko 2011	Frovatriptan	Prophylaxis for fasting-induced migraine
Barbanti 2012	Rizatriptan	Migraine with unilateral cranial autonomic symptoms
Cady 2009	Rizatriptan ODT	Early treatment, combined with patient education
Seeburger 2012	Rizatriptan orally disintegrating tablet	Patients taking topiramate for migraine prophylaxis
Seeburger 2011	Rizatriptan orally disintegrating tablet	Nonresponders to sumatriptan
Schulman 2012	Sumatriptan transdermal system	Migraine patients with baseline nausea
Djupesland 2010	Sumatriptan nasal powder	Device (Optinose®) not yet FDA-approved
Kostic 2010	Sumatriptan injection vs placebo vs intravenous prochlorperazine	Emergency department
Mathew 2009	Sumatriptan-naproxen fixed dose combination product	Poor responders to triptan monotherapy
Cady 2011	Sumatriptan-naproxen fixed dose combination product	Menstrual migraine
Derosier 2012a	Sumatriptan-naproxen fixed dose combination product	Adolescents (ages 12-17)
Derosier 2012b	Sumatriptan-naproxen fixed dose combination product vs placebo vs butalbital	Patients with moderate to severe migraine who had used butalbital-containing medications in the past

*Shading indicates trials identified in this scan; others were identified in previous scan.

Appendix A. Abstracts of new comparative effectiveness reviews of triptans (N=2)

Acute Migraine Treatment in Emergency Settings. Sumamo Schellenberg E, Dryden DM, Pasichnyk D, Ha C, Vandermeer B, Friedman BW, Colman I, Rowe BH. Comparative Effectiveness Review No. 84. (Prepared by the University of Alberta Evidence based Practice Center under Contract No. 290-2007-10021-I.) AHRQ Publication No. 12(13)-EHC142-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/289/1323/CER84_Migraine_FinalReport_20121119.pdf

Structured Abstract

Objectives. To compare the effectiveness and safety of parenteral pharmacological interventions to treat migraine headaches in adults presenting to the emergency department (ED).

Data sources. In consultation with a librarian, we searched 10 electronic databases, conference proceedings, clinical trials registers, and reference lists.

Methods. Two reviewers independently selected studies, assessed risk of bias, extracted data, and graded the strength of evidence (SOE). Data were pooled using a random-effects model. A mixed-treatment analysis was performed for pain relief and akathisia.

Results. Nine classes of drugs were investigated in 71 controlled trials. Risk of bias was low for 28 percent of the trials, unclear for 61 percent, and high for 11 percent. Overall, active interventions were more effective than placebo for pain relief and headache recurrence. Most head-to-head comparisons for pain reduction were based on single trials resulting in insufficient SOE. The mixed-treatment analysis showed that the most effective treatments were combination therapy (i.e., dihydroergotamine [DHE] added to either neuroleptics or metoclopramide) or neuroleptic monotherapy (low SOE), with a pain reduction of approximately 40 mm on a visual analog scale (VAS). Metoclopramide monotherapy, opioids, and nonsteroidal antiinflammatories (NSAIDs) were the next most effective treatments, with a pain reduction of approximately 24 mm (low SOE). Other agents (e.g., DHE, triptans, orphan agents) were less effective, with a pain reduction of approximately 12-16 mm.

Short-term side effects were infrequent, and considered minor and self-limiting. No two studies reported the same side effects for the same pair of interventions; therefore, the SOE is insufficient to conclude which treatment results in more or fewer adverse effects. Based on the mixed-treatment analysis, the odds of experiencing akathisia symptoms following administration of metoclopramide or neuroleptic agents were 9.4 and 10.7 times greater than with placebo, respectively. The risk of sedation following administration of metoclopramide or neuroleptic agents was 17 percent. The most common short-term side effects for triptans were skin reactions, local reactions, and sedation. For patients receiving DHE, the most common side effects were skin and local reactions, sedation, digestive issues, nausea or vomiting, and chest symptoms. Few side effects were reported for NSAIDS or opioids. In patients receiving magnesium sulfate, high rates of skin flushing and local reactions were reported.

The available evidence failed to identify variable responsiveness based on subgroups.

Migraine relapse can be prevented with intravenous systemic corticosteroids provided in the ED, particularly in patients with prolonged headaches (>72 hours).

Conclusion. Many agents are effective in the treatment of acute migraine headache when compared with placebo. Several treatments provide insufficient evidence for continued use.

Neuroleptic monotherapy and DHE in combination with either metoclopramide or neuroleptics appear to be the most effective options for pain relief (VAS). Systemic corticosteroids effectively prevent headache relapse, especially in patients with prolonged headaches. More research is required to identify the most effective parenteral treatments for adults with acute migraine.

Triptans for Migraine Headaches: A Review of Clinical Evidence on Safety. Rapid Response Report, Summary with Critical Appraisal. March 2012. Available at: <http://www.cadth.ca/media/pdf/htis/mar-2012/RC0333%20Triptans%20Final.pdf>

RESEARCH QUESTION

What is the clinical evidence on the safety and harms of triptans for migraine headaches?

KEY MESSAGE

While no consistent differences were found between triptans in the rates of overall AEs, a small number of studies suggest oral, intranasal and subcutaneous sumatriptan are associated with chest pain and tachycardia. The most common AEs include dizziness, drowsiness, paresthesia, nausea and fatigue. One study suggests that providing a clinical limit of 27 rizatriptan ODT 10 mg/month did not reduce the number of migraine days compared with providing a formulary limit of 9 tablets per month. Regardless of quantity, rizatriptan ODT 10 mg was well tolerated as AEs were similar between groups.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

A drug class review suggests there are no consistent differences between triptan monotherapies in rates of overall AEs. The most common AEs include dizziness, drowsiness, paresthesia, nausea and fatigue. Systematic reviews of sumatriptan and zolmitriptan suggest AEs are transient, mild and increase with dose but there is no significant difference between triptans and comparators for most AEs. Oral, intranasal and subcutaneous sumatriptan were associated with chest pain tachycardia. One in every 44 people treated with oral sumatriptan 100 mg experience chest pain. While no evidence was found regarding AEs as a result of triptan overuse, an observer-blind randomized parallel group study showed that providing a clinical limit of 27 rizatriptan ODT 10 mg/month did not reduce the number of migraine days compared with providing 9 tablets/month. Regardless of quantity, rizatriptan was well tolerated as AEs were similar between groups.

Appendix B. Abstracts of potentially relevant new trials of triptans

Head-to-head trials (N=5 new trials and 2 subgroup analyses)

Allais, G., V. Tullo, et al. (2011). "Efficacy of frovatriptan in the acute treatment of menstrually related migraine: analysis of a double-blind, randomized, multicenter, Italian, comparative study versus zolmitriptan." *Neurological Sciences* 32 Suppl 1: S99-104.

Menstrually related migraine (MRM) is a particularly difficult-to-treat pain condition, associated with substantial disability. Aim of this study was to compare the efficacy and safety of frovatriptan and zolmitriptan in the treatment of MRM attacks, analyzing data from a multicenter, randomized, double blind, cross-over study. We analyzed the subset of 76 regularly menstruating women who participated in one head-to-head multicenter, randomized, double blind, cross-over clinical trial and who took the study drugs to treat MRM attacks. In a randomized sequence, each patient received frovatriptan 2.5mg or zolmitriptan 2.5mg: after treating three episodes of migraine in no more than 3months with the first treatment, the patient had to switch to the other treatment. MRM was defined according to the criteria listed in the Appendix of the last Classification of Headache disorders of the International Headache Society. A total of 73 attacks, classified as MRM, were treated with frovatriptan and 65 with zolmitriptan. Rate of pain relief at 2h was 52% for frovatriptan and 53% for zolmitriptan ($p=NS$), while rate of pain free at 2h was 22 and 26% ($p=NS$), respectively. At 24h, 74 and 83% of frovatriptan-treated and 69 and 82% of zolmitriptan-treated patients were pain free and had pain relief, respectively ($p=NS$). Recurrence at 24h was significantly ($p<0.05$) lower with frovatriptan (15 vs. 22% zolmitriptan). Frovatriptan proved to be effective in the immediate treatment of MRM attacks, similarly to zolmitriptan, but showed lower recurrence rates, and thus a better sustained relief.

Bartolini, M., M. A. Giamberardino, et al. (2011). "A double-blind, randomized, multicenter, Italian study of frovatriptan versus almotriptan for the acute treatment of migraine." *Journal of Headache & Pain* 12(3): 361-368.

The objective of this study was to evaluate patients' satisfaction with acute treatment of migraine with frovatriptan or almotriptan by preference questionnaire. One hundred and thirty three subjects with a history of migraine with or without aura (IHS 2004 criteria), with at least one migraine attack in the preceding 6months, were enrolled and randomized to frovatriptan 2.5mg or almotriptan 12.5mg, treating 1-3 attacks. The study had a multicenter, randomized, double blind, cross-over design, with treatment periods lasting <3months. At study end patients assigned preference to one of the treatments using a questionnaire with a score from 0 to 5 (primary endpoint). Secondary endpoints were pain free and pain relief episodes at 2 and 4h, and recurrent and sustained pain free episodes within 48h. Of the 133 patients (86%, intention-to-treat population) 114 of them expressed a preference for a triptan. The average preference score was not significantly different between frovatriptan (3.1+/-1.3) and almotriptan (3.4+/-1.3). The rates of pain free (30% frovatriptan vs. 32% almotriptan) and pain relief (54% vs. 56%) episodes at 2h did not significantly differ between treatments. This was the case also at 4h (pain free: 56% vs. 59%; pain relief: 75% vs. 72%). Recurrent episodes were significantly ($P<0.05$) less frequent under frovatriptan (30% vs. 44%), also for the attacks treated within 30min. No significant differences were observed in sustained pain free episodes (21% vs. 18%).

