OSU Oregon State University College of Pharmacy

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

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, March 29, 2012 1:00-4:00 PM
Hewlett-Packard Building
4070 27th Ct SE
Salem, OR 97302

MEETING AGENDA

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

I. CALL TO ORDER 1:00 pm – 1:05 pm
- a. Roll Call & Introductions — B. Origer (Chair)
- b. Conflict of Interest Declaration — R. Citron (OSU)
- c. Approval of Agenda and Minutes — B. Origer (Chair)

II. OLD BUSINESS 1:05 pm – 1:20 pm
- a. Hepatitis C Follow-up from February* — M. Herink (OSU)
  1. Hepatologist Survey: Biopsy, Blood Counts
  2. Proposed Updated PA Criteria
  3. Public Comment
  4. Discussion of Clinical Recommendations to OHA
- b. Dose Consolidation* — R. Citron (OSU)
  1. Proposed List of Medications (Separate Handout)
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA

III. NEW BUSINESS 1:20 pm – 2:20 pm
- a. Short Acting Opioids Drug Use Evaluation* — T. Williams (OSU)
  1. Proposed PA Criteria
  2. Public Comment
  3. Discussion of clinical recommendations to OHA
- b. MS Class Update and New Drug Reviews* — M. Herink (OSU)
  1. Gilenya (fingolimod)
  2. Ampyra (dalframpridine)
  3. Public Comment
  4. Discussion of clinical recommendations to OHA
- c. Antipsychotic Class Update and New Drug Evaluation* — A. Wheeler (OSU)
  1. Latuda (lurasidone)
  2. Class Update
  3. Public Comment
  4. Discussion of clinical recommendations to OHA

BREAK 2:20 pm – 2:30 pm

Agenda items with an asterisk 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)

III. NEW BUSINESS (continued) 2:30 pm – 3:30 pm

d. Statin Class Update* — B. Liang (OSU)
    1. Livalo (pitavastatin)
    2. Public Comment
    3. Discussion of clinical recommendations to OHA
e. New Drug Evaluation* — B.Fouts (OSU)
    1. Firazyr (icatibant)
    2. Public Comment
    3. Discussion of clinical recommendations to OHA
f. ADHD Class Update* — T. Williams (OSU)
    1. DERP Report
    2. Public Comment
    3. Discussion of clinical recommendations to OHA
g. Drug Class Scans* — M. Herink (OSU)
    1. Sedative Hypnotics
    2. Skeletal Muscle Relaxants
    3. Triptans
    4. Public Comment
    5. Discussion of clinical recommendations to OHA

IV. EXECUTIVE SESSION 3:30 pm

V. RECONVENE for PUBLIC RECOMMENDATIONS*

VI. ADJOURN

Agenda items with an asterisk 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)

Suggested PA Criteria

Hepatitis C Oral Protease Inhibitors

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code:	**Yes:** Go to #2	**No:** Pass to RPh, Deny For Appropriateness
2. Does the patient have documented HCV genotype 1? Record Genotype:	**Yes:** Go to #3	**No:** Pass to RPh, Deny For Appropriateness
3. Is the patient also being prescribed peginterferon alfa-2a or -2b and ribavirin and has been granted prior authorization or meets criteria for pegylated interferon-alfa and ribavirin?	**Yes:** Go to #4	**No:** Pass to RPh, Deny For Appropriateness
4. Is the request for continuation of therapy? (Patient has been on triple therapy with a oral antiviral agent in preceding 6 weeks)	**Yes**: Go to "Continuation of Therapy	**No**: Go to #5
5. Does the patient have a Child-Pugh score < 7 (compensated liver disease)?	**Yes:** Go to #6	**No:** Pass to RPh, Deny For Appropriateness
6. Is the medication being prescribed by or in consultation with a specialist in the field of gastroenterology, infectious disease, or hepatitis C?	**Yes:** Go to #7	**No:** Pass to RPh, Deny For Appropriateness
7. If the patient has been treated with peginterferon and ribavirin before, do they have documented compliance/adherence to their previous treatment?	**Yes:** Go to #8	**No:** Pass to RPh, Deny For Appropriateness
8. Does the patient have a biopsy to indicate moderate to severe fibrosis (stage 2 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis? OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins).	**Yes:** Go to #9	**No:** Pass to RPh, Deny For Appropriateness
9. Does the patient have a HIV coinfection?	**Yes:** Pass to RPh, Deny For Appropriateness	**No:** Go to #10
10. Has the patient previously been treated with boceprevir or telaprevir?	**Yes**: Pass to RPh, Deny for appropriateness	**No:** Go to #11
11. Is the request for telaprevir 750mg (two tabs) TID for 12 weeks?	**Yes:** Approve for 6 weeks to allow for 4 week viral load check to continue for a maximum of 12 weeks	**No:** Go to #12 (If dose is different pass to RPh for appropriateness)
12. Is the request for boceprevir 800mg (four tabs) TID and the patient has completed 4 weeks of lead-in treatment with ribavirin and peginterferon?	**Yes:** Approve for 10 weeks to allow for 8 week viral load check to continue for a maximum of 24, 32, or 40 weeks based on response	**No:** Pass to RPh; Deny for appropriateness

Continuation of Therapy- Telaprevir		
1. Is the patient treatment-naïve or a prior relapse patient and has undetectable HCV RNA or measured at 4 and 12 weeks?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for 12 weeks (total treatment duration of 24 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
2. Is the patient treatment-naïve or a prior relapse patient and has detectable (1000 IU/mL or less) at Weeks 4 and/or 12	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
3. Is the patient a prior partial or null responder?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness)
4. Is the patient treatment-naïve with documented cirrhosis that has undetectable HCV-RNA at weeks 4 and 12?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.

***TREATMENT FUTILITY RULES**
Week 4 or Week 12: HCV-RNA greater than 1000 IU/mL: Discontinue INCIVEK and peginterferon alfa and ribavirin (INCIVEK treatment complete at 12 weeks)
Week 24: Detectable Discontinue peginterferon and ribavirin.
If peginterferon alfa or ribavirin is discontinued for any reason, INCIVEK must also be discontinued

Continuation of Therapy- Boceprevir		
1. Is the patient treatment-naïve and have undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 14 weeks of boceprevir for total treatment duration of 28 weeks (4 week lead-in, 24 weeks triple therapy)	**No:** DENY (Medical Appropriateness)
2. Is the patient treatment-naïve and have detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)
3. Is the patient a previous partial responder or relapser and has undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir for total treatment duration of 36 weeks (4 week lead-in, 32 weeks triple therapy)	**No:** DENY (Medical Appropriateness)
4. Is the patient a previous partial responder or relapser and has detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)
5. Does the patient have documented cirrhosis or is documented as a null responder and does not meet the futility rules at treatment weeks 8, 12, and 24?	**Yes:** Approve as follows: • Continue triple therapy with boceprevir for a total treatment duration of 48 weeks (4 week lead-in, 44 weeks triple therapy).	**No:** DENY (Medical Appropriateness)
***TREATMENT FUTILITY RULES** If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.		

Clinical Notes:

Staging the degree of fibrosis:

Stage	IASL	Batts-Ludwig	Metavir
0	No fibrosis	No fibrosis	No fibrosis
1	Mild fibrosis	Fibrous portal expansion	Periportal fibrotic expansion
2	Moderate fibrosis	Rare bridges or septae	Periportal septae 1 (septum)
3	Severe fibrosis	Numerous bridges or septae	Porto-central septae
4	Cirrhosis	Cirrhosis	Cirrhosis

Drug Use Evaluation: Short Acting Opioids (SAO)

Summary

- Short acting opioid analgesics are one of the most prescribed (top 10) and highest cost (top 20) medication classes for the Oregon Fee For Service (FFS) Medicaid program
- A minority of members without medical claims for cancer treatment are receiving short acting opioids exceeding daily doses recommended by current evidence based guidelines
- Of these members, a significant proportion have medical claims suggesting increased risk of developing misuse or abuse of these medications

Recommendations

- Apply the same prior authorization criteria to both short and long acting opioids. Applying these criteria will:
    - Minimize the use of opioid analgesics at doses exceeding current guidelines
    - Increased surveillance for misuse/abuse
    - Provide prescriber education regarding the risks of high dose opioids
- Monitor the effects of the new PA criteria on:
    - Proportion of members on high vs. low dose SAO
    - Proportion of members using SAO vs. LAO
    - Members with dose escalations exceeding recommended doses
- Monitor the impact on workload on FFS Medicaid Pharmacy Benefits Management vendor:
    - Track the number of PA requested for high dose SAO
    - Track the number of PA appeals for denied requests for high dose SAO

Drug Use Evaluation: Short Acting Opioids (SAO)

Background

As discussed in detail in the DURM Long Acting Opioid (LAO) Drug Use Evaluation (DUE), the off label use of opioids has increased significantly in the general US population as well as the Oregon Medicaid Program.[1] Studies evaluating mortality rates have conflicting results with some studies showing increased mortality associated with increasing prescriptions of opioids.[2] Chronic opioid use has been associated with effects on hormone levels, abuse and addiction, tolerance and hyperalgesia.[3] Mental health diagnoses and a history of substance abuse have been associated with a greater risk of increase utilization and opioid abuse.[4,5] The treatment of chronic pain with opioids has been shown to have little effect on functional status.[6]

Concerns over misuse and abuse have garnered national and regional attention. In 2011 the Executive Office of the President stated: "Prescription drug misuse and abuse is a major public health and public safety crisis."[7] The Director of the Center for Disease Control (CDC) described misuse and abuse of prescriptions as an "epidemic."[8] The Centers for Medicare and Medicaid Services (CMS) in 2011 indicated that Prior Authorizations are a part of a "robust state controlled prescription drug program."[9] Washington State enacted House Bill 2876 mandating pain specialist consultations for patients exceeding 120 morphine equivalents daily (MED). Multnomah county currently restricts patients to 180 MED, with plans to further reduce to 60 MED in 2012.

Opioid analgesic use accounts for significant expenditures in Oregon Medicaid Fee For Service (FFS) and is the fifth highest cost medication class.[10] Generic oxycodone alone is the third most frequently prescribed medication.[11]

Drug Use Evaluation

In response to safety concerns, Oregon FFS Medicaid performed a Drug Use Evaluation (DUE) for SAO analgesics. This DUE sought to determine if SAO are used in high risk patients at doses exceeding those recommended by current guidelines. Additionally, we sought to determine the potential benefits of applying current LAO PA criteria to SAO.