The tolerability profile was similar between the two drugs. In conclusion, our study suggests that frovatriptan has a similar efficacy of almotriptan in the short-term, while some advantages are observed during long-term treatment.

Bartolini, M., M. A. Giamberardino, et al. (2012). "Frovatriptan versus almotriptan for acute treatment of menstrual migraine: analysis of a double-blind, randomized, cross-over, multicenter, Italian, comparative study." *Journal of Headache & Pain* 13(5): 401-406.

The objective of the study was to compare the efficacy and safety of frovatriptan and almotriptan in women with menstrually related migraine (IHS Classification of Headache disorders) enrolled in a multicenter, randomized, double-blind, cross-over study. Patients received frovatriptan 2.5mg or almotriptan 12.5mg in a randomized sequence: after treating 3 episodes of migraine in no more than 3months with the first treatment, the patient was switched to the other treatment. 67 of the 96 female patients of the intention-to-treat population of the main study had regular menstrual cycles and were thus included in this subgroup analysis. 77 migraine attacks classified as related to menses were treated with frovatriptan and 78 with almotriptan. Rate of pain relief at 2 and 4h was 36 and 53% for frovatriptan and 41 and 50% for almotriptan ($p=NS$ between treatments). Rate of pain free at 2 and 4h was 19 and 47% with frovatriptan and 29 and 54% for almotriptan ($p=NS$). At 24h, 62% of frovatriptan-treated and 67% of almotriptan-treated patients had pain relief, while 60 versus 67% were pain free ($p=NS$). Recurrence at 24h was significantly ($p<0.05$) lower with frovatriptan (8 vs. 21% almotriptan). This was the case also at 48h (9 vs. 24%, $p<0.05$). Frovatriptan was as effective as almotriptan in the immediate treatment of menstrually related migraine attacks. However, it showed a more favorable sustained effect, as shown by a lower rate of migraine recurrence.

Muller, T. and L. Lohse (2011). "Efficacy of parecoxib, sumatriptan, and rizatriptan in the treatment of acute migraine attacks." *Clinical Neuropharmacology* 34(6): 206-209.

Triptans and analgetic nonsteroidal inflammatory drugs reduce acute pain syndromes in migraine. A further treatment option for an acute headache attack in patients with migraine may be the application of cyclooxygenase-2-specific inhibitors, as they have anti-inflammatory and analgesic properties. The objective of this pilot study was to investigate the effects of an oral fast-dissolving tablet of 10 mg of rizatriptan, an intravenous infusion of 40 mg of parecoxib, and a subcutaneous pen injection of sumatriptan (6 mg/0.5 mL) on pain relief in 3 cohorts of patients with episodic migraine. They were treated owing to the acute onset of a pain attack as a case of emergency. They were randomized to treatment with sumatriptan, rizatriptan, or parecoxib. The participants completed a visual analog scale for pain intensity at baseline before the drug administration and then after intervals of 20, 30, 60, and 120 minutes. Rizatriptan, parecoxib, and sumatriptan reduced pain symptoms. Twenty and 30 minutes after drug intake, rizatriptan was more efficacious than parecoxib and sumatriptan, and parecoxib was more effective than sumatriptan. Only a significant difference between rizatriptan and sumatriptan was found after 60 and 120 minutes. This trial demonstrates the effectiveness of a parecoxib infusion in the treatment of acute migraine and that the circumvention of the first pass effect of the liver by rizatriptan may be beneficial for fast pain relief.

Savi, L., S. Omboni, et al. (2011). "A double-blind, randomized, multicenter, Italian study of frovatriptan versus rizatriptan for the acute treatment of migraine." *Journal of Headache & Pain* 12(2): 219-226.

The objective of this study was to assess patient satisfaction with acute treatment of migraine with frovatriptan or rizatriptan by preference questionnaire. 148 subjects with a history of migraine with or without aura (IHS 2004 criteria), with at least one migraine attack per month in the preceding 6 months, were enrolled and randomized to frovatriptan 2.5 mg or rizatriptan 10 mg treating 1-3 attacks. The study had a multicenter, randomized, double-blind, cross-over design, with treatment periods lasting <3 months. At the end of the study, patients assigned preference to one of the treatments using a questionnaire with a score from 0 to 5 (primary endpoint). Secondary endpoints were pain-free and pain relief episodes at 2 h, and recurrent and sustained pain-free episodes within 48 h. 104 of the 125 patients (83%, intention-to-treat population) expressed a preference for a triptan. The average preference score was not significantly different between frovatriptan (2.9+-1.3) and rizatriptan (3.2+-1.1). The rates of pain-free (33% frovatriptan vs. 39% rizatriptan) and pain relief (55 vs. 62%) episodes at 2 h were not significantly different between the two treatments. The rate of recurrent episodes was significantly ($p<0.001$) lower under frovatriptan (21 vs. 43% rizatriptan). No significant differences were observed in sustained pain-free episodes (26% frovatriptan vs. 22% rizatriptan). The number of patients with adverse events was not significantly different between rizatriptan (34) and frovatriptan (25, $p=NS$). The results suggest that frovatriptan has a similar efficacy to rizatriptan, but a more prolonged duration of action. Springer-Verlag 2010

Savi, L., S. Omboni, et al. (2011). "Efficacy of frovatriptan in the acute treatment of menstrually related migraine: analysis of a double-blind, randomized, cross-over, multicenter, Italian, comparative study versus rizatriptan." *Journal of Headache & Pain* 12(6): 609-615.

The objectives of this study are to assess the efficacy and safety of frovatriptan, and rizatriptan in the subgroup of women with menstrually related migraine of a multicenter, randomized, double blind, cross-over study. Each patient received frovatriptan 2.5mg or rizatriptan 10mg in a randomized sequence: after treating 3 episodes of migraine in not more than 3months with the first treatment, the patient had to switch to the other treatment. Menstrually related migraine was defined according to the criteria listed in the Appendix of the last IHS Classification of Headache disorders. 99 out of the 125 patients included in the intention-to-treat analysis of the main study were of a female gender: 93 had regular menstrual cycles and were, thus, included in this analysis. A total of 49 attacks classified as menstrually related migraine were treated with frovatriptan and 59 with rizatriptan. Rate of pain relief at 2h was 58% for frovatriptan and 64% for rizatriptan ($p=NS$), while rate of pain free at 2h was 31 and 34% ($p=NS$), respectively. At 24h, 67 and 81% of frovatriptan-treated, and 61 and 74% of rizatriptan-treated patients were pain free and had pain relief, respectively ($p=NS$). Recurrence at 24h was significantly ($p<0.01$) lower with frovatriptan (10 vs. 32% rizatriptan). Frovatriptan was as effective as rizatriptan in the immediate treatment of menstrually related migraine attacks while showing a favorable sustained effect with a lower rate of migraine recurrence. These results need to be confirmed by randomized, double-blind, prospective, large clinical trials.

Tullo, V., G. Allais, et al. (2010). "Frovatriptan versus zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study." Neurological Sciences 31 Suppl 1: S51-54.

The objective of this study is to assess patients' satisfaction with migraine treatment with frovatriptan (F) or zolmitriptan (Z), by preference questionnaire. 133 subjects with a history of migraine with or without aura (IHS criteria) were randomized to F 2.5 mg or Z 2.5 mg. The study had a multicenter, randomized, double-blind, cross-over design, with each of the two treatment periods lasting no more than 3 months. At the end of the study, patients were asked to assign preference to one of the treatments (primary endpoint). The number of pain-free (PF) and pain-relief (PR) episodes at 2 h, and number of recurrent and sustained pain-free (SPF) episodes within 48 h were the secondary study endpoints. Seventy-seven percent of patients expressed a preference. Average score of preference was 2.9 +/- 1.3 (F) versus 3.0 +/- 1.3 (Z; p = NS). Rate of PF episodes at 2 h was 26% with F and 31% with Z (p = NS). PR episodes at 2 h were 57% for F and 58% for Z (p = NS). Rate of recurrence was 21 (F) and 24% (Z; p = NS). Time to recurrence within 48 h was better for F especially between 4 and 16 h (p < 0.05). SPF episodes were 18 (F) versus 22% (Z; p = NS). Drug-related adverse events were significantly (p < 0.05) less under F (3 vs. 10). In conclusion, our study suggests that F has a similar efficacy of Z, with some advantage as regards tolerability and recurrence.

Placebo-controlled trials (N=12)

Allais, G., G. Bussone, et al. (2011). "Almotriptan 12.5 mg in menstrually related migraine: a randomized, double-blind, placebo-controlled study." Cephalgia 31(2): 144-151.

BACKGROUND: Menstrually related migraine (MRM) affects more than half of female migraineurs. Because such migraines are often predictable, they provide a suitable target for treatment in the mild pain phase. The present study was designed to provide prospective data on the efficacy of almotriptan for treatment of MRM.

METHODS: Premenopausal women with MRM were randomized to almotriptan (N = 74) or placebo (N = 73), taken at onset of the first perimenstrual migraine. Patients crossed over to the other treatment for the first perimenstrual migraine of their second cycle, followed by a two-month open-label almotriptan treatment period.

RESULTS: Significantly more patients were pain-free at two hours (risk ratio [RR] = 1.81; p = .0008), pain-free from 2-24 hours with no rescue medication (RR = 1.99; p = .0022), and pain-free from 2-24 hours with no rescue medication or adverse events (RR = 1.94; p = .0061) with almotriptan versus placebo. Nausea (p = .0007) and photophobia (p = .0083) at two hours were significantly less frequent with almotriptan. Almotriptan efficacy was consistent between three attacks, with 56.2% of patients pain-free at two hours at least twice. Adverse events were similar with almotriptan and placebo.

CONCLUSION: Almotriptan was significantly more effective than placebo in women with MRM attacks, with consistent efficacy in longer-term follow-up.

Barbanti, P., L. Fofi, et al. (2012). "Rizatriptan in migraineurs with unilateral cranial autonomic symptoms: a double-blind trial." Journal of Headache & Pain 13(5): 407-414.

The objective and background is to confirm in a double-blind, placebo-controlled study the high triptan response rates we had previously reported in an open study in migraine patients with unilateral cranial autonomic symptoms. In this randomized, double-blind, placebo-controlled study 80 migraineurs with unilateral cranial autonomic symptoms were assigned to receive rizatriptan 10mg wafer or placebo (ratio 1:1) and treated for a single moderate or severe migraine attack. The primary endpoints were pain freedom at 2h and total migraine freedom at 2h. Secondary endpoints included pain relief, no associated symptoms and sustained pain freedom or relief. Significantly more patients reported pain freedom at 2h after taking rizatriptan (54%) than after placebo (8%) (therapeutic gain 46% [28%; 64%]; P<0.001). Similarly, significantly more patients reported total migraine freedom at 2h after rizatriptan (51%) than after placebo (8%) (therapeutic gain 43% [26%; 61%]; P<0.001). Rizatriptan was also more effective than placebo on most secondary endpoints. We confirm in a placebo-controlled study our previous data suggesting that the presence of unilateral cranial autonomic symptoms in migraineurs predicts a positive response to triptans, probably owing to intense trigeminal peripheral afferent activation which strongly recruits peripheral neurovascular 5-HT1B/1D receptors. Acute and preventive pharmacological trials in migraine should focus also on this subset of migraine patients.

Cady, R. K., M. L. Diamond, et al. (2011). "Sumatriptan-naproxen sodium for menstrual migraine and dysmenorrhea: satisfaction, productivity, and functional disability outcomes." *Headache* 51(5): 664-673.

OBJECTIVE: To evaluate the impact of a sumatriptan/naproxen sodium combination tablet on patient satisfaction, productivity, and functional disability in menstrual migraine treated during the mild pain phase of a single menstrual migraine attack associated with dysmenorrhea.

BACKGROUND: Menstrual migraineurs with dysmenorrhea represent a unique patient population not previously studied. When health outcomes end points are analyzed alongside traditional efficacy end points in migraine studies, a more comprehensive and robust understanding of the many factors that may influence patients' choice of and adherence to pharmacological treatments for migraine is observed.

METHODS: In 2 replicate, multicenter, randomized, double-blind, placebo-controlled trials, participants with menstrual migraine and dysmenorrhea treated a single menstrual migraine attack with a single fixed-dose tablet of sumatriptan 85mg formulated with RT TechnologyTM and naproxen sodium 500mg (sumatriptan-naproxen sodium) or placebo.

RESULTS: Participants randomized to sumatriptan-naproxen sodium were significantly more satisfied than those randomized to placebo at 24 hours post dose, as demonstrated by higher satisfaction subscale scores for efficacy (P<.001 for both studies), functionality (P=.003 for study 1; P<.001 for study 2), and ease of use (P=.027 for study 1; P=.011 for study 2). There was little bothersomeness of side effects associated with either treatment. Use of sumatriptan-naproxen sodium was also associated with lower reported "lost-time equivalents" in work and leisure time (pooled analysis, P=.003) and lower rates of functional disability (P=.05, study 1; P<.001, study 2) compared with placebo.

CONCLUSION: A fixed-dose combination tablet containing sumatriptan and naproxen sodium significantly improved patient satisfaction, productivity, and restoration of normal

functioning in menstrual migraineurs with dysmenorrhea. 2011 American Headache Society.

Derosier, F., F. Sheftell, et al. (2012). "Sumatriptan-naproxen and butalbital: a double-blind, placebo-controlled crossover study." *Headache* 52(4): 530-543.

OBJECTIVES: The primary objective was to compare the efficacy of a sumatriptan and naproxen combination medication (SumaRT/Nap-85mg sumatriptan and 500mg naproxen sodium), a butalbital-containing combination medication (BCM-50mg butalbital, 325mg acetaminophen, 40mg caffeine), and placebo when used to treat moderate to severe migraine headache pain in subjects who used BCMs in the past.

BACKGROUND: Despite the lack of Food and Drug Administration approval and the absence of placebo-controlled trials to demonstrate efficacy, butalbital-containing medications are among the most commonly prescribed acute migraine treatments in the United States. Butalbital-containing medications are associated with serious and undesirable side effects, and have been linked to the chronification of migraine and development of medication-overuse headaches. This study compares the relative efficacy, safety, and tolerability of a fixed dose SumaRT/Nap versus a BCM and placebo.

METHODS: Enrolled subjects were required to have treated at least 1 migraine with a butalbital medication in the past. Enrolled subjects treated 3 moderate to severe migraines using each of the 3 study treatments once in a randomized sequence. The primary endpoint compared SumaRT/Nap versus BCM for sustained pain freedom at 2-24 hours without the use of any rescue medication. This study combines data from 2 identical outpatient, randomized, multicenter, double-blind, double-dummy, 3 attack crossover studies in adult migraineurs (International Classification of Headache Disorders, 2nd edition).

RESULTS: A total of 442 subjects treated at least 1 attack with study medication. The majority of the treated subjects were female (88%) with a mean age 43 years, who reported that their migraines had a severe impact on their lives (78% with Headache Impact Test-6 of >59). At screening, 88% of subjects reported current butalbital use; 68% had used butalbital for more than 6 weeks; and 82% reported satisfaction with butalbital. Across treatment groups, 28-29% of subjects took study medication within 15 minutes of migraine onset, 34-37% of subjects took study medication >15 minutes to 2 hours after onset, and 32-36% of subjects took study medication more than 2 hours after onset. This study did not detect a difference at the nominal 0.05 level in percent sustained pain-free between SumaRT/Nap (8%), BCM (6%), and placebo (3%). SumaRT/Nap was superior to BCM for pain free at 2, 4, 6, 8, 24, 48 hours ($P \leq .044$); pain relief (mild or no pain) at 2, 4, 6, 8, 24, 48 hours ($P \leq .01$); sustained pain relief 2-24 hours ($P < .001$); migraine free (pain free with no nausea, photophobia, or phonophobia) at 4, 6, 8, 24, 48 hours ($P \leq .046$); and complete symptom free (migraine free with no neck/sinus pain) at 4, 6, 8, 48 hours ($P \leq .031$). Adverse event incidence was similar for all treatments (10%, 12%, and 9% for placebo, SumaRT/Nap, and BCM, respectively). Nausea was the most frequent adverse event (2%, 2%, and <1% for placebo, SumaRT/Nap, and BCM, respectively). Five serious adverse events were reported by 3 subjects: viral meningitis and colon neoplasm (placebo); chest pain and hypertension 17 days postdose (SumaRT/Nap); and breast cancer (BCM). Investigators judged no serious adverse events related to study medication.

CONCLUSIONS: This study primarily included subjects whose migraines significantly impacted their lives. Before the study, these subjects used butalbital-containing medications as part of their current migraine treatment regimen and were satisfied with it, suggesting they were butalbital responders who had found a workable treatment strategy for themselves. When treated with SumaRT/Nap versus BCM in this study, however, a significant proportion of subjects reported better treatment outcomes for themselves for both migraine pain and associated symptoms. Use of SumaRT/Nap was also associated with less rescue medication use and a longer time before use of rescue medication compared with both BCM and placebo. 2011 American Headache Society.

Derosier, F. J., D. Lewis, et al. (2012). "Randomized trial of sumatriptan and naproxen sodium combination in adolescent migraine." *Pediatrics* 129(6): e1411-1420.

BACKGROUND: Treatment of adolescent migraine remains a significant unmet medical need. We compared the efficacy and safety of 3 doses of sumatriptan and naproxen sodium (suma/nap) combination tablets to placebo in the acute treatment of adolescent migraine.

METHODS: This randomized, parallel group study in 12 to 17 year olds required 2 to 8 migraines per month (typically lasting >3 hours untreated) for \geq 6 months. Subjects entered a 12-week run-in phase, treating 1 moderate-to-severe migraine (attack 1) with single-blind placebo. Subjects reporting headache pain 2 hours after dosing were randomly assigned into a 12-week double-blind phase, treating 1 moderate-to-severe migraine (attack 2) with placebo (n = 145), suma/nap 10/60 mg (n = 96), 30/180 mg (n = 97), or 85/500 mg (n = 152). The primary end point was the percentage of subjects pain-free at 2 hours.

RESULTS: The attack 2 adjusted (age; baseline pain severity) 2-hour pain-free rates were higher with suma/nap 10/60 mg (29%; adjusted P = .003), 30/180 mg (27%; adjusted P = .003), and 85/500 mg (24%; adjusted P = .003) versus placebo (10%). Posthoc primary end-point analyses did not demonstrate differences among the 3 doses or an age-by-treatment interaction. Statistically significant differences were found for 85/500 mg versus placebo for sustained pain-free 2 to 24 hours (23% vs 9%; adjusted P = .008), 2-hour photophobia-free (59% vs 41%; adjusted P = .008), and 2-hour phonophobia-free (60% vs 42%; adjusted P = .008). Analyses of other pain, associated symptoms, rescue medication use, and health outcome end points supported higher efficacy for active doses versus placebo. All active doses were well tolerated.

CONCLUSIONS: All doses of suma/nap were well tolerated, providing similarly effective acute treatment of adolescent migraine pain and associated symptoms, as compared with placebo.