Methods

Selection criteria included all FFS pharmacy prescription claims for SAO from January 1, 2009 thru November 30, 2011. SAO are defined as medications in standard therapeutic class 40 with formulations dosed more than twice daily which are not in extended release formulations or transdermal patches. Diagnoses were determined based on medical claims data starting 6 months before the study period through the end of the study period (i.e. July 1, 2008 - November 30, 2011). Cancer was identified from ICD-9 codes 140.0-239.9 and 338.3. Mental Health disorders were identified by ICD-9 codes 293-302.9 and 306-331.6. Fibromyalgia was identified by ICD-9 729.1. Substance abuse was identified by ICD-9 codes 303-305 (excluding 305.1), 291, 292, V46, and V681. Costs and utilization trends are reported as

member per month (PMPM) values. Prescription costs include only the amount paid by the FFS program; third party payments are not included.

Several short acting opioids were excluded from our analysis. Parenteral formulations were excluded from analysis. Tramadol and propoxyphene were excluded due to low abuse potential. Sublingual buprenorphine/naltrexone (Suboxone®) is not approved for the treatment of chronic pain and was also excluded. Pentazocine was excluded due to lack of a reliable conversion factor. Butorphanol and opium were excluded as they have particular uses and are not used for the general management of pain. Tapentadol (Nucynta®) was excluded, because the package insert specifies a maximum daily dose.[12] Prescriptions for a supply of less than five days can skew dose calculations and therefore these claims have been excluded from analysis involving dose levels.

High dose (HD) opioids are defined as total dose exceeding 120 MED. Acceptable doses (AD) are defined as dosages less than or equal to 120 MED. Morphine dose equivalents were calculated by converting each opioid into morphine equivalents per dispensable unit. The number of units prescribed per day was multiplied by the morphine equivalent per dispensable unit to determine the MED. A complete table of opioid formulations encountered and the corresponding MED results are included in Appendix A.

Members receiving chronic SAO therapy were identified as a subgroup of interest. Chronic therapy is defined as at least three calendar months of opioid therapy during the study period with the quantity supplied for all prescriptions totaling at least half the number of calendar days of therapy. This is intended to include patients who take less than the prescribed quantity continuously and patients who have temporarily stopped what would be considered chronic therapy.

Results

Figure 1 demonstrates the total opioid utilization, with SAO compromising 72-78% of all prescriptions. Total PMPM prescriptions declined during the study period, but the proportion of SAO to LAO was not significantly affected.

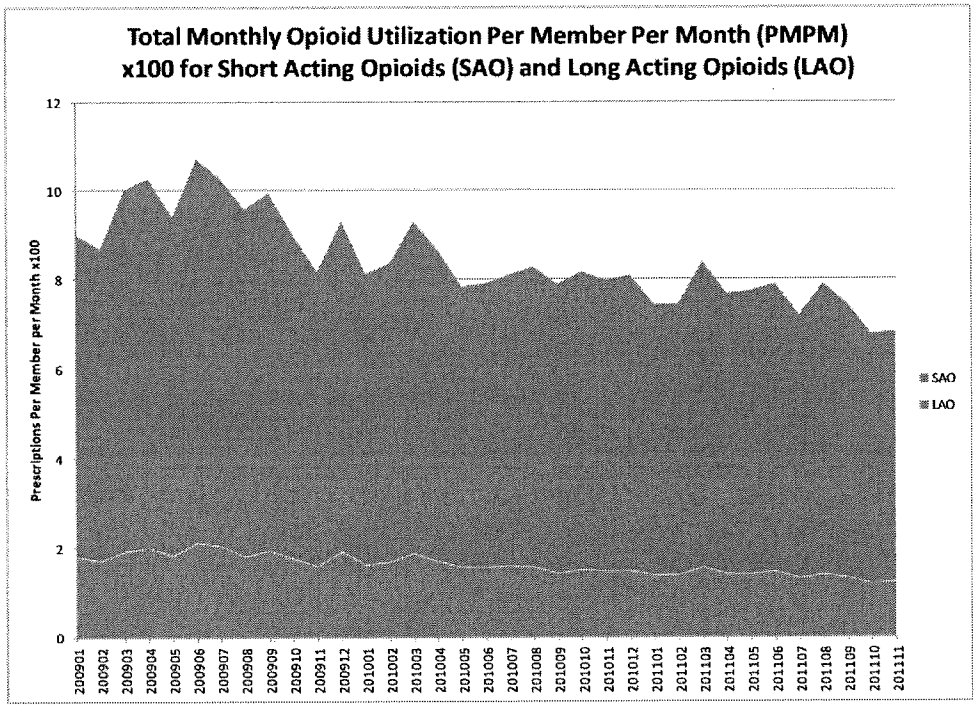


Figure 1. Trend of opioid utilization and proportion of SAO vs. LAO

Figure 2 compares SAO volume and cost PMPM. January 2011 shows a significant drop in cost PMPM. This timing is consistent with a change in pharmacy reimbursement rules for FFS member claims and the implementation of the SAO preferred drug list (PDL).

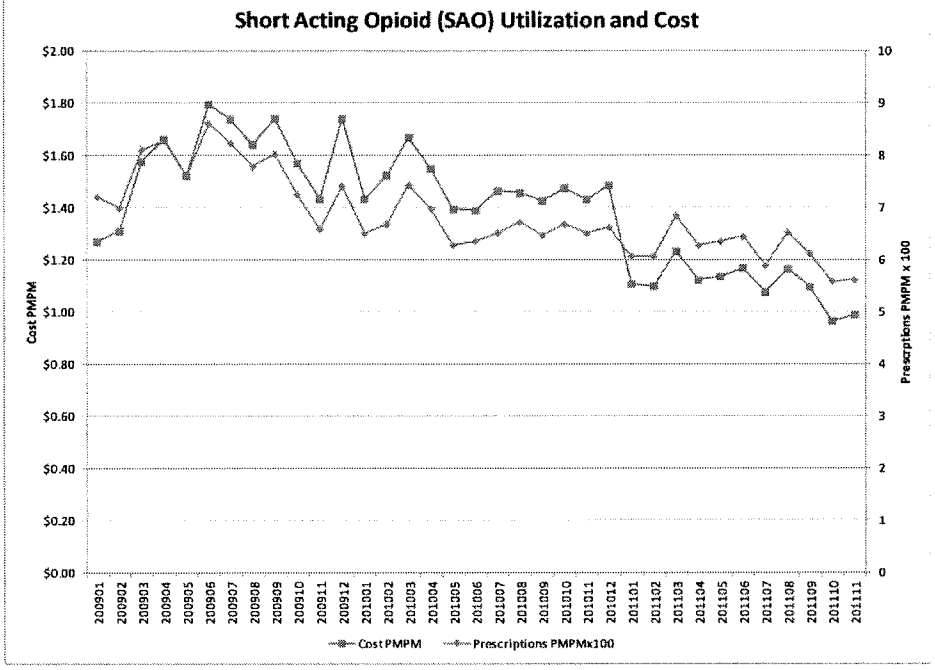


Figure 2. Trend in Utilization volume and costs for SAO

Figure 3 illustrates the average MED (lines) for HD and AD as well as the total volume of prescriptions (bars). The average MED for AD members was relatively stable, varying from 38-41 MED (approximately eight Vicodin® daily). The average dose for HD patients varied from 217 – 263 MED.

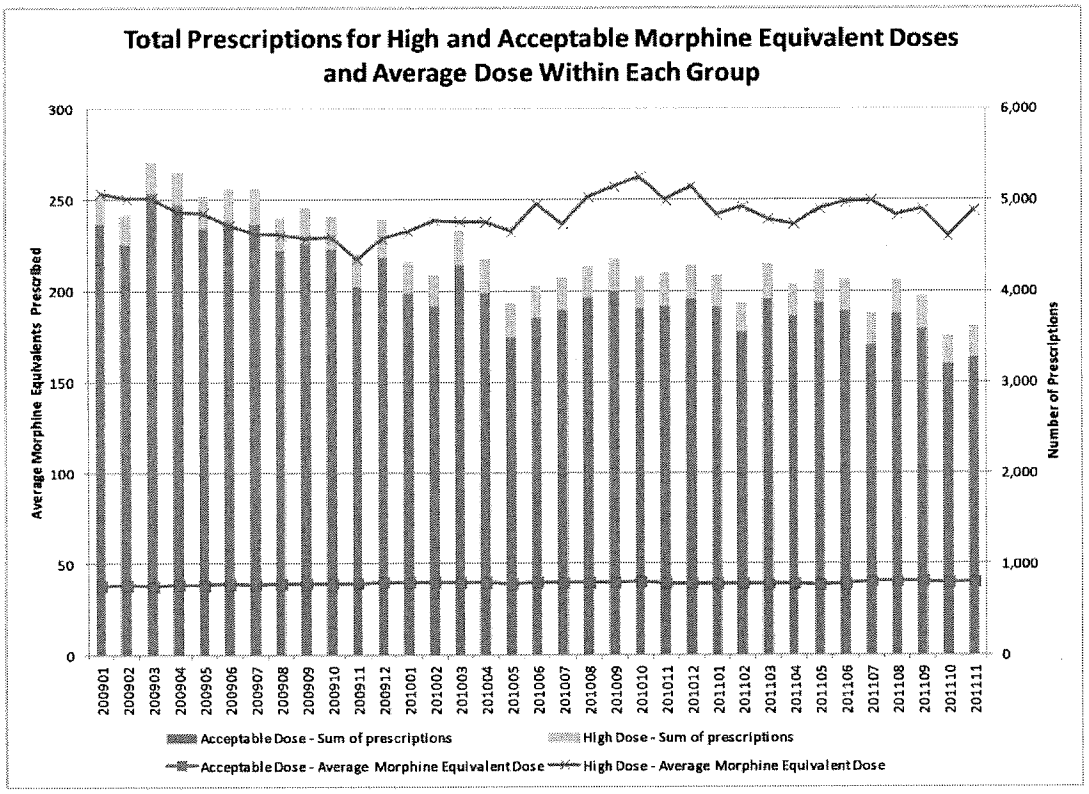


Figure 3. Total Prescription volume (bars) and average MED (lines) for AD and HD prescriptions

Of all patients receiving HD SAO, 47% have had at least one cancer-related medical claim (Figure 4, Table 1). Figures 5 and 6 show members without cancer claims receiving HD SAO who have claims suggesting an increased risk of developing substance abuse/misuse. Fifteen percent of patients with dose escalations of at least 50% have a final dose exceeding 120 MED (figure 7). Finally figure 8 demonstrates for all non-cancer patients receiving chronic SAO therapy, the proportion of HD vs. AD remains essentially unchanged during the study period (~95% AD, ~5% HD).

Category	Members	Prescriptions	Total Paid ($)	Average MED
Overall	1,753	29,391	1,614,229	243
Cancer	824	13,874	789,916	258
Non-Cancer	929	15,517	824,313	230

Table 1. Members receiving at least one SAO prescription exceeding 120 MED with and without cancer-associated medical claims

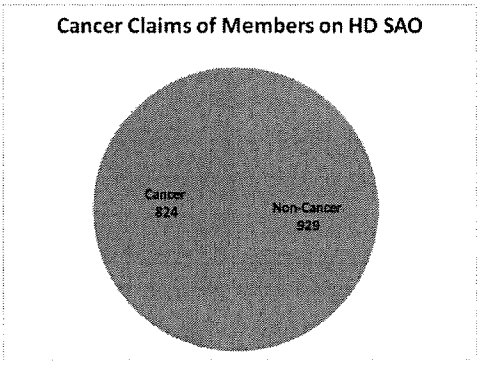


Figure 4 HD SAO use in cancer and non-cancer patients

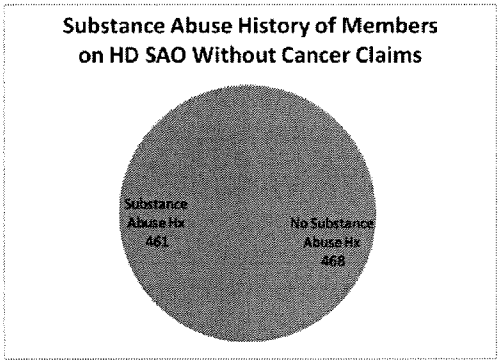


Figure 5 HD SAO use in non-cancer patients with a history of substance abuse

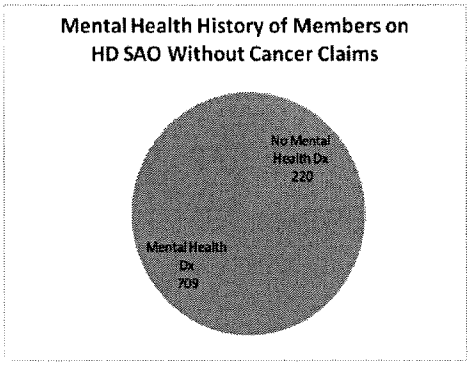


Figure 6 HD SAO use in non-cancer patients with a history of mental health disorders

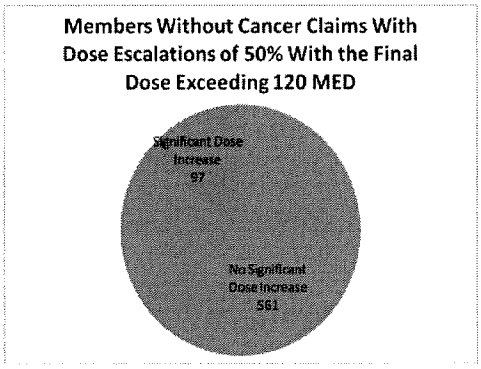


Figure 7 Dose escalations to high dose levels

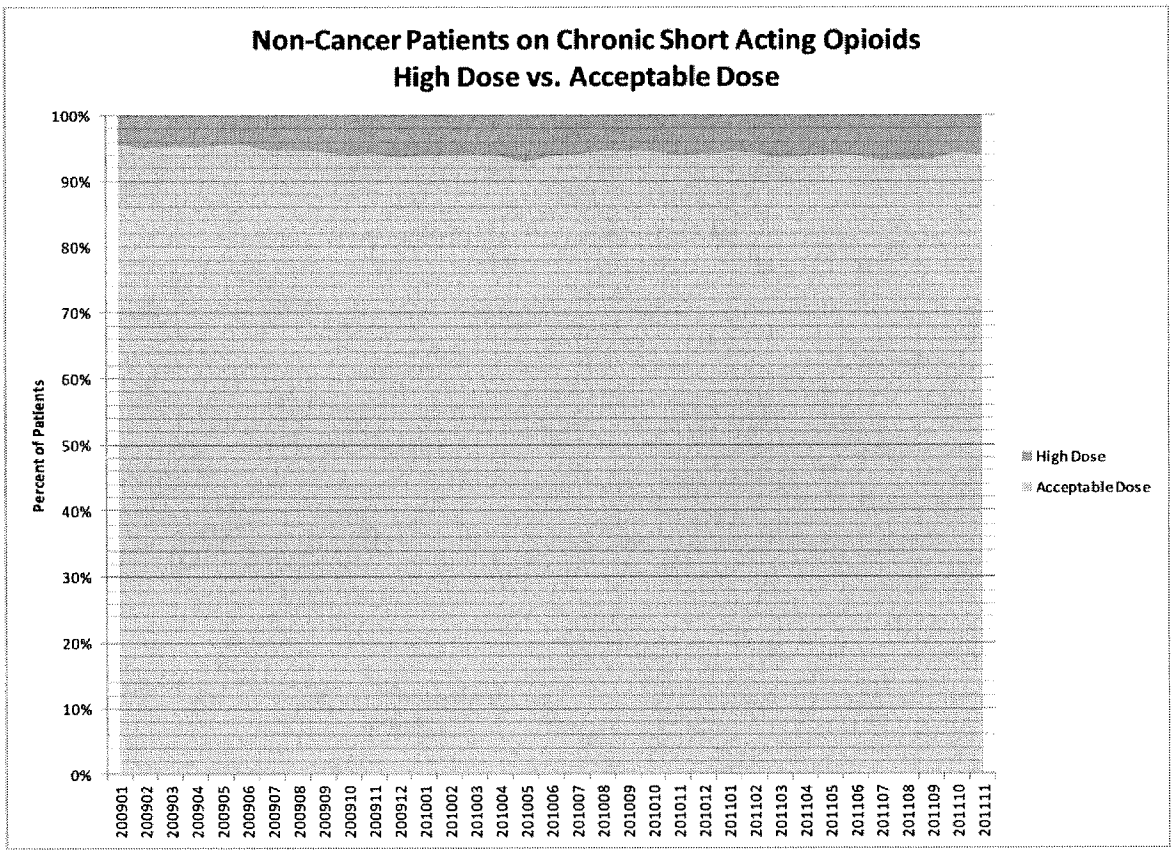


Figure 8. Proportion of non-cancer chronic SAO patients on high and acceptable dosages

Discussion

Over half of the members receiving HD SAO do not have claims indicating a diagnosis of cancer. Of these patients, 76% have a mental health diagnosis which has been identified as a risk factor for future or current substance abuse and drug seeking behaviors.[13] Patients with a recent history of substance abuse compose 50% of the members on HD SAO who do not have claims indicating cancer. These data suggest that many of these members may be at elevated risk of developing substance abuse and misuse behaviors.

The risk factors of overuse and misuse found in the LAO DUE are also found in patients receiving SAO therapy.1 Most members (~95%) using SAO are treated at dosages consistent with current pain treatment guidelines (i.e. acceptable dosage group). Yet there are a significant number of patients receiving HD SAO who have a history of substance abuse or risk factors for substance abuse or misuse. The LAO DUE recommended changes to the Prior Authorization to restrict use to address these concerns (See Appendix B). Applying these same criteria should decrease use of HD SAO in non-cancer patients, as well as improve monitoring in patients with risk factors for misuse and abuse through the Pharmacy Management Program (a.k.a. Lock-In Program).

Attention to patient care and adequate pain control is essential for the success of this program. Approximately 5% of patients receiving SAO therapy would qualify for evaluation of PA criteria (i.e. exceeding 120MED for non-cancer pain). According to the proposed LAO criteria, patients already being treated for above the line pain diagnoses receiving opioids from one provider and one pharmacy would generally be approved for 6 month extensions after the prescriber acknowledges the risks associated with high dose opioids. This will protect 95% of SAO users for burdensome and unnecessary prior authorization requests, while providing additional safety controls for the minority of members at elevated risk of abuse and misuse.

Limitations

Analysis of claims data has many limitations. Diagnosis data may be incomplete, inaccurate, or untimely. Medical claims typically appear in 6 months, but a minority of claims may not be submitted for over one year. Our data analysis is limited to FFS Medicaid members and associated claims. Managed Care Organization (MCO) medical claims data was included, but not prescription data. Members of Oregon Medicaid change from FFS to MCO plans regularly. Such switches could cause members chronic treated for pain appear as intermittently treated. Any prescriptions which were purchased for cash or paid for by other third party payers would not appear in our analysis. The Oregon Medicaid Program is not currently allowed access to the Oregon Prescription Drug Monitoring Program (PDMP) database, without which cash claims cannot be assessed.

Recommendations

- Apply the same prior authorization criteria to both short and long acting opioids (Appendix B). Applying these criteria will:
    - Manage the use of opioid analgesics at doses exceeding 120MED
    - Increased surveillance for misuse/abuse
    - Provide prescriber education regarding the risks of high dose opioids
- Monitor the effects of the new PA criteria on:
    - Proportion of members on high vs. low dose SAO
    - Proportion of members using SAO vs. LAO
    - Members with dose escalations exceeding 120 MED
    - Members with dose reduction from above 120 MED to below 120MED
- Monitor the impact on workload on FFS Medicaid Pharmacy Benefits Management vendor:
    - Track the number of PA requested for high dose SAO
    - Track the number of PA appeals for denied requests for high dose SAO