Diener, H.-C., P. Barbanti, et al. (2011). "BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study." *Cephalgia* 31(5): 573-584.

METHODS: Four hundred and sixty-one adult subjects with migraine were randomised to one of five treatments, the oral antagonist at the calcitonin gene-related peptide (CGRP) receptor BI 44370 TA (50mg, 200mg, 400mg), active comparator eletriptan 40mg or placebo. The analysis included 341 subjects who took study medication.

RESULTS: The primary endpoint, pain-free after two hours, was reached by significantly more subjects in the BI44370TA 400mg (20/73=27.4%) and eletriptan 40mg (24/69=34.8%)

groups compared to placebo ($6/70=8.6\%$, $p=.0016$), but not by subjects in the BI 44370 TA 200mg group ($14/65=21.5\%$). The effect of 50mg BI44370TA ($5/64=7.8\%$) was similar to that of placebo. Analysis of secondary endpoints supported the conclusion from the primary analysis. The frequency of adverse events was low in all groups.

CONCLUSION: Efficacy of BI 44370 TA was shown in a dose-dependent manner in the treatment of acute migraine attacks.

Djupesland, P. G., P. Docekal, et al. (2010). "Intranasal sumatriptan powder delivered by a novel breath-actuated bi-directional device for the acute treatment of migraine: A randomised, placebo-controlled study." *Cephalgia* 30(8): 933-942.

INTRODUCTION: Intranasal sumatriptan is an option for the treatment of migraine; however, nasal delivery using conventional spray pumps is suboptimal.

METHODS: Adult subjects ($n = 117$) with migraine were enrolled in a multicentre, randomised, double-blind, parallel group, placebo-controlled study. A single migraine attack was treated in-clinic with sumatriptan 10 mg, sumatriptan 20 mg or placebo administered intranasally by a novel bi-directional powder delivery device when migraine was moderate or severe.

RESULTS: A greater proportion of subjects who received sumatriptan were pain-free at 120 minutes compared with those who received placebo (10 mg/20 mg sumatriptan vs. placebo = 54%/57% vs. 25%, $P < .05$). Significant benefits were also observed for pain relief at 120 minutes (84%/80% vs. 44%, $P < .001/.01$) and as early as 60 minutes (73%/74% vs. 38%, $P < .01$) and for 48 hours sustained pain-free ($P < .05$). Treatment-related adverse events were rare, with a metallic taste being the most commonly reported (10%/13%).

CONCLUSIONS: Sumatriptan nasal powder administered using the new device during a migraine attack was effective and well tolerated.

Kostic, M. A., F. J. Gutierrez, et al. (2010). "A prospective, randomized trial of intravenous prochlorperazine versus subcutaneous sumatriptan in acute migraine therapy in the emergency department." *Annals of Emergency Medicine* 56(1): 1-6.

STUDY OBJECTIVE: Intravenous (IV) prochlorperazine with diphenhydramine is superior to subcutaneous sumatriptan in the treatment of migraine patients presenting to the emergency department (ED).

METHODS: In this randomized, double-blind, placebo-controlled trial, after providing written informed consent, patients presenting to the ED with a chief complaint of migraine received a 500-mL bolus of IV saline solution and either 10 mg prochlorperazine with 12.5 mg diphenhydramine IV plus saline solution placebo subcutaneously or saline solution placebo IV plus 6 mg sumatriptan subcutaneously. Pain intensity was assessed with 100-mm visual analog scales (visual analog scale at baseline and every 20 minutes for 80 minutes). The primary outcome was change in pain intensity from baseline to 80 minutes or time of ED discharge if subjects remained in the ED for fewer than 80 minutes after treatment. Sedation and nausea were assessed every 20 minutes with visual analog scale scales, and subjects were contacted within 72 hours to assess headache recurrence.

RESULTS: Sixty-eight subjects entered the trial, with complete data for 66 subjects. Baseline pain scores were similar for the prochlorperazine/diphenhydramine and sumatriptan groups (76 versus 71 mm). Mean reductions in pain intensity at 80 minutes or time of ED

discharge were 73 mm for the prochlorperazine/diphenhydramine group and 50 mm for those receiving sumatriptan (mean difference 23 mm; 95% confidence interval 11 to 36 mm). Sedation, nausea, and headache recurrence rates were similar.

CONCLUSION: IV prochlorperazine with diphenhydramine is superior to subcutaneous sumatriptan in the treatment of migraine. Copyright 2009 American College of Emergency Physicians. Published by Mosby, Inc. All rights reserved.

Latsko, M., S. Silberstein, et al. (2011). "Frovatriptan as preemptive treatment for fasting-induced migraine." *Headache* 51(3): 369-374.

OBJECTIVE: To examine frovatriptan's efficacy as preemptive treatment for fasting-induced migraine.

BACKGROUND: Fasting is a common migraine trigger that cannot always be avoided. The development of a short-term preemptive approach would be of benefit. Because of its longer half-life, frovatriptan has been effectively used for short-term daily use to prevent menstrually related migraines and might prove useful in the prevention of fasting-induced migraine.

METHODS: This was a double-blind, placebo-controlled, randomized, parallel-group trial.

SUBJECTS: With a history of fasting-induced episodic migraine were randomly assigned to receive either frovatriptan (5.0mg) or placebo (ratio 1:1).

SUBJECTS: Took a single dose of study medication at the start of their 20-hour fast. Information about headache intensity, associated symptoms, and use of rescue medication was captured at defined time points from the start of the fast through 20 hours post-fast.

RESULTS: Of the 75 subjects screened, 74 subjects were randomized and 71 subjects completed the study. Demographic characteristics of the placebo and frovatriptan treatment groups were not statistically different. Thirty-three subjects received active drug. Twelve (36.4%) developed a headache between 6 and 20 hours after the start of the fast (1/33 mild, 11/33 moderate or severe). In the placebo group, 18/34 (52.9%) developed a headache (4/34 mild, 14/34 moderate or severe). The difference between the 2 treatment groups did not achieve statistical significance; Pearson chi-square, P=.172. Kaplan-Meier survival analysis showed no difference between the 2 treatment groups with respect to the time of onset of headache of any intensity (log rank, P=.264) and for the time of onset of a moderate or severe intensity (log rank, P=.634).

CONCLUSION: More subjects on placebo developed a headache than those on frovatriptan. Perhaps because of the small number of subjects involved, the differences in headache incidences observed did not achieve statistical significance. 2011 American Headache Society.

Schulman, E. A. (2012). "Transdermal sumatriptan for acute treatment of migraineurs with baseline nausea.[Erratum appears in Headache. 2012 Jun;52(6):1062]." *Headache* 52(2): 204-212.

OBJECTIVE: To evaluate the efficacy and safety of transdermal sumatriptan in migraine patients who have baseline nausea.

BACKGROUND: Migraine-associated nausea and vomiting can limit the effectiveness of acute treatment with oral agents by causing delays, avoidance, or incomplete absorption of medication due to post-dose vomiting.

METHODS: In a multicenter, randomized, double-blind, placebo-controlled study in adult (aged 18-66 years) migraineurs, 530 patients were randomized to receive transdermal sumatriptan or a placebo patch and remained in the study until they had treated a single moderate to severe migraine attack or had gone 2 months without treatment. At baseline (before applying the study patch), patients recorded headache pain intensity and the presence or absence of migraine-associated symptoms, including nausea. The use of analgesic or anti-emetic rescue medications within 2 hours of patch activation was prohibited. Post-hoc analyses were conducted to assess the proportion of patients with nausea at baseline who experienced headache relief and who were free from nausea, photophobia, and phonophobia at 1 and 2 hours post-activation.

RESULTS: A total of 454 patients were included in the intent-to-treat population for efficacy analyses. Baseline demographic and migraine headache characteristics were generally similar between the treatment groups. In the overall study population, transdermal sumatriptan was significantly superior to placebo at 1 hour post-activation for pain relief (29% vs 19%, respectively; $P < .0135$) and freedom from nausea (71% vs 58%, respectively; $P < .05$) and at 2 hours post-activation for freedom from pain (18% vs 9%, respectively; $P < .009$), pain relief (53% vs 29%, respectively; $P < .0001$), freedom from nausea (84% vs 63% respectively; $P < .001$), freedom from photophobia (51% vs 36%, respectively; $P < .0028$), freedom from phonophobia (55% vs 39%, respectively; $P < .0002$); and freedom from migraine (16% vs 8%, respectively; $P < .0135$). In the post-hoc analysis, transdermal sumatriptan was markedly superior to placebo for pain relief and freedom from pain, nausea, photo-, and phonophobia at 1 and 2 hours post-activation.

CONCLUSIONS: Transdermal sumatriptan is superior to oral triptans for migraine patients whose baseline nausea causes them to delay or avoid acute treatment. 2012 American Headache Society.

Seeburger, J. L., R. K. Cady, et al. (2012). "Rizatriptan for treatment of acute migraine in patients taking topiramate for migraine prophylaxis." *Headache* 52(1): 57-67.

OBJECTIVE: To assess efficacy and tolerability of rizatriptan orally disintegrating tablet (ODT) for treatment of acute migraine in patients using topiramate for migraine prophylaxis.

BACKGROUND: There are limited data from prospective controlled trials demonstrating the benefit of triptans in patients who experience migraine attacks while taking prophylactic medication.

METHODS: This was a worldwide, randomized, placebo-controlled, double-blind, multiple-attack study in adults with a >1-year history of migraine taking a stable dose of topiramate for migraine prophylaxis and experiencing ≥ 2 moderate/severe attacks per month. Participants treated 3 moderate/severe attacks in crossover fashion (2 with rizatriptan 10-mg ODT, 1 with placebo) following random assignment to 1 of 3 treatment sequences. The primary end point was 2-hour pain relief.