Appendix A – Morphine Equivalents

Generic	Formulation Strength	Form	Unit Type	Opioid Per Unit	Conversion Factor	Morphine Equivalent Per Unit
ACETAMINOPHEN WITH CODEINE	120 mg-12 mg/5 mL	ELIXIR	ML	2.4	0.15	0.36
ACETAMINOPHEN WITH CODEINE	120 mg-12 mg/5 mL	ORAL SUSP	ML	2.4	0.15	0.36
ACETAMINOPHEN WITH CODEINE	300 mg-15 mg	TABLET	EA	15	0.15	2.25
ACETAMINOPHEN WITH CODEINE	300 mg-30 mg	TABLET	EA	30	0.15	4.5
ACETAMINOPHEN WITH CODEINE	300 mg-60 mg	TABLET	EA	60	0.15	9
ASPIRIN/CODEINE PHOSPHATE	325 mg-30 mg	TABLET	EA	30	0.15	4.5
CODEINE PHOS/CARISOPRODOL/ASA	16 mg-200 mg-325 mg	TABLET	EA	16	0.15	2.4
CODEINE SULF	15 mg	TABLET	EA	15	0.15	2.25
CODEINE SULF	30 mg	TABLET	EA	30	0.15	4.5
CODEINE SULF	60 mg	TABLET	EA	60	0.15	9
CODEINE/BUTALBIT/ACETAMIN/CAFF	30 mg-50 mg-325 mg-40 mg	CAPSULE	EA	30	0.15	4.5
CODEINE/BUTALBITAL/ASA/CAFFEIN	30 mg-50 mg-325 mg-40 mg	CAPSULE	EA	30	0.15	4.5
FENTANYL	12 mcg/hour	PATCH TD72	PER DAY	12	4.00	48
FENTANYL	25 mcg/hour	PATCH TD72	PER DAY	25	4.00	100
FENTANYL	50 mcg/hour	PATCH TD72	PER DAY	50	4.00	200
FENTANYL	75 mcg/hour	PATCH TD72	PER DAY	75	4.00	300
FENTANYL CITRATE	200 mcg	LOZENGE HD	EA	200	0.03	6
FENTANYL CITRATE	400 mcg	LOZENGE HD	EA	400	0.03	12
FENTANYL CITRATE	1,200 mcg	LOZENGE HD	EA	1200	0.03	36
FENTANYL CITRATE	1,600 mcg	LOZENGE HD	EA	1600	0.03	48
FENTANYL CITRATE	100 mcg	TABLET EFF	EA	100	0.12	12
FENTANYL CITRATE	200 mcg	TABLET EFF	EA	200	0.12	24
HYDROCODONE BIT/ACETAMINOPHEN	7.5 mg-325 mg/15 mL	SOLUTION	ML	0.5	1.00	0.5
HYDROCODONE BIT/ACETAMINOPHEN	7.5 mg-500 mg/15 mL	SOLUTION	ML	0.5	1.00	0.5
HYDROCODONE BIT/ACETAMINOPHEN	7.5 mg-500 mg/15 mL (15 mL)	SOLUTION	ML	0.5	1.00	0.5
HYDROCODONE BIT/ACETAMINOPHEN	2.5 mg-500 mg	TABLET	EA	2.5	1.00	2.5
HYDROCODONE BIT/ACETAMINOPHEN	5 mg-325 mg	TABLET	EA	5	1.00	5
HYDROCODONE BIT/ACETAMINOPHEN	5 mg-500 mg	TABLET	EA	5	1.00	5
HYDROCODONE BIT/ACETAMINOPHEN	7.5 mg-325 mg	TABLET	EA	7.5	1.00	7.5
HYDROCODONE BIT/ACETAMINOPHEN	7.5 mg-500 mg	TABLET	EA	7.5	1.00	7.5
HYDROCODONE BIT/ACETAMINOPHEN	7.5 mg-650 mg	TABLET	EA	7.5	1.00	7.5
HYDROCODONE BIT/ACETAMINOPHEN	7.5 mg-750 mg	TABLET	EA	7.5	1.00	7.5
HYDROCODONE BIT/ACETAMINOPHEN	10 mg-325 mg	TABLET	EA	10	1.00	10
HYDROCODONE BIT/ACETAMINOPHEN	10 mg-400 mg	TABLET	EA	10	1.00	10
HYDROCODONE BIT/ACETAMINOPHEN	10 mg-500 mg	TABLET	EA	10	1.00	10
HYDROCODONE BIT/ACETAMINOPHEN	10 mg-650 mg	TABLET	EA	10	1.00	10
HYDROCODONE BIT/ACETAMINOPHEN	10 mg-660 mg	TABLET	EA	10	1.00	10
HYDROCODONE BIT/ACETAMINOPHEN	10 mg-750 mg	TABLET	EA	10	1.00	10
HYDROCODONE/IBUPROFEN	7.5 mg-200 mg	TABLET	EA	7.5	1.00	7.5
HYDROCODONE/IBUPROFEN	10 mg-200 mg	TABLET	EA	10	1.00	10
HYDROMORPHONE HCL	1 mg/mL	LIQUID	ML	1	4.00	4
HYDROMORPHONE HCL	3 mg	SUPP.RECT	EA	3	4.00	12
HYDROMORPHONE HCL	8 mg	TAB ER 24	EA	8	4.00	32
HYDROMORPHONE HCL	12 mg	TAB ER 24	EA	12	4.00	48
HYDROMORPHONE HCL	16 mg	TAB ER 24	EA	16	4.00	64
HYDROMORPHONE HCL	2 mg	TABLET	EA	2	4.00	8
HYDROMORPHONE HCL	4 mg	TABLET	EA	4	4.00	16
HYDROMORPHONE HCL	8 mg	TABLET	EA	8	4.00	32
IBUPROFEN/OXYCODONE HCL	400 mg-5 mg	TABLET	EA	5	1.50	7.5
LEVORPHANOL TARTRATE	2 mg	TABLET	EA	2	30.00	60
MEPERIDINE HCL	50 mg	TABLET	EA	50	0.10	5
MEPERIDINE HCL	100 mg	TABLET	EA	100	0.10	10
METHADONE HCL	10 mg/mL	ORAL CONC	ML	10	3.75	37.5
METHADONE HCL	5 mg/5 mL	SOLUTION	ML	1	3.75	3.75
METHADONE HCL	10 mg/5 mL	SOLUTION	ML	2	3.75	7.5
METHADONE HCL	5 mg	TABLET	EA	5	3.75	18.75
METHADONE HCL	10 mg	TABLET	EA	10	3.75	37.5
METHADONE HCL	40 mg	TABLET SOL	EA	40	3.75	150
MORPHINE SULFATE	10 mg	CAP ER PEL	EA	10	1.00	10
MORPHINE SULFATE	20 mg	CAP ER PEL	EA	20	1.00	20

Generic	Formulation Strength	Form	Unit Type	Opioid Per Unit	Conversion Factor	Morphine Equivalent Per Unit
MORPHINE SULFATE	30 mg	CAP ER PEL	EA	30	1.00	30
MORPHINE SULFATE	50 mg	CAP ER PEL	EA	50	1.00	50
MORPHINE SULFATE	60 mg	CAP ER PEL	EA	60	1.00	60
MORPHINE SULFATE	80 mg	CAP ER PEL	EA	80	1.00	80
MORPHINE SULFATE	100 mg	CAP ER PEL	EA	100	1.00	100
MORPHINE SULFATE	30 mg	CPMP 24HR	EA	30	1.00	30
MORPHINE SULFATE	60 mg	CPMP 24HR	EA	60	1.00	60
MORPHINE SULFATE	75 mg	CPMP 24HR	EA	75	1.00	75
MORPHINE SULFATE	90 mg	CPMP 24HR	EA	90	1.00	90
MORPHINE SULFATE	120 mg	CPMP 24HR	EA	120	1.00	120
MORPHINE SULFATE	10 mg/5 mL	SOLUTION	ML	2	1.00	2
MORPHINE SULFATE	20 mg/5 mL	SOLUTION	ML	4	1.00	4
MORPHINE SULFATE	100 mg/5 mL (20 mg/mL)	SOLUTION	ML	20	1.00	20
MORPHINE SULFATE	5 mg	SUPP.RECT	EA	5	1.00	5
MORPHINE SULFATE	10 mg	SUPP.RECT	EA	10	1.00	10
MORPHINE SULFATE	20 mg	SUPP.RECT	EA	20	1.00	20
MORPHINE SULFATE	15 mg	TABLET	EA	15	1.00	15
MORPHINE SULFATE	30 mg	TABLET	EA	30	1.00	30
MORPHINE SULFATE	15 mg	TABLET ER	EA	15	1.00	15
MORPHINE SULFATE	30 mg	TABLET ER	EA	30	1.00	30
MORPHINE SULFATE	60 mg	TABLET ER	EA	60	1.00	60
MORPHINE SULFATE	100 mg	TABLET ER	EA	100	1.00	100
MORPHINE SULFATE	200 mg	TABLET ER	EA	200	1.00	200
MORPHINE SULFATE/NALTREXONE	20 mg-0.8 mg	CAP ER PEL	EA	20	1.00	20
MORPHINE SULFATE/NALTREXONE	100 mg-4 mg	CAP ER PEL	EA	100	1.00	100
OXYCODONE HCL	5 mg	CAPSULE	EA	5	1.50	7.5
OXYCODONE HCL	20 mg/mL	ORAL CONC	ML	20	1.50	30
OXYCODONE HCL	20 mg/mL (1 mL)	ORAL CONC	ML	20	1.50	30
OXYCODONE HCL	5 mg/5 mL	SOLUTION	ML	1	1.50	1.5
OXYCODONE HCL	10 mg	TAB ER 12H	EA	10	1.50	15
OXYCODONE HCL	15 mg	TAB ER 12H	EA	15	1.50	22.5
OXYCODONE HCL	20 mg	TAB ER 12H	EA	20	1.50	30
OXYCODONE HCL	30 mg	TAB ER 12H	EA	30	1.50	45
OXYCODONE HCL	40 mg	TAB ER 12H	EA	40	1.50	60
OXYCODONE HCL	60 mg	TAB ER 12H	EA	60	1.50	90
OXYCODONE HCL	80 mg	TAB ER 12H	EA	80	1.50	120
OXYCODONE HCL	5 mg	TABLET	EA	5	1.50	7.5
OXYCODONE HCL	10 mg	TABLET	EA	10	1.50	15
OXYCODONE HCL	15 mg	TABLET	EA	15	1.50	22.5
OXYCODONE HCL	20 mg	TABLET	EA	20	1.50	30
OXYCODONE HCL	30 mg	TABLET	EA	30	1.50	45
OXYCODONE HCL/ACETAMINOPHEN	5 mg-500 mg	CAPSULE	EA	5	1.50	7.5
OXYCODONE HCL/ACETAMINOPHEN	5 mg-325 mg/5 mL	SOLUTION	ML	1	1.50	1.5
OXYCODONE HCL/ACETAMINOPHEN	2.5 mg-325 mg	TABLET	EA	2.5	1.50	3.75
OXYCODONE HCL/ACETAMINOPHEN	5 mg-325 mg	TABLET	EA	5	1.50	7.5
OXYCODONE HCL/ACETAMINOPHEN	5 mg-500 mg	TABLET	EA	5	1.50	7.5
OXYCODONE HCL/ACETAMINOPHEN	7.5 mg-325 mg	TABLET	EA	7.5	1.50	11.25
OXYCODONE HCL/ACETAMINOPHEN	7.5 mg-500 mg	TABLET	EA	7.5	1.50	11.25
OXYCODONE HCL/ACETAMINOPHEN	10 mg-325 mg	TABLET	EA	10	1.50	15
OXYCODONE HCL/ACETAMINOPHEN	10 mg-650 mg	TABLET	EA	10	1.50	15
OXYCODONE HCL/ASPIRIN	4.8355 mg-325 mg	TABLET	EA	4.8355	1.50	7.25325
OXYCODONE HCL/OXYCODON TER/ASA	4.5 mg-0.38 mg-325 mg	TABLET	EA	4.5	1.50	6.75
OXYMORPHONE HCL	5 mg	TAB ER 12H	EA	5	3.00	15
OXYMORPHONE HCL	7.5 mg	TAB ER 12H	EA	7.5	3.00	22.5
OXYMORPHONE HCL	10 mg	TAB ER 12H	EA	10	3.00	30
OXYMORPHONE HCL	15 mg	TAB ER 12H	EA	15	3.00	45
OXYMORPHONE HCL	20 mg	TAB ER 12H	EA	20	3.00	60
OXYMORPHONE HCL	30 mg	TAB ER 12H	EA	30	3.00	90
OXYMORPHONE HCL	40 mg	TAB ER 12H	EA	40	3.00	120
OXYMORPHONE HCL	5 mg	TABLET	EA	5	3.00	15
OXYMORPHONE HCL	10 mg	TABLET	EA	10	3.00	30

Appendix B – Proposed Opioid Prior Authorization Criteria

Opioid Analgesics

Goal(s):

- Limit the use of high dose opioid therapy to above-the-line diagnoses that are supported by the medical literature
- Limit the use of non-preferred products
- Promote the safe use of opioids.
  - Opioids have been associated with an increasing proportion of deaths in Oregon and the US.
  - Opioid deaths in Oregon are often associated with concurrent use of other drugs (e.g. other opioids, benzodiazepines, skeletal muscle relaxants)
  - Opioid deaths in Oregon are often associated with patients with a history of drug abuse.
  - Buprenorphine, Fentanyl and Methadone carry FDA Black Box Warnings and have been associated with adverse cardiac effects associated with QTc prolongation and/or life-threatening hypoventalation.
    - This risk is increased with concurrent use of other drugs prolonging the QTc interval or other drugs affecting metablolism of methadone or fentanyl.
  - See Oregon DUR Board newsletter at:
    - http://pharmacy.oregonstate.edu/drug_policy/pages/dur_board/newsletter/articles/volume11/DURV11I2.pdf
    - http://pharmacy.oregonstate.edu/drug_policy/pages/dur_board/newsletter/articles/volume5/DURV5I5.pdf

Initiative:

Long and Short Acting Opioid quantity and dose limits: preferred agents, approved indications, and dose limits.

Length of Authorization:

Up to 6 months

Covered Alternatives:

A list of preferred long acting opioids is available at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Requires a PA:

- All non-preferred opioids and preferred opioids exceeding the dose threshold in the table below, not to exceed a Morphine Equivalent Dose (MED) of 120mg per day.
- Patient with terminal diagnosis, hospice, and metastatic neoplasm (ICD9 = 190xx – 199xx) are exempt from the PA requirements.

-Approved Prior Authorizations may be subject to quantity limits

Dosing Threshold adapted from Washington State Agency Medical Directors Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain 2010 (www.agencymeddirectors.wa.gov)

Opioid	Dose threshold	Recommended starting dose for opioid-naïve patients	Considerations
Buprenorphine Transdermal	20mcg/hour (q 7 days)	5mcg/hr patch q 7 days	May increase dose q72 hours patients up to a max of 20mcg/hr q 7 days. Doses >20mcg/hr q7days increase risk of QTc prolongation.
Fentanyl Transdermal	50mcg/hour (q 72 hr)	Use only in opioid-tolerant patients who have been taking ≥ 60mg MED daily for a week or longer	
Hydromorphone	30mg per 24 hours	2mg q 4–6 hours	
Methadone	80mg per 24 hours	2.5-5mg BID – TID	Methadone is difficult to titrate due to its half-life variability. It may take a long time to reach a stable level in the body. Methadone dose should not be increased more frequently than every 7 days. Do not use as PRN or combine with other long-acting (LA) opioids.
Morphine	120mg per 24 hours	Immediate-release: 10mg q 4 hours Sustained-release: 15mg q 12 hours	Adjust dose for renal impairment.
Oxycodone	80mg per 24 hours	Immediate-release: 5mg q 4–6 hours Sustained Release: 10mg q 12 hours	See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing acetaminophen (maximum dose = 4000mg/day x <10day or 2500mg/day for 10 days or more)
Oxymorphone	40mg per 24 hours	Immediate-release: 5–10mg q 4–6 hours Sustained Release: 10mg q 12 hours	**Use with extreme caution due to potential fatal interaction with alcohol or medications containing alcohol.**

Dosing Threshold for select short acting opioids

Opioid	Dose threshold	Considerations
Codeine	800mg/day	
Hydrocodone	120mg/day	Dosing limits based on combinations ingredients (e.g. acetaminophen, ibuprofen) may lower the maximum daily dose dictated by morphine equivalents

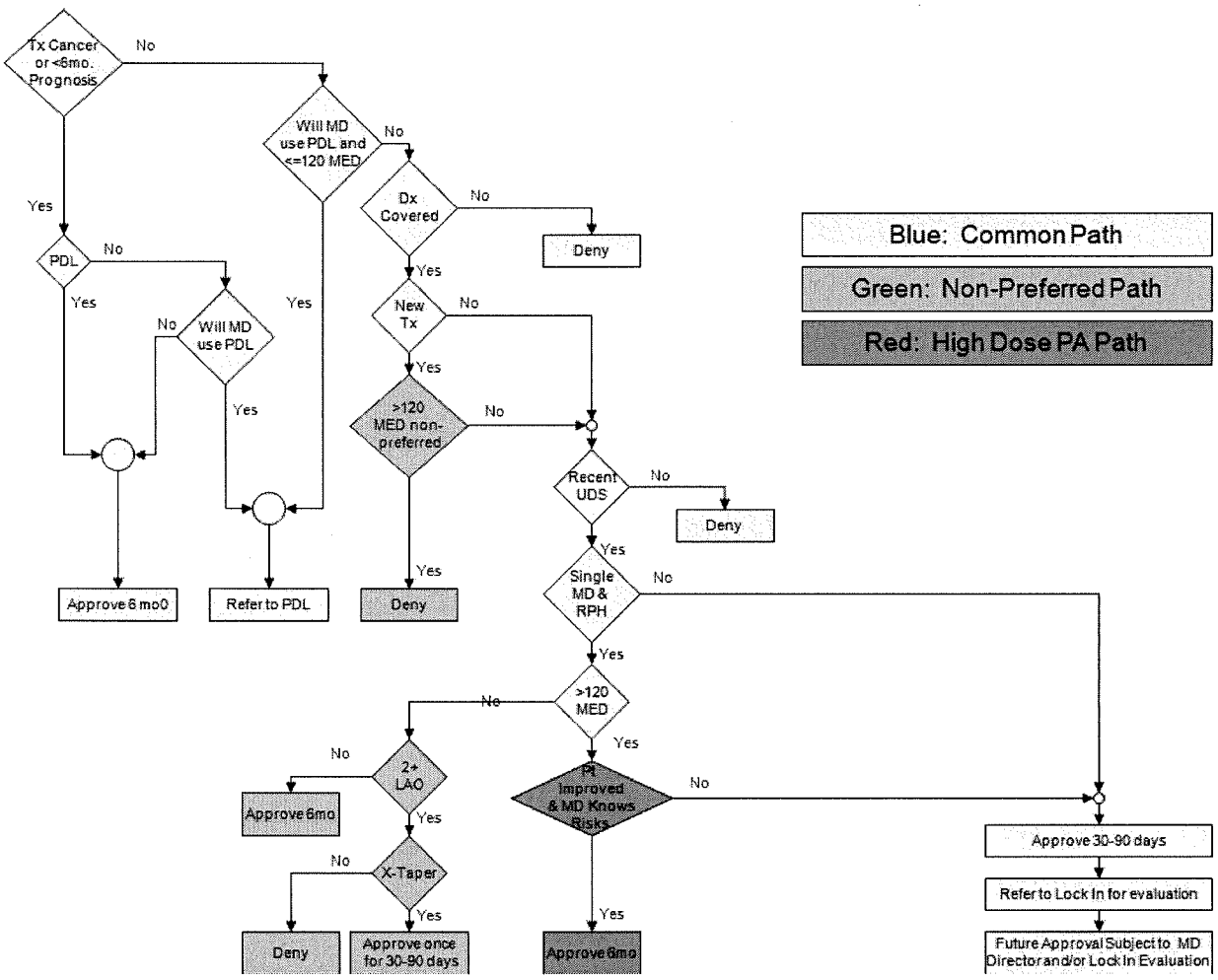
Common indications OHP does not cover:*	ICD9 Codes
Disorders of soft tissue (including Fibromyalgia)	*729.0-729.2,* *729.31-729.39,* *729.4-729.9,* *V53.02*
Acute and chronic disorders of spine without one of the following neurologic impairments: a. Reflex loss b. Dermatomal muscle weakness c. Dermatomal sensory loss d. EMG or NCV evidence of nerve root impingement e. Cauda equina syndrome f. Neurogenic bowel or bladder	*721.0* *721.2-721.3* *721.7-721.8* *721.90* *722.0-722.6* *722.8-722.9* *723.1* *723.5-723.9* *724.1-724.2* *724.5-724.9* *739* *839.2* *847*

*Covered diagnoses are dependent on funding levels. A list of currently funded diagnoses can be found at http://www.oregon.gov/OHA/OHPR/HSC/current_prior.shtml

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD9	
2. Is the patient being treated for any of the following: a. Oncology pain (ICD-9 338.3) b. Terminal diagnosis (<6 months) c. Hospice care	**Yes**: Go to #3	**No**: Go to #5
3. Is the requested medication a preferred agent?	**Yes:** Approve for up to 6 months	**No**: Go to #4
4. Will the prescriber consider a change to a preferred product?	**Yes**: Inform provider of covered alternatives in class.	**No**: Approve for up to 6 months
5. Will the prescriber consider a change to a preferred product not to exceed 120mg MED?	**Yes**: Inform provider of covered alternatives in class.	**No:** Go to #6
6. Is the diagnosis covered by the OHP?	**Yes**: Go to #7	**No:** Pass to RPh, Deny (Not Covered by the OHP)
7. Is this new therapy (i.e. no previous prescription for the same drug, same dose last month)?	**Yes**: Go to #8	**No**: Go To #10
8. Does the total daily opioid dose exceed 120mg MED?	**Yes: Pass to RPh, Deny** (Medical Appropriateness) In general, the total dose of opioid should not exceed 120mg MED Risks substantially increase at doses at or above 100mg MED. Alternatives: Preferred NSAIDs or LAOs @ doses less than 120mg MED.	**No**: Go to #9
9. Has the patient had a recent urinary drug screen (within the past 90 days)?	**Yes**: Go to #10	**No**: Pass to RPH: Deny (Medical Appropriateness) Recommend Urine Drug Screen
10. Is the patient seeing a single prescribing practice & pharmacy for pain treatment (short and long acting opioids)?	**Yes**: Go To #11	**No:** <u>Approve 30-90 days;</u> Refer to Rx Lock-In program for evaluation. Further approvals pending RetroDUR / Medical Director review of case.
11. Does the total daily opioid dose exceed 120mg MED?	**Yes**: Go to #12	**No:** Go to #13