RESULTS: Two-hour pain relief was significantly greater with rizatriptan compared with placebo (55.0% vs 17.4%, $P < .001$). Response rates also favored rizatriptan for sustained pain relief from 2-24 hours (32.6% vs 11.1%, $P < .001$), 2-hour pain freedom (36.0% vs 6.5%, $P < .001$), normal functional ability at 2 hours (42.2% vs 12.7%, $P < .001$), and overall treatment satisfaction at 24 hours (60.8% vs 33.6%, $P < .001$). Few participants

reported adverse experiences (16 [15.8%] with rizatriptan, 3 [3.2%] with placebo); none were serious.

CONCLUSION: Rizatriptan 10-mg ODT was superior to placebo at all pain end points for treatment of acute migraine in patients using topiramate for migraine prophylaxis. Rizatriptan was generally well tolerated in this population. These results are comparable with those from clinical trials in patients not using prophylaxis, suggesting that the use of topiramate does not affect the efficacy or tolerability of rizatriptan for acute migraine treatment. 2011 American Headache Society.

Seeburger, J. L., F. R. Taylor, et al. (2011). "Efficacy and tolerability of rizatriptan for the treatment of acute migraine in sumatriptan non-responders." *Cephalalgia* 31(7): 786-796.

OBJECTIVE: The study was carried out to assess the efficacy and tolerability of rizatriptan orally disintegrating tablet (ODT) for treating acute migraine in patients who are non-responders to sumatriptan.

BACKGROUND: Many migraineurs report dissatisfaction with sumatriptan efficacy. It is unclear whether sumatriptan 100mg non-responders will respond to other triptans.

METHODS: This was a randomized, placebo-controlled, double-blind study in adults with >1-year history of ICHD-II (International Classification of Headache Disorders, second edition) migraine who reported that they generally do not respond to sumatriptan (>=50% unsatisfactory response). In the baseline phase, participants treated a single moderate/severe migraine attack with open-label generic sumatriptan 100mg. Those who continued to experience moderate/severe pain at two hours post-dose were eligible to enter the double-blind treatment phase, during which participants treated three migraine attacks in crossover fashion (two with rizatriptan 10-mg ODT, one with placebo) after being randomly assigned to one of three treatment sequences (1:1:1 ratio). The primary endpoint was two-hour pain relief.

RESULTS: A total of 102 (94%) participants treated at least one study migraine. Pain relief at two hours was significantly greater with rizatriptan compared with placebo (51% vs. 20%, p<.001). Response rates also favored rizatriptan on two-hour pain freedom (22% vs. 12%, p=.013) as well as 24-hour sustained pain relief (38% vs. 14%, p<.001) and sustained pain freedom (20% vs. 11%, p=.036). Treatment was generally well tolerated.

CONCLUSION: Rizatriptan 10-mg ODT was superior to placebo at providing two-hour pain relief and two-hour pain freedom in the treatment of acute migraine in those who do not respond to sumatriptan 100mg. Rizatriptan was generally well tolerated in this population.



Month/Year of Review: July 2013
PDL Classes: Short Acting Opioids (SAO)

Date of Last Review: March 2010
Source Document: Provider Synergies

Current Status of PDL Class:

- **Preferred Agents:** CODEINE SULFATE TABLET AND SOLUTION, HYDROCODONE/ACETAMINOPHEN TABLETS (10MG/325MG, 10MG/500MG, 10MG/650MG, 10MG/660MG, 10MG/750MG, 2.5MG/500MG, 5MG/325MG, 7.5MG/325MG, 7.5MG/500MG, 7.5MG/650MG, 7.5MG/750MG STRENGTHS), HYDROMORPHONE HCL TABLET, MORPHINE SULFATE TABLET AND SOLUTION, OXYCODONE HCL TABLET AND SOLUTION, OXYCODONE HCL/ACETAMINOPHEN CAPSULES, OXYCODONE/ACETAMINOPHEN TABLETS (10MG/325MG, 10MG/650MG, 2.5MG/325MG, 5MG/325MG, 7.5MG/325MG, 7.5MG/500MG STRENGTHS) TRAMADOL HCL
- **Non-Preferred Agents:** CODEINE/CARISOPRODOL/ASPIRIN, DIHYDROCODEINE/ACETAMINOPHEN/CAFFEINE, DIHYDROCODINE/ASPIRIN/CAFFEINE (SYNALGOS-DC®), FENTANYL CITRATE SPRAY (LAZANDA®), FENTANYL CITRATE FILM (ONSOLIS®), FENTANYL CITRATE LOZENGE, FENTANYL CITRATE SUBLINGUAL (ABSTRAL®), FENTANYL CITRATE EFFORVESCENT (FENTORA®), HYDROCODONE/ACETAMINOPHEN CAPSULE (STAGESIC®), HYDROCODONE/ACETAMINOPHEN SOLUTION, HYDROCODONE-ACETAMINOPHEN TABLETS (10MG/300MG, 10MG/400MG, 5MG/300MG, 5MG-400MG, 7.5MG/300MG, 7.5-400MG STRENGTHS), HYDROMORPHONE LIQUID, MEPERIDINE HCL SOLUTION AND TABLET, OXYCODONE CAPSULE AND ORAL CONCENTRATE, OXYCODONE TABLET ORL (OXECTA®), OXYCODONE/ACETAMINOPHEN SOLUTION (ROXICET®), OXYCODONE/ACETAMINOPHEN TABLET (PRIMLEV®, MAGNACET®), OXYCODONE/ASPIRIN, PENTAZOCINE/ACETAMINOPHEN, PENTAZOCINE/NALOXONE, TAPENTADOL (NUCYNTA®), TRAMDOL TAB RAPDIS (RYBIX ODT®), TRAMADOL/ACETAMINOPHEN, BUTORPHANOL TARTRATE SPRAY, FENTANYL SPRAY (SUBSYS®)

Previous Recommendations:

- Fentanyl products only be used in opioid tolerant patients
- Should have long acting analgesic therapy instituted
- Consider quantity limits
- Consider edit based on acetaminophen dosage

Current PA Criteria: Prior authorization is in place for fentanyl transmucosal and buccal (Appendix 1) to ensure that Actiq/Fentora/Onsoils is appropriately prescribed in accordance to FDA black box warnings.

Methods:

A Medline OVID search was conducted with the following search terms: codeine, hydrocodone, oxycodone, hydromorphone, morphine, oxymorphone, fentanyl, buprenorphine, tramadol, tapentadol, acetaminophen, opioids, opioid analgesics, short-acting opioids, pain, pain relief, and treatment. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to June week two 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Trials (Appendix 1):

A total of 624 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, two relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Ashburn¹ et al assessed the efficacy of buccal fentanyl compared with oral oxycodone in decreasing pain intensity of breakthrough pain in opioid-tolerant patients. This was a double-blind multi-center crossover study with multiple phases that lasted up to a total of eight weeks. Subjects (n=323) with chronic pain were randomized to titrate up to a successful dose of fentanyl or oxycodone; this was followed by a washout then titration period for the other study medication. After the titrations, subjects were re-randomized to take either buccal fentanyl and an oral placebo or buccal placebo and oral oxycodone to use for ten breakthrough pain incidents. This was followed by a crossover treatment period where subjects now received the other active medication plus placebo for another ten breakthrough pain incidents. The primary endpoint was improvement in pain intensity fifteen minutes after taking the medication as measured by an 11 point scale. Fentanyl significantly decreased pain intensity compared with oxycodone after 15 minutes (mean difference 0.82 vs. 0.6, 95% CI 0.18 to 0.29). Fentanyl maintained a significant difference over oxycodone at all other time points (5, 30, 45, and 60 minutes) measured as secondary efficacy endpoints. This was a fair quality study with good descriptions of patient baseline characteristics, inclusion and exclusion criteria. Allocation concealment, randomization and blinding procedures were not explicitly described.

Davies² et al compared intranasal fentanyl spray with immediate release oral morphine for relief from breakthrough pain in cancer patients. This double-blind multi-center randomized crossover trial was conducted in phases up to seven weeks duration. After completing an open label titration phase, patients (n=110) were randomly assigned to five treatments with either fentanyl spray and oral placebo or morphine tablet and placebo nasal spray (10 treatments total). The primary endpoint was improvement in pain intensity measured by an 11 point scale. Measurements were taken at 5, 10, 15, 30, 45, and 60 minute intervals. Intranasal fentanyl improved pain intensity by statically significant difference at the 10 minute (reduction in pain intensity: 52.4 versus 45.4, p<0.05) and the 15 minute (75.5 vs. 69.3, p<0.05) measurements. By 30 minutes there was no statistical difference between the two medications. This was a poor quality study. Although allocation concealment was discussed, blinding and randomization methods were not and there appeared to be multiple opportunities for bias (i.e. leading questions for patient satisfaction).

New drugs:

None

New Formulations/Indications:

Several new formulations have been approved since the last review. Two new combination hydrocodone solutions are now available.

Two new oxycodone products were approved in an effort to decrease misuse. OxyContin⁵ (controlled release oxycodone) was relaunched in April 2010 as a new chemical entity with additional non-active ingredients to help prevent breakability and discourage crushing. OxyContin is indicated for the management of moderate to severe pain when a continuous opioid analgesic is needed for extended period of time. Oxecta⁶ (oxycodone) approved in June 2011 also contains additional non-active ingredients to prevent dissolution and crushing. Oxecta is indicated for the management of acute and chronic moderate to severe pain.

Two new extended release opioids were recently approved. Exalgo⁷ (hydromorphone) extended release tablets were approved in March 2010 for the indication of moderate to severe pain in opioid tolerant patients needing chronic continuous analgesia. Opana ER⁸, an extended release oxymorphone oral tablet, was approved in December 2011 to treat chronic moderate to severe pain in patients requiring continuous pain coverage.

Three new formulations of fentanyl are now available.

In January 2011, Abstral⁹ (fentanyl citrate) a sublingual tablet was approved. Lazanda¹⁰ a fentanyl nasal spray was approved in June 2011. In January 2012, the fentanyl sublingual spray Subsys¹¹ was approved. Abstral, Lazanda and Subsys are all indicated for the management of breakthrough pain in adult opioid-tolerant cancer patients on concurrent continuous opioids. All patients must be enrolled in the TIRF REMS Access program to receive these medications.

Finally, a new extended release tapentadol oral tablet was approved in August 2011. Nucynta ER¹² is indicated for the management of chronic moderate to severe pain or neuropathic pain associated with diabetic peripheral neuropathy in adults who need continuous analgesia. In addition, a new oral solution of immediate release Nucynta¹³ was approved in October 2012 for treatment of moderate to severe pain in adults.

New FDA safety alerts:

In February 2013, the FDA issued a Drug Safety Communication for codeine¹⁴. A Black Box Warning was added to codeine to restrict use in children for post-operative pain. Deaths have occurred post-operatively in children with obstructive sleep apnea who received codeine following a tonsillectomy and/or adenoidectomy. These children had evidence of being ultra-rapid metabolizers of codeine causing fatal amounts of morphine in the body. The Contraindication, Warnings/Precautions, Pediatric Use, and Patient Counseling Information sections of the drug label were also updated with this information.

In October 2012, the FDA issued a Safety Communication detailing an increased risk of developing thrombotic thrombocytopenic purpura (TTP) with Opana ER misuse.¹⁵ This blood disorder has been seen in people crushing and intravenously injecting the medication. The FDA cautions that TTP has not been found in patients correctly using the oral medication.

In July 2012, the FDA approved a risk evaluation and mitigation strategy (REMS) for extended-release and long-acting opioids.¹⁶ The REMS introduces safety measures designed to reduce risks and improve the safe use of these opioid formulations, while continuing to ensure access to patients in pain.

In April 2012, the FDA released a Safety Communication reminding patients, caregivers, and healthcare professionals of the importance of careful handling, storage and disposal of fentanyl patches.¹⁶ Accidental exposure to fentanyl can cause hospitalization and even death. Children were singled out as the population at greatest risk of exposure.

In January 2011, the FDA issued a Safety Alert to recommend manufacturers limit the amount of acetaminophen to 325 mg or less for individual dosages.¹⁷ In addition, a Black Box Warning was added to all prescription acetaminophen formulation label information highlighting the risk of severe liver injury with over use. This labeling change will affect all opioid acetaminophen combination products.

Lastly, the FDA requested propoxyphene products be removed from the market in November 2010. In a Safety Communication, the FDA detailed the reasons for the recommendation; most significantly new data had shown propoxyphene can cause severe cardiac toxicity even at therapeutic doses.¹⁸

New Systematic Reviews: (Appendix 2)

Two new systematic reviews were identified. Please see Appendix 2 for the full abstracts.

Vissers¹⁹ et al compared the efficacy of immediate release fentanyl products and oral morphine in reducing pain intensity of breakthrough cancer pain. This systematic review included six randomized control trials with a total of 594 patients. Trial quality was not assessed. Five trials used a placebo comparator with intranasal fentanyl spray, transmucosal fentanyl or buccal fentanyl; one trial compared oral morphine with transmucosal fentanyl; and one trial compared transmucosal and intranasal fentanyl. The meta analysis endpoint was pain intensity difference (PID) reported on a 0 to 10 scale at 15 minute intervals up to 60 minutes after intake. The results of all trials were analyzed with a mixed comparison technique and reported with 95% credible interval (Crl). Intranasal fentanyl showed the greatest reduction in pain relative to placebo: PID 1.7 points (95% Crl: 1.4; 1.9) at 15 minutes. PID for transmucosal and buccal fentanyl relative to placebo were 0.4 (95% Crl: 0.0; 0.8) and 0.5 (95% Crl: 0.3; 0.7) at 15 minutes. All fentanyl treatments provided a reduction in pain superior to placebo at other time points. Oral morphine was not significantly different from placebo at 15 or 30 minutes, but achieved significance at 45 and 60 minutes: PID at 45 minutes 0.8 (95% Crl: 0.1 to 1.5) and 1.0 (95% Crl: 0.2 to 1.8). In head to head comparisons, intranasal fentanyl provided a greater reduction in PID at 15 minutes than morphine, transmucosal and buccal fentanyl. Differences in PID favoring intranasal fentanyl were 1.2 points (95% Crl: 0.8; 1.5) relative to buccal fentanyl, 1.3 (95% Crl: 0.9 to 1.6) points relative to transmucosal fentanyl and 1.7 (95% Crl: 1.1 to 2.3) points relative to oral morphine.

Reimsma²⁰ et al performed a systematic review to compare tapentadol with other schedule II opioids for the treatment of severe chronic pain. Two different analyses were conducted: one for trials with subjects in serious pain and another for trials which included subjects with either moderate or severe pain. The primary endpoint of the meta analysis was decrease in pain intensity measured by a standardized 0 to 100 point scale. Twelve

trials were included to compare patients in severe pain. Of these four were combined to show tapentadol as superior to oxycodone with respect to difference in pain intensity (mean difference -2.64 [95% CI: -4.84 to -0.44]). Tapentadol was also compared with placebo in five pooled trials and found to have a statistically significant difference in pain intensity (mean difference -6.33 [95% CI: -8.55 to -4.11]). Forty-two trials were included to compare patients in moderate to severe pain. Of these trials, seven were pooled to show tapentadol as statistically superior to oxycodone in decreasing pain intensity (mean difference -2.45 [95% CI: -4.04 to -0.86]). There were statistically significant differences in pain relief of 30% and of 50% at the end of treatment in favor of tapentadol, in comparison with oxycodone based on four trials (RR 0.72; 95% CI 0.59 to 0.88 and RR 0.74, 95% CI 0.59 to 0.94, respectively). For this population, tapentadol was compared with placebo in six trials. Overall, the pooled mean difference showed a statistically significant difference in pain intensity in favor of tapentadol (mean difference -6.91, 95% CI:-9.80 to -4.02). Indirect comparisons were made by network analysis between tapentadol and morphine (mean difference -3.93, 95% CI:-6.86 to -1.00), and between tapentadol and hydromorphone (mean difference -8.00, 95% CI: -11.59 to -4.41) for pain intensity. All other comparisons (buprenorphine, fentanyl, and oxymorphone) showed non-significant differences in pain intensity. In terms of 30% pain relief tapentadol was superior to oxycodone (OR 0.58, 95% CI: 0.49 to 0.69), hydromorphone (OR 0.59, 95% CI: 0.37 to 0.95), and placebo (OR 0.74, 95% CI: 0.64 to 0.86). These figures were similar for 50% pain relief. Trial quality varied widely, with the authors' acknowledgment that more than half of the included trials were of low quality. Data from this review is difficult to interpret as the included trials were of various lengths; with many types of chronic pain (nociceptive or neuropathic, malignant or nonmalignant, etc.); and utilizing all formulations of study medications (immediate versus extended release). Inclusion criteria for meta analysis was not transparent (i.e. twelve trials were included for review but four were pooled). For the network analyses, the population designations of severe and moderate to severe were abandoned. Overall, the quality of the review was poor.

Guidelines:

The updated opioid prescribing guidelines from the American Society of Interventional Pain Physicians²¹ were reviewed. As was the joint guideline for the treatment of diabetic neuropathy from the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine and the American Academy of Physical Medicine and Rehabilitation²². The National Institute for Health Care Excellence clinical guideline for Opioid use in Palliative Care²³ from the UK was also reviewed. Finally, the updated VA/DoD guideline for the Management of Opioid Therapy for Chronic Pain²⁴ was evaluated. No changes regarding the use of medications were found.

Recommendations:

- No further research or review needed at this time.
- There is no clinical evidence necessitating changes to current PDL status. Evaluate comparative costs in executive session.
- Update PA criteria to include new spray formulations of fentanyl to current PA criteria.