12. Can the prescriber provide documentation of sustained improvement in both function and pain AND the patient is not on concurrent benzodiazepines or other LAO?	**Yes: Approve up to 6 months.** **Quantity Limits Apply, e.g.:** Avinza®: 1 dose / day Butrans®: 1 patch / week Embeda®: 2 doses / day Exalgo®: 1 dose / day Fentanyl: 1 patch / 72 hours Kadian®: 2 doses / day Opana XR®: 2 doses / day Oxycodone ER: 2 doses / day	**No:** Approve 30-90 days to allow for potential tapering of dose. Refer to Rx Lock-In program for evaluation. Further approvals pending RetroDUR / Medical Director review of case.
13. Is the patient concurrently on more than one long-acting opioid (e.g. fentanyl patches, methadone, or long-acting morphine, long-acting oxycodone, long-acting oxymorphone)?	**Yes**: Go to #14	**No**: Approve for up to 6 months
14. Is the duplication due to tapering or switching products? The concurrent use of multiple long-acting opioids is not recommended unless tapering and switching products. Consider a higher daily dose of a single long-acting opioid combined with an immediate release product for breakthrough pain.	**Yes**: Approve for 30-90 days at which time duplication LAO therapy will no longer be approved.	**No: Deny** (Medical Appropriateness) **May approve for taper only.** Refer to Rx Lock-In program for evaluation. If necessary, inform prescriber of provider reconsideration process.

Appendix C – Graphical representation of Opioid Prior Authorization Criteria



References

[1]Oregon State University College of Pharmacy Drug Utilization Research and Management Group. Drug Use Evaluation: Long Acting Opioids (LAO). 2010.

[2] The American Pain society/American Academy of Pain Medicine. Guidelines for the use of chronic opioid therapy in chronic non-cancer pain. http://www.ampainsoc.org/pub/pdf/LBPEvideREv.pdf

[3] Chou R, Fanciullo G, Fine P et al. Clinical Guidelines for the Use of chronic opioid therapy in chronic noncancer pain. The Journal of Pain 2009; 10:113-130.

[4] Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. Pain 2007;129:355-362.

[5] Sullivan MD; Edlund MJ, Zhang L, et al. Association Between Mental Health Disorders, Problem Drug Use, and Regular Prescription Opioid Use Arch Intern Med. 2006;166:2087-2093.

[6] Sullivan, MD, Edlund, MJ, Steffick, D, Unutzer, J. Regular use of prescribed opioids: association with common psychiatric disorders. Pain 2005;119:95-103.

[7] Executive Office of the President of the United States. Epidemic: Responding to America's Prescription Drug Abuse Crisis. Published 2011.

[8] Prescription Painkiller Overdoses in the US. CDC VitalSigns November 2011. Accessed 12/19/2011 at http://www.cdc.gov/vitalsigns/PainkillerOverdoses/index.html

[9] Drug Diversion in the Medicaid Program: State Strategies for Reducing Prescription Drug Diversion in Medicaid. August 2011.

[10] OHP FFS Average Cost PMPM Top 30 Drug Class – Third Quarter 2011. Accessed on 12/8/2011 at http://pharmacy.oregonstate.edu/drug_policy/index.php?nav=reports

[11] OHP FFS Average Cost PMPM Top 40 Drugs (brand name) - Third Quarter 2011. Accessed on 12/8/2011 at http://pharmacy.oregonstate.edu/drug_policy/index.php?nav=reports

[12] NUCYNTA® (tapentadol) immediate-release oral tablets. Package Insert. Janssen Pharmaceuticals, Inc. 2009. Downloaded 12/19/2011 from http://www.nucynta.com/sites/default/files/pdf/Nucynta-PI.pdf

[13] Webster LR, Webster RM. Predicting Aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. Pain Med. 2005;6:432-42.

Oregon State University
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

Multiple Sclerosis (MS) Class Update

Month/Year of Review: March 2012
PDL Class: Neurologic: MS Drugs
Current Status of PDL Class:

- Preferred Agents: Interferon beta-1a IM (Avonex®), Glatiramer Acetate SC (Copaxone®)
- Non Preferred: Interferon Beta-1b SC (Betaseron® and Extavia®), Interferon beta-1a SC (Rebif®), Natalixumab IV (Tysabri®), Mitoxantrone IV

Previous HRC Conclusions (May 2008):

1. All included drugs are modestly effective compared to placebo in relapse prevention and disease progression.
2. There is no evidence of clinical superiority of any of the studied drugs.
3. Limited data suggests that neutralizing antibodies (in β-interferon therapy) may negatively affect relapse rate 3-4 years after treatment.
4. There was no difference in withdrawal rates among studied drugs noted; however, in general adverse event reporting was poor.
5. For β-interferons:
    a) There is insufficient evidence to determine a comparative difference between the β-interferons for flu-like symptoms.
    b) There is insufficient evidence to determine a relative difference in ALT elevations for the β-interferons.
6. Interferon β1a IM (Avonex®) appears to have a lower injection site reaction compared to the other β-interferons and glatiramer acetate.
7. Therapy related acute leukemia was reported in 2/1620 patients (both were women) taking mitoxantrone.
8. Estimates of progressive multifocal leukoencephalopathy (PML) incidence with natalizumab (Tysabri®) use is 1.0/1000 patients based on three known cases. Because of concerns regarding this, the company instituted a risk management plan in cooperation with the FDA known as the TOUCH prescribing program. Patients may only get this medication through this program.
9. There is insufficient evidence to determine a comparative difference between the β-interferons in reducing the probability of converting from clinically isolated syndrome (CIS) to clinically definite MS. There is no data on prevention of conversion for any of the other included drugs.

Reason for Review:

In 2008, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness evidence of the disease-modifying drugs (DMDs) for MS. Since this review, in 2010 the Oregon Evidence-based Practice Center (EPC) Drug Effectiveness Review Project (DERP) completed an updated report for the drug class review.[1] This full report can be found on the Oregon EPC website at http://derp.ohsu.edu/about/final-document-

display.cfm. There were also two new medications FDA approved indicated in the treatment of MS. Fingolimod (Gilenya®) is the first oral DMD indicated for patients with MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.[2] Dalfampridine (Ampyra®) was approved to improve walking in patients with MS.[3] Dalfampridine is not indicated to decrease relapse rate or prevent the accumulation of disability. These individual drug monographs can be found on the Oregon Pharmacy and Therapeutics website: http://pharmacy.oregonstate.edu/drug_policy/meetings. In 2009, the FDA also approved Extavia, a new branded version of interferon beta-1b, which is the same product as Betaseron and contains the same active ingredient.[4]

Conclusions:

The DERP MS class update concluded that there was fair evidence that interferon beta-1a IM (Avonex®) is less effective than interferon beta-1a SC (Rebif®) and interferon beta-1b (Betaseron®) for preventing relapse in patients with relapsing remitting multiple sclerosis (RRMS) based on four fair-quality head-to-head trials. Interferon beta-1a SC (Rebif®) and interferon beta-1b (Betaseron®) were similarly efficacious for preventing relapse.[1] There was conflicting evidence in disease progression outcomes between the interferons, and it is likely that any differences are small and clinically insignificant. Overall evidence was moderate for patients with relapsing remitting MS while the strength of the evidence in other populations was low. On other outcomes and in other populations, direct evidence is either lacking or shows few differences in effectiveness or safety among the DMDs used to treat MS, including in progressive forms of MS and in patients with clinically isolated syndrome.

There was also fair quality evidence that interferon beta-1a IM (Avonex®) appears to have the lowest immunogenicity compared to the other beta-interferons. While there is insufficient evidence to conclude there is an impact on disease progression, there was fair quality evidence that consistent positive neutralizing antibody status with high titer adversely affects the impact of these drugs on relapse rates during long periods of follow-up. No studies met criteria to be a true effectiveness study and applicability of the results remains limited. There was insufficient evidence to determine a comparative difference in subpopulations. There was also moderate evidence that the beta interferons are similar in harms and discontinuations due to adverse events, while adverse event reporting remained poor.[1]

The American Academy of Neurology, the National MS Society, and the National Institute for Clinical Excellence recommend first line treatment with glatiramer acetate or an interferon beta in MS patients.[5–7] The clinical guidelines have not been updated to reflect the place for oral fingolimod. The best evidence for effectiveness is in patients with RRMS, but therapy may also be considered in certain patients with clinically isolated syndrome and progressive disease.

Recommendations:

- Due to similar efficacy and potential difference in relapse outcomes between the interferon products, evaluate costs of interferon beta-1a SC (Rebif®), interferon beta-1b SC (Betaseron® and Extavia®), and interferon beta-1a IM (Avonex®) for further decision making.
- Include dalfampridine (Ampyra®) as a non-preferred agent on the PDL and include clinical criteria for use including:
    - Has a walking disability that requires the use of a walking aid.
    - Be able to complete the T25FW in 8-45 seconds.
    - Does not have renal impairment or a history of seizure disorder or epileptiform activity on an EEG.

- Include fingolimod (Gilenya®) as a non-preferred disease modifying medication for MS and develop clinical criteria to restrict based on the following:
    - Prescribed by or in consultation with a neurologist
    - Patient has relapsing remitting MS
    - Is not currently on therapy with an injectable DMT
    - Has failed or cannot tolerate a full course of a first line interferon or glatiramer

Background:

MS is an inflammatory disease of the central nervous system and the vast majority of patients with MS have relapsing-remitting MS. The majority of available direct evidence continues to reside in patients with relapsing-remitting MS rather than progressing forms MS. Progression of MS is measured by the disability caused by the disease. The Expanded Disability Status Scale (EDSS) the most widely used validated measure of disability and is often a primary clinical outcome in MS clinical studies. The scale ranges from 0 to 10, with <6 indicating the patient can walk without aid for limited distance, 6-8 indicating patient is severely restricted in movement with aids or assistance, and > 8 indicating a person is restricted to a bed. Treatment of MS falls into three main categories: symptomatic therapy to improve the patient's quality of life, treatment of acute attacks, and DMDs to alter the natural course of the disease and reduce progressive disability over time. Acute relapses are treated with corticosteroids and symptoms are treated accordantly with appropriate agents. The development of neutralizing antibodies to interferon beta medications may lead to a decreased efficacy of these agents. However, the long term impact of neutralizing antibodies on clinical outcomes has not been fully determined.

DMDs are indicated to prevent relapses and progression of disability and modify the immune response through immunomodulatory or immunosuppressive effects. There are currently 5 injectable DMDs available and one oral. Four of the disease modifying medications are type 1 beta interferons and include interferon beta-1b SC (Betaseron® and Extavia®) and interferon beta-1a IM and SC (Avonex® and Rebif®). In 2009, the FDA approved Extavia® with the same active ingredient and registration trials as Betaseron 250 mcg. The 5th agent is glatiramer SC and fingolimod is the first oral DMD. Natalizumab IV and mitoxantrone IV are also FDA-approved for the treatment of RRMS. Natalizumab and mitoxantrone are

not recommended for first-line use due to safety concerns with progressive multifocal leukoencephalopathy and cardiotoxicity, respectively. Natalizumab is reserved for patients with rapidly advancing disease who have failed other therapies.

Currently there are four other oral therapies in addition to fingolimod in development for the treatment of relapsing-remitting MS and while better patient compliance is expected with the oral agents compared with the injectables, the safety profiles of these new oral drugs will have to be monitored carefully.[8] In December of 2011, the FDA released a drug safety review of a reported death within 24 hours of taking the first dose of fingolimod.[9] Reports of eleven deaths through November 2011 in patients taking fingolimod have prompted a safety investigation.[10] There is no evidence yet that the drug was responsible for the deaths. Heart rhythm and electrical conductivity abnormalities are both recognized risks after initial dosing.[10]

Methods:

A literature search was conducted since the end of the literature included in the DERP report for new randomized controlled trials (RCT's) comparing medications head-to-head in the treatment of MS. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were 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. After review of the 99 total citations resulted from Medline OVID search, 2 new relevant head-to-head trials, 2 new systematic reviews from the Cochrane Library, 1 systematic review from the Oregon Evidence based Practice Center, and three new FDA safety alerts were identified and evaluated.

Systematic Reviews:

DERP:

In patients with RRMS, there were five fair quality head-to-head trials providing direct evidence for the comparative efficacy of the beta interferons. This included the addition of one since the 2008 MS class review.[1] Overall, these studies supported the use of the beta interferons for improving relapse-related outcomes, with less effect on the disability-related outcomes. These trials found higher rates of patients who were relapse free in the interferon beta-1a SC (Rebif®) and interferon beta-1b SC (Betaseron®) groups compared with interferon beta-1a IM (Avonex®) and disability-related outcomes were not found to be statistically significant (Betaseron vs. Avonex; % relapse-free RR 1.51, 95% CI 1.11 to 2.07; NNT 6).[1]

There were two fair quality and one good quality trial comparing glatiramer to another DMD (no direct evidence in previous report), 2 comparing to interferon beta-1b (Betaseron®) and 1 comparing to interferon beta-1a (Rebif®). In the direct comparison studies, no significant differences were found in relapse-related or disease progression outcomes, while previous observational studies that compared glatiramer to the interferons

found a significantly greater reduction in relapse rate at 2 years with glatiramer.[1] Further good-quality direct comparison studies are needed to further confirm the direct findings.

There were no studies comparing natalizumab or mitoxantrone to another DMD for relapsing-remitting MS, and both were more effective than placebo for both disease progression and relapse rate based on a small number of trials. On other outcomes and in other populations with progressive forms of MS, direct evidence is either lacking or shows few differences in effectiveness among the DMDs. Only indirect evidence is available in patients with secondary progressive MS and primary progressive MS.[1]

Two new key questions were identified for the update evaluating the importance and effects of interferons on neutralizing antibodies.[1] Neutralizing antibodies are known to develop in some patients taking beta interferons, potentially interfering with effectiveness. There was fair quality evidence that interferon beta-1a IM appears to have the lowest immunogenicity, with rates of development of neutralizing antibodies of 2-8.5% reported, starting around 9 months of treatment, while evidence displayed that interferon beta-1a SC antibodies occur at rates from 12% to 46% of patients. With interferon beta-1b SC (Betaseron®), neutralizing antibodies appeared as early as 3 months in 30% to 40% of patients. There is fair quality evidence that consistent positive neutralizing antibody status with high titer adversely affects the impact of these drugs on relapse rates during long periods of follow-up (> 2 years) and there is insufficient evidence to conclude there is an impact on disease progression.[1]

There is fair quality evidence that there is no difference in withdrawal rates among beta interferons in head-to-head trials, although adverse events were generally poorly reported. Withdrawal rates ranged from 3% (glatiramer) to 9% (Betaseron®) in placebo controlled trials.[1] Although generally well tolerated, adverse events were reported frequently with all three beta interferon products and differences between the products were evident. Interferon beta-1b IM (Avonex®) had higher rates of flu-like syndrome (62.2% vs. 41.7% Betaseron vs. 28.7% Rebif), fatigue, and depression while interferon beta-1a SC (Rebif®) had much higher rates of injection site reactions compared to the other interferons (60.6% vs. 58.9% Betaseron vs. 8.5% Avonex).[1]

Compared to beta interferon, glatiramer showed similar tolerability with higher rates of injection site reactions and post-injection systemic response. Long term safety data demonstrate that lipoatrophy is associated with prolonged use of glatiramer.[1] In placebo controlled trials, mitoxantrone use was associated with amenorrhea, nausea and vomiting, and urinary tract infections, and a non-significant decrease in left ventricular ejection fraction below 50% which associated with higher cumulative doses in a subgroup analysis, although this did not reach statistical significance (P=0.06). Risk of permanent amenorrhea may be associated with older age (odds ratio 1.18 95% CI 1.10 to 1.27; p=0.01) and higher cumulative dose (odds ratio 1.02, 95% CI 1.01 to 1.04; p=0.01) based on 1 observational study (N=189).[1]

Natalizumab has been linked to progressive multifocal leukoencephalopahy (PML) and now contains a black box warning with risk directly proportional to cumulative dose. In March 2011, a FDA safety alert revised the drug label to warn of the risk of PML in patients taking natalizumab for treatment of MS and Crohn's Disease. This alert also included information on a newly identified risk factor for the development of PML. Patient's who took an immune system suppressing medication prior to natalizumab have been shown to be at an increased risk for developing

PML.[11] The label previously included that there was an increased risk for using an immune suppression medication at the same time as natalizumab. In January of this year an additional FDA safety communication was released informing the public that testing positive for anti-JC virus antibodies is an additional risk factor for PML.[12] Patients with all three risk factors (presence of anti-JC virus antibodies, longer duration of treatment (beyond 2 years), and prior or current treatment with an immunosuppressant medication have an estimated risk of PML of 11/1,000 users.[12]

There is some evidence that response to beta interferons and glatiramer differs in men and women, but there was no evidence that this difference favors one product over another. There is insufficient data to make conclusions about the use of these drugs in other subpopulations based on demographics, socioeconomic status, other medications, severity of disease, or co-morbidities.

Cochrane Library:

La Mantia, et al. aimed toward determining clinical efficacy and safety of glatiramer in patients with MS by evaluating all RCTs comparing glatiramer and placebo in patients with both relapsing remitting and progressive MS.[13] Based on 6 efficacy trials, in patients with relapsing remitting MS a decrease in the mean EDSS score was found without any significant effect on sustained disease progression. Three trials were given a full score on the Jadad quality rating scale and two were given a score of three due to unclear allocation concealment and insufficient details on blinding. In patients with RRMS, a slight decrease in the EDSS score favored glatiramer at two years (mean difference -0.33 95% CI -0.58 to -0.08, p=0.009) and at 25 months (-0.45, 95% CI -0.77 to -0.13, p=0.006). The reduction of mean number of relapse was also evident. Relative risks of experiencing no exacerbation were 1.28 at 1 year, 1.39 at 2 years, and 1.33 at 35 months (p=0.03, p=0.06, p=NS, respectively).[13] No benefit was seen in patients with progressive MS on relapse outcomes or disease progression, based on five hundred and forty patients in the analysis.

A second Cochrane review evaluated interferon beta in patients with secondary progressive multiple sclerosis (SPMS) compared to placebo in disease progression and concluded that there is high quality evidence that interferon does not prevent the development of permanent physical disability in SPMS and its anti-inflammatory effect is unable to hinder progression.[14] Based on five RCT's and 3122 treated patients, interferon therapy did not decrease the risk of progression at sustained 6 months (RR 0.98, 95% CI 0.82 to 1.16) after three years of treatment. A significant decrease in the risk of progression sustained at 3 months (RR 0.88, 95% CI 0.9 to 0.97) and in the risk of developing new relapses at three years (RR 0.91, 95% CI 0.84 to 0.97) were found.[14]

Randomized Controlled Trials:

One new open-label, fair quality, randomized controlled trial compared the efficacy of interferon beta-1a (Avonex, REbif) and interferon beta 1-b (Betaseron) in 90 individuals with MS on the expanded disability status scale (EDSS) and relapse rate.[15] There was no statistical difference in reducing EDSS shown by the average EDSS change from baseline (Avonex 1.28, Betaseron 1.30, Rebif 1.28, p=0.998). There was no significant difference in the decrease in relapse rate between the three treatment groups (Avonex 0.40, Betaseron 0.60, Rebif 1.2, p-0.447). This study included a higher proportion of females compared to previous studies and included patients with an average lower age of onset (31.11 years).

Another RCT compared the efficacy of mitoxantrone induction therapy prior to interferon beta-1b SC with interferon beta-1b SC alone in patients with aggressive relapsing-remitting MS on the time to worsen by at least one EDSS point confirmed at 3 months.[16] Due to the associated adverse effects, it was not possible to double blind the intervention, and results should be interpreted with caution. Only the clinical outcomes were evaluated in a blinded fashion. In the group receiving mitoxantrone induction therapy, the time to a >1 EDSS point was delayed ($p<0.012$) and the proportion of patients who remained relapse-free was increased compared to the interferon group (52.7%, 27.8%, $p<0.008$, NNT 4).[16] Overall, patients receiving mitoxantrone had a higher incidence of adverse events, including upper respiratory tract infections, leukcopenia, nausea, and reduced ventricular ejection fraction. The overall dropout rate was quite high at 44%.

References:

1. Smith B, Carson S, Fu R, et al. Drug Class Review: Disease-modifying Drugs for Multiple Sclerosis. Update 1. Available at: http://derp.ohsu.edu/about/final-products.cfm. Accessed February 10, 2012.

2. Gilenya. Prescribing Information. Novartis Pharmaceuticals Corp; Available at: http://www.pharma.us.novartis.com/product/pi/pdf/gilenya.pdf.