Current PDI Status	Generic Name	Brand Name	Form	Strength	SumOfQryDispensed 2013	SumOfQryClaim Count Q1-2013	SumOf Day Supply Q1-2013	SumOf Market Share Q1-2013
Y	HYDROCODONE BIT/ACETAMINOPHEN	HYDROCODONE-ACETAMINOPHEN	TABLET	10 mg-325 mg	125231	1125	26495	30.62%
Y	HYDROCODONE BIT/ACETAMINOPHEN	HYDROCODONE-ACETAMINOPHEN	TABLET	5 mg-500 mg	48689	727	15493	17.90%
Y	HYDROCODONE BIT/ACETAMINOPHEN	HYDROCODONE-ACETAMINOPHEN	TABLET	5 mg-325 mg	38908	605	11118	12.85%
Y	OXYCODONE HCL/ACETAMINOPHEN	OXYCODONE HCl-ACETAMINOPHEN	TABLET	10 mg-325 mg	33337	298	7332	8.47%
Y	OXYCODONE HCL/ACETAMINOPHEN	OXYCODONE-ACETAMINOPHEN	TABLET	5 mg-325 mg	25759	405	7878	9.10%
Y	HYDROCODONE BIT/ACETAMINOPHEN	HYDROCODONE-ACETAMINOPHEN	TABLET	7.5 mg-325 mg	25820	277	6441	7.44%
Y	HYDROCODONE BIT/ACETAMINOPHEN	HYDROCODONE-ACETAMINOPHEN	TABLET	7.5 mg-500 mg	1314	119	3056	3.53%
N	HYDROCODONE BIT/ACETAMINOPHEN	HYDROCODONE-ACETAMINOPHEN	SOLUTION	7.5 mg-500 mg/15 mL	8346	17	232	0.27%
Y	HYDROCODONE BIT/ACETAMINOPHEN	HYDROCODONE-ACETAMINOPHEN	TABLET	10 mg-500 mg	8322	80	1830	2.11%
Y	OXYCODONE HCL/ACETAMINOPHEN	OXYCODONE-ACETAMINOPHEN	TABLET	7.5 mg-325 mg	7164	76	1852	2.14%
Y	HYDROCODONE BIT/ACETAMINOPHEN	HYDROCODONE-ACETAMINOPHEN	TABLET	7.5 mg-750 mg	5616	70	1762	2.04%
Y	OXYCODONE HCL/ACETAMINOPHEN	ENDOCET	TABLET	10 mg-325 mg	5277	49	1162	1.34%
Y	HYDROCODONE BIT/ACETAMINOPHEN	HYDROCODONE-ACETAMINOPHEN	TABLET	10 mg-660 mg	2142	30	559	0.65%
Y	OXYCODONE HCL/ACETAMINOPHEN	OXYCODONE HCl-ACETAMINOPHEN	TABLET	10 mg-650 mg	1552	16	379	0.44%
Y	HYDROCODONE BIT/ACETAMINOPHEN	HYDROCODONE-ACETAMINOPHEN	TABLET	10 mg-650 mg	1354	12	323	0.37%
Y	OXYCODONE HCL/ACETAMINOPHEN	ENDOCET	TABLET	5 mg-325 mg	820	7	117	0.14%
Y	OXYCODONE HCL/ACETAMINOPHEN	ENDOCET	TABLET	7.5 mg-500 mg	540	3	86	0.10%
N	OXYCODONE HCL/ACETAMINOPHEN	ROXICET	SOLUTION	5 mg-325 mg/5 mL	500	1	10	0.01%
Y	OXYCODONE HCL/ACETAMINOPHEN	ENDOCET	TABLET	10 mg-650 mg	425	6	114	0.13%
Y	HYDROCODONE BIT/ACETAMINOPHEN	NORCO	TABLET	10 mg-325 mg	416	2	56	0.06%
Y	OXYCODONE HCL/ACETAMINOPHEN	OXYCODONE-ACETAMINOPHEN	CAPSULE	5 mg-500 mg	415	7	135	0.16%
Y	OXYCODONE HCL/ACETAMINOPHEN	ENDOCET	TABLET	7.5 mg-325 mg	350	2	45	0.05%
Y	OXYCODONE HCL/ACETAMINOPHEN	OXYCODONE HCl-ACETAMINOPHEN	TABLET	7.5 mg-500 mg	240	4	59	0.07%

86534

References:

1. Ashburn MA, Slevin KA, Messina J, Xie F. The Efficacy and Safety of Fentanyl Buccal Tablet Compared with Immediate-Release Oxycodone for the Management of Breakthrough Pain in Opioid-Tolerant Patients with Chronic Pain. *Anesthesia & Analgesia*. 2011;112(3):693–702. doi:10.1213/ANE.0b013e318209d320.
2. Davies A, Sitte T, Elsner F, et al. Consistency of Efficacy, Patient Acceptability, and Nasal Tolerability of Fentanyl Pectin Nasal Spray Compared with Immediate-Release Morphine Sulfate in Breakthrough Cancer Pain. *Journal of Pain and Symptom Management*. 2011;41(2):358–366. doi:10.1016/j.jpainsymman.2010.11.004.
3. Vituz (hydrocodone bitartrate and chlorpheniramine maleate) Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204307s000lbl.pdf. Accessed June 23, 2013.
4. Zutripro (hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride) Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022439s000lbl.pdf. Accessed June 23, 2013.
5. OxyContin (oxycodone HCl) Product Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf. Accessed June 23, 2013.
6. Oxecta (oxycodone hydrochloride) tablet label - 202080s001lbl.pdf. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202080s001lbl.pdf. Accessed June 23, 2013.
7. Exalgo (hydromorphone hydrochloride) tablet label - 021217s005lbl.pdf. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021217s005lbl.pdf. Accessed June 23, 2013.
8. Opana ER (oxymorphone hydrochloride) tablets label - 201655s004lbl.pdf. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/201655s004lbl.pdf. Accessed June 24, 2013.
9. Abstral (fentanyl) Sublingual tablets Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022510s005lbl.pdf. Accessed June 24, 2013.
10. Lazanda (fentanyl) Nasal Spray Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022569s007lbl.pdf. Accessed June 24, 2013.
11. Subsys (fentanyl) Sublingual Spray Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202788s002lbl.pdf. Accessed June 24, 2013.
12. Nucynta ER (tapentadol) Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/200533s001lbl.pdf. Accessed June 24, 2013.
13. Nucynta (tapentadol) Oral Solution Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203794s000lbl.pdf. Accessed June 24, 2013.
14. Drug Safety and Availability > FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm>. Accessed June 24, 2013.
15. Drug Safety and Availability > FDA warns about serious blood disorder resulting from misuse of Opana ER. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm322432.htm>. Accessed June 24, 2013.
16. Drug Safety and Availability > FDA Reminds the Public about the Potential for Life-Threatening Harm from Accidental Exposure to Fentanyl Transdermal Systems ("Patches"). Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm300747.htm>. Accessed June 24, 2013.
17. Drug Safety and Availability > FDA Drug Safety Communication: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm>. Accessed June 24, 2013.

18. Drug Safety and Availability > FDA Drug Safety Communication: FDA recommends against the continued use of propoxyphene. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm234338.htm>. Accessed June 24, 2013.
19. Vissers D, Stam W, Nolte T, Lenre M, Jansen J. Efficacy of intranasal fentanyl spray versus other opioids for breakthrough pain in cancer. *Current Medical Research and Opinion*. 2010;26(5):1037–1045. doi:10.1185/03007991003694340.
20. Riemsma R, Forbes C, Harker J, et al. Systematic review of tapentadol in chronic severe pain. *Current Medical Research and Opinion*. 2011;27(10):1907–1930. doi:10.1185/03007995.2011.611494.
21. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2--guidance. *Pain Physician*. 2012;15(3 Suppl):S67–116.
22. Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011;76(20):1758–1765. doi:10.1212/WNL.0b013e3182166ebe.
23. Opioids in palliative care: safe and effective prescribing of strong...CG140 Introduction. *NICE Clinical Guidelines*. Available at: <http://publications.nice.org.uk/opioids-in-palliative-care-safe-and-effective-prescribing-of-strong-opioids-for-pain-in-palliative-cg140>. Accessed June 24, 2013.
24. VA/DOD Management of Opioid Therapy for Chronic Pain. Available at: http://www.healthquality.va.gov/COT_312_Fuller.pdf. Accessed June 24, 2013.

Appendix 1: Prior Authorization Criteria**Fentanyl Transmucosal and Buccal**

The purpose of this prior authorization policy is to ensure that Actiq/Fentora/Onsolis is appropriately prescribed in accordance to FDA black box warning:

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

Initiative: MAP: Actiq/Fentora

Length of Authorization: Up to 6 months (w/qty limit)

Covered Alternatives: Preferred alternatives listed at
http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

The following requires PA: Non-preferred drugs

GSN	GENERIC	BRAND
022358, 022360, 041339, 041340, 041341, 041342	Fentanyl Citrate	Actiq
061492, 061493, 063177, 061495, 061496, 061497	Fentanyl Citrate	Fentora
65552, 65553, 65554, 65555, 65556	Fentanyl Citrate	Onsolis

Approval Criteria

1. What is the diagnosis for which Actiq/Fentora/Onsolis is being requested?		Record ICD9 code and reject/internal error code
2. Is the pain diagnosis above the line or below the line? (for DMAP, Actiq/Fentora/Onsolis is not limited to cancer pain but must be severe chronic pain)	Above the line: go to #3.	Below the line: No, Pass to RPH; Deny, (Not Covered by the OHP).
3. Is the prescriber an oncologist or pain specialist?	Yes: Go to #4.	No: Pass to RPH; Deny, (Medical Appropriateness), with message: <i>"The described use is not consistent with the FDA labeling which Actiq/Fentora/Onsolis be used only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain."</i>
4. Is client tolerant to opioids (Check profile), defined as chronic long-acting opioid dose of: <ul style="list-style-type: none"> • Morphine greater than 60 mg per day? <u>OR</u> • Transdermal fentanyl 50 mcg per hour? <u>OR</u> • Equianalgesic dose of another opioid for at least one week? 	Yes: Go to #5.	No: Pass to RPH; Deny, (Medical Appropriateness), with message: <i>"Your request was reviewed and denied because it is not consistent with the FDA labeling. A trial of immediate release morphine or oxycodone is recommended prior to use of Actiq/Fentora/Onsolis."</i>
5. Has the client tried and failed immediate release morphine or oxycodone? OR is the client allergic, unable to swallow or intolerant to morphine and oxycodone?	Yes: Go to #6.	No: Pass to RPH; Deny, (Medical Appropriateness), with message: <i>"Your request was reviewed and denied based on the following: A trial of immediate release morphine or oxycodone is recommended prior to use of Actiq/Fentora/Onsolis."</i>
6. Is the quantity >4 doses per day?	Yes: Pass to RPH; Deny, (Medical Appropriateness), with message: <i>"Your request for a quantity greater than 4 has been denied because it exceeds limits."</i>	No: Approve for up to 6 months with quantity limit of 4 lollipops/tablets per day (i.e. 120/30 days).

DUR Board Action: 3/18/10 (DO); 12-3-09 (KS), 9-15-05, 5-12-05
 Revision(s): 4/26/10 (DO); 4/1/08, 6/1/08, 1/1/10
 Initiated: 9-1-06

Appendix 1

Randomized Control Trials

Ashburn MA, Slevin KA, Messina J, Xie F. The Efficacy and Safety of Fentanyl Buccal Tablet Compared with Immediate-Release Oxycodone for the Management of Breakthrough Pain In Opioid-Tolerant Patients with Chronic Pain. *Anesthesia & Analgesia*. 2011;112(3):693–702. doi:10.1213/ANE.0b013e318209d320.

Context. We recently reported that fentanyl pectin nasal spray (FPNS) provides superior pain relief from breakthrough cancer pain (BTCP) compared with immediate-release morphine sulfate (IRMS), with significant effects by five minutes and clinically meaningful pain relief from 10 minutes postdose.

Objectives. To report the consistency of efficacy, tolerability, and patient acceptability of FPNS vs. IRMS.

Methods. Patients ($n = 110$) experiencing one to four BTCP episodes/day while taking ≤ 60 mg/day oral morphine (or equivalent) for background pain entered a double-blind, double-dummy (DB/DD), multiple-crossover study. Those who completed an open-label titration phase ($n = 84$) continued to a DB/DD phase; 10 episodes were randomly treated with FPNS and overencapsulated placebo or IRMS and nasal spray placebo (five episodes each). Pain intensity (PI) and pain relief scores were assessed. Patient acceptability scores were assessed at 30 and 60 minutes. Safety and tolerability were assessed by adverse events (AEs) and nasal assessments.

Results. Per-episode analysis revealed that FPNS consistently provided relief from pain more rapidly than IRMS; by 10 minutes, there were significant differences in PI difference scores and in the percentages of episodes showing clinically meaningful pain relief ($P < 0.05$). Overall acceptability scores were significantly greater for FPNS than for IRMS at 30 ($P < 0.01$) and 60 ($P < 0.05$) minutes. Patients were “satisfied/very satisfied” with the convenience (79.8%).

Davies A, Slite T, Elsner F, et al. Consistency of Efficacy, Patient Acceptability, and Nasal Tolerability of Fentanyl Pectin Nasal Spray Compared with Immediate-Release Morphine Sulfate in Breakthrough Cancer Pain. *Journal of Pain and Symptom Management*. 2011;41(2):358–366. doi:10.1016/j.jpainsymman.2010.11.004.

BACKGROUND: Current clinical guidelines have identified the need for studies comparing the effect of different short-acting or rapid-onset opioids for the treatment of breakthrough pain (BTP). In this study we evaluated the efficacy and safety of treatment with fentanyl buccal tablet (FBT) in comparison with immediate-release oxycodone in alleviating BTP in opioid-tolerant patients with chronic pain.

METHODS: In this cross-over design study, opioid-tolerant patients were randomized to open-label titration with FBT (200, 400, 600, 800 mcg) followed by oxycodone (15, 30, 45, 60 mg) or vice versa for the management of BTP. After titration to a successful dose of both study drugs, patients were rerandomized to double-blind treatment for 10 BTP episodes with 1 of the already identified successful doses of study drug followed by cross-over to double-blind treatment for 10 BTP episodes with the other study drug. The primary efficacy measure was the difference in pain intensity (based on an 11-point numerical scale) 15 minutes after administration of study drug (PID15). Other efficacy measures included PID at other time points postdose (5 through 60 minutes), the sum of pain intensity differences (SPID) at 30 and 60 minutes postdose, pain relief (5 through 60 minutes), proportion of BTP episodes for which patients experienced meaningful reduction in pain intensity, and patient preference for BTP medication. Adverse events were also recorded.

RESULTS: Of the 323 patients enrolled, 203 achieved a successful dose of both study drugs, 191 completed the titration phase, and 180 completed the double-blind phase. PID15 was significantly greater after FBT versus oxycodone (mean [SD], 0.82 [1.12] vs. 0.60 [0.88]; 95% confidence interval [CI] = 0.18, 0.29; $P = 0.0001$). Secondary efficacy measures favored FBT and showed differences versus oxycodone from 5 minutes postdose for PID and 10 minutes postdose for pain relief. SPID30 and SPID60 were greater with FBT than with oxycodone ($P = 0.0001$ for both measures). A 33% improvement in pain intensity occurred in a larger proportion of FBT-treated episodes versus oxycodone beginning 15 through 45 minutes postdose ($P = 0.05$). FBT was preferred by 52% of patients, oxycodone by 33%. Adverse events with both study drugs were generally typical of opioids, and the majority occurred during titration. Two serious adverse events (pneumonia) were reported in 1 patient; both occurrences were considered unrelated to study drug.

CONCLUSION: FBT resulted in more rapid onset of analgesia and was generally well tolerated in comparison with oxycodone for the treatment of BTP in opioid-tolerant patients.

Appendix II

Systematic Reviews

Vissers D, Stam W, Nolte T, Lenre M, Jansen J. Efficacy of intranasal fentanyl spray versus other opioids for breakthrough pain in cancer. *Current Medical Research and Opinion*. 2010;26(5):1037–1045. doi:10.1185/03007991003694340.

Objective: To compare the efficacy of intranasal fentanyl spray (INFS), oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablet (FBT) and oral morphine (OM) for the treatment of breakthrough cancer pain (BTCP).

Methods: A systematic literature review (Medline, EMBASE, BIOSIS; 1996–2007) identified six randomised controlled trials (RCTs) investigating the effects of INFS, OTFC, FBT and OM for the treatment of BTCP. The endpoint of interest was pain Intensity difference (PID, reported on a 0–10 numeric rating scale [NRS]) up to 60 minutes after intake. Results of all trials were analysed simultaneously with a mixed treatment comparison (extended meta-analysis). MTC can be considered a valid method when included studies are comparable regarding effect modifying baseline patient and study characteristics.

Results: INFS provided the greatest reduction in pain relative to placebo: PID 1.7 points (95% CI: 1.4; 1.9) at 15 minutes, 2.0 (1.6; 2.3) at 30 minutes, 2.0 (1.5; 2.4) at 45 minutes and 1.9 (1.5; 2.4) at 60 minutes. PID for OTFC and FBT relative to placebo were 0.4 (0.0; 0.8) and 0.5 (0.3; 0.7) at 15 minutes. Both treatments provided a reduction in pain superior to placebo at other time points. INFS displayed a more than 99% probability of providing the greatest pain reduction out of all interventions compared at 15 minutes after intake. This was maintained for any measured time point before 45 minutes when compared to FBT and for any measured time point before 60 minutes when compared to OTFC. Only from 45 minutes onwards did OM show a greater pain reduction than placebo.

Conclusion: Based on currently available evidence, INFS is expected to provide the greatest improvement in the treatment of BTCP. Due to its slow onset to effect OM cannot be considered an efficacious treatment for BTCP.

Riemssma R, Forbes C, Harker J, et al. Systematic review of tapentadol in chronic severe pain. *Current Medical Research and Opinion*. 2011;27(10):1907–1930. doi:10.1185/03007995.2011.611494.

Aim: A systematic review of chronic pain treatment with strong opioids (step 3 WHO pain ladder) and a comparison to a new drug recently approved for the treatment of severe chronic pain in Europe, tapentadol (Palexia, Nucynta*), were performed.

Methods: Thirteen electronic databases were searched as well as a number of other sources from 1980 up to November 2010 for relevant randomized controlled clinical trials in chronic moderate and severe pain investigating at least one step 3 opioid. Chronic pain could be nociceptive or neuropathic, malignant or nonmalignant, all systemic administrations were considered as well as trials of different lengths. Two separate analyses were performed, one only for trials which reported (at least as sub-groups) the outcome in patients with severe pain, the other including both moderate and severe pain conditions. With the exception of the direct comparison between tapentadol, oxycodone and placebo, indirect comparisons were performed based on a network analysis. Trials with an enriched or an

Date: July 2013

enriched withdrawal design were excluded. Primary (pain intensity) and a number of secondary endpoints were evaluated, including pain relief (30% and 50%), patient global impression of change, quality of life, quality of sleep, discontinuations, as well as serious adverse events and selected adverse events.

Results: Only 10 trials were eligible for analysis of patients with severe pain (eight investigating tapentadol and two trials comparing buprenorphine patch vs placebo). For moderate and severe pain, 42 relevant trials were identified and indirect comparisons with transdermal buprenorphine, transdermal fentanyl, hydromorphone, morphine, and oxymorphone were performed. This report focuses on the network analysis. Tapentadol showed statistically favourable results over oxycodone for pain intensity, 30% and 50% pain relief, patient global impression of change (PGIC), and quality of life. Furthermore, some of the most important adverse events of chronic opioid treatment were significantly less frequent with tapentadol as compared to oxycodone, i.e. constipation, nausea, and vomiting; discontinuations due to these adverse events were found significantly reduced with tapentadol. Similar results were obtained for the network analysis, i.e. tapentadol was superior for the primary outcome (pain intensity) to hydromorphone and morphine, whereas fentanyl and oxymorphone showed trends in favour of these treatments. Significantly less frequent gastrointestinal adverse events of tapentadol were observed in comparison with fentanyl, hydromorphone, morphine, and oxymorphone, apparently leading to significantly reduced treatment discontinuations (for any reason).

Conclusions: Taken together, the benefit-risk ratio of tapentadol appears to be improved compared to step 3 opioids.

Date: July 2013