3. Ampyra. prescribing information. Acorda Therapeutics. Available at: http://ampyra.com/local/files/PI.pdf.

4. Extavia Prescribing Information. Novartis Pharmaceuticals Corporation. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/extavia.pdf.

5. Goodin DS, Frohman EM, Garmany GP Jr. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002;58(2):2161–2169.

6. NICE. Beta interferon and glatiramer acetate for the treatment of multiple sclerosis: guideline. 2002. Available at: http://www.nice.org.uk.

7. National Clinical Advisory Board of the National Multiple Sclerosis Society. MS Disease Management Consensus Statement. 2008. Available at: www.nationalmssociety.org.

8. Gold R. Oral therapies for multiple sclerosis: a review of agents in phase III development or recently approved. *CNS Drugs*. 2011;25(1):37–52.

9. FDA Drug Safety Communication. Safety Review of a Reported Death after the first dose. 2011. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm284355.htm.

10. Samson, Kurt. Health Officials Launch Investigation in Deaths of Patients Taking Fingolimod. *Neurology Today*. 2012;12(4):1,27–28.

11. FDA Drug Safety Communication. Safety update on Progressive Multifocal Leukoencephalopathy associated with Tysabri (natalizumab). 2011. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm199965.htm. Accessed February 10, 2012.

12. FDA Drug Safety Communication. New risk factor for Progressive Multifocal Leukoencephalopathy associated with Tysabri (natalizumab). 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm288186.htm. Accessed February 10, 2012.

13. La Mantia L, Munari LM, Lovati R. Glatiramer acetate for multiple sclerosis. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004678.pub2/abstract. Accessed February 10, 2012.

14. La Mantia L, Vacchi L, Di Pietrantonj C, et al. Interferon beta for secondary progressive multiple sclerosis. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005181.pub3/abstract. Accessed February 10, 2012.

15. Mazdeh M, Afzali S, Jaafari MR. The therapeutic effect of Avonex, Rebif and Betaferon on EDSS and relapse in multiple sclerosis: a comparative study. *Acta Med Iran*. 2010;48(2):83–88.

16. Edan G, Comi G, Le Page E, et al. Mitoxantrone prior to interferon beta-1b in aggressive relapsing multiple sclerosis: a 3-year randomised trial. *J. Neurol. Neurosurg. Psychiatr.* 2011;82(12):1344–1350.

Oregon State University
College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | Fax 503-947-1119

(50)

Generic Name: Fingolimod
PDL Class: Multiple Sclerosis Drugs
Preferred: Glatiramer (Copaxone), Interferon Beta-1a (Avonex), Interferon Beta-1a/Albumin (Avonex Administration Pack)
Non-Preferred: Mitoxantrone, Interferon Beta-1b (Betaseron), Natalizumab (Tysabri)

Brand Name (Manufacturer): Gilenya® (Novartis)
Comparator Therapies: Disease modifying treatments (Injectable)
Dossier received: Yes
Month/Year of Review: March 2012

EXECUTIVE SUMMARY:

FDA Approved Indications:[1] Fingolimod is a sphingosine 1- phosphate receptor modulator indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

Background/Reason for Review: Fingolimod is the first oral agent approved by the FDA as a disease modifying treatment (DMT) for MS. Previously available DMT agents are only available as injections or infusions. These five injectable medications were reviewed in comparison with each other by the Oregon Health Resources Commission in May 2008. This monograph will evaluate the available evidence of safety, tolerability, efficacy, and other considerations to help determine fingolimod's role in therapy.

Issues/Key questions:

1) What is the comparative effectiveness of fingolimod and other disease-modifying treatments for MS?
2) Do fingolimod and other disease-modifying treatments for MS differ in harms?
3) Are there subgroups of patients based on demographics, socioeconomic status, other medications, severity of disease, or co-morbidities for which fingolimod is more effective or associated with fewer adverse events than other disease-modifying treatments?

Efficacy: Results of two phase 3 studies in patients with relapsing-remitting MS (RRMS) evaluated the efficacy and safety of fingolimod including one placebo-controlled 24-month trial (FREEDOMS) and a 12-month head-to-head trial with comparator interferon (IFN) beta-1a (TRANSFORMS).[2, 3] These trials included doses (1.25 mg daily) that are higher than the FDA approved dose of 0.5 mg once daily for treating RRMS. The FREEDOMS trial was a

randomized placebo-control trial comparing two doses of fingolimod (0.5 mg daily and 1.25 mg daily) with placebo. Both fingolimod doses showed a statistically significant difference compared to placebo in all measured outcomes in this study, including annualized relapse rate (0.18 vs. 0.4; RR 0.55, fingolimod 0.5 mg and IFN beta-1a, respectively) and disability progression (17.7% vs. 24.2%; RR 0.73).[2] There were no significant differences between the two fingolimod doses. In TRANSFORMS, fingolimod 0.5 mg and 1.25 mg were compared to treatment with intramuscular IFN beta 1-a 30 μg given weekly over 12 months. Fingolimod 0.5mg once daily and 1.25mg once daily resulted in lower annualized relapse rates compared to interferon beta-1a (0.16, 0.20, and 0.33 respectively; P<0.001) and resulted in more patients having no confirmed relapse at 1 year compared with interferon beta-1a (82.5%, 80.5%, and 70.1%; p<0.001; NNT 8.3 for fingolimod 0.5mg and NNT 10 for fingolimod 1.25mg). This study failed to show a significant difference in disability progression.[3] In a 12-month extension of this trial, patients who switched from interferon to fingolimod demonstrated a lower ARR after switching (fingolimod 0.5mg: 0.31 at year 1 vs. 0.22 at year 2; fingolimod 1.25mg 0.29 at year 1 vs. 0.18 at year 2).[4]

Safety: It was clear through the trials that higher doses lead to more frequent and more severe adverse events. The FDA has suggested that studies of lower doses, including 0.25 mg daily, be further evaluated. The most common adverse effects include influenza virus infections, headaches, diarrhea, and elevated liver enzymes. Macular edema occurred in 4 patients in the 1.25 fingolimod group (1%), 2 in the 0.5 mg group (0.5%), and none in the interferon group.[3] The risk of discontinuing drug due to an adverse event increased with fingolimod 1.25 mg once daily compared with fingolimod 0.5mg and with interferon beta-1a. After the first dose of fingolimod, 1.2% of patients taking 1.25mg, 0.6% taking 0.5mg experienced bradycardia, compared to 0.2% taking placebo and 0% taking interferon.[5] Due to the concern of bradycardia and atrioventricular block, patients must be observed for 6 hours after the initial dose.[1] The FDA released a safety announcement in December 2011 regarding a patient with MS who died within 24 hours of taking the first dose of fingolimod. At this time, the FDA cannot conclude whether the drug resulted in the patient's death and is continuing to evaluate the case.[6]

Conclusions:

- Based on only one head to head trial, there is low strength evidence that fingolimod results in lower annualized relapse rates than interferon beta-1a in patients with RMMS and that there is no difference in efficacy between the high or low dose of fingolimod (1.25mg vs. 0.5mg). There was no difference in disease progression.
- There is insufficient evidence to evaluate comparative effectiveness of fingolimod with any of the other disease modifying treatments approved for treatment of MS.
- The higher dose of fingolimod (1.25 mg) resulted in higher numbers and more severe adverse effects, as well as more patients discontinuing treatment.
- Further unanswered issues exist including:
    - Comparative effectiveness of fingolimod with different disease modifying treatments and of longer durations.
    - Further evaluation of safety concerns including the risk of macular edema, the effect of lung function, cancers, and serious viral infections. Fingolimod has a unique set of safety issues and a relatively small body of evidence to support long term safety
    - Applicability of these results to general MS population due to the narrow patient population included in study

Author

Recommendations:

- Develop PA criteria to manage utilization of fingolimod and restrict use to neurologists, patients with RMMS, and ensure patients are not currently on therapy with an injectable DMT due to lack of safety and efficacy data.
- Consider requiring a failure to respond to a full and adequate course of interferon treatment.

BACKGROUND/CURRENT LANDSCAPE

MS is a chronic, autoimmune disease of the central nervous system affecting 2.1 million people worldwide and approximately 250,000 to 400,000 people in the United States.[8] The highest prevalence of MS occurs in Caucasian women who live in northern latitudes. In 2004, MS costs were estimated at $47,215 per patient per year, including 34% of these costs towards disease modifying drugs for treatment.[8] Four different clinical courses of MS have been defined and include relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive –relapsing MS (PRMS).[9] About 85% of patients have RRMS and most cases eventually develop into a SPMS.[5,8] The efficacy of fingolimod has been demonstrated in patients with RRMS. RRMS is the most common type of MS and rarely progresses between relapses, although the patient may never fully recover after a relapse.

The treatment of multiple sclerosis involves acute relapse treatment with corticosteroids, symptom management, and disease modification with disease-modifying drugs. The goal of disease-modifying drugs is to prevent relapses and progression of disability rather than treat individual symptoms or disease exacerbations.[8] Progression of disease is measured by the disability caused by MS and is commonly measured by the Expanded Disability Status Scale (EDSS) which is a scale from 0 (normal neurological examination) to 10 (death due to MS).

First-line drugs for the treatment of MS include interferon beta-1a (Avonex®), interferon beta-1b (Betaseron®), and glatiramer acetate (Copaxone®). These DMT's have shown positive safety profiles but have lower efficacy (approximately 30% reduction in annual relapse rate), compared to second-line treatments which have greater efficacy but many safety concerns. Second-line treatments include natalizumab (Tysabri®) and mitoxantrone (Novantrone®) and are generally used for patients who either did not respond or did not tolerate first-line injections. There are several clinical treatment guidelines for MS there is variability among the treatment guidelines and the principle and most comprehensive of them including from the American Academy of Neurology and the National Institute of Clinical Excellence are quite outdated (2002 and 2003).[10]

Subpopulations:[1,7]

Geriatrics: Clinical MS studies of GILENYA did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients. GILENYA should be used with caution in patients aged 65 years and over, reflecting the greater frequency of decreased hepatic, or renal, function and of concomitant disease or other drug therapy.

Pediatrics: The safety and effectiveness of GILENYA in pediatric patients with MS below the age of 18 have not been established.

Gender, race, ethnicity: Potential differences not evaluated due to differences in gender, race, or ethnicity.

CLINICAL PHARMACOLOGY[1,11]

Fingolimod is a structural analogue of endogenous sphingosine and undergoes phophyorlyation to produce finoglimod phosphate, the active moiety. Fingolimod targets MS through its effects on the immune system and involves reduction of lymphocyte migration into the central nervous system.

PHARMACOKINETICS[1,11]

Parameter	Result
Oral Bioavailability	93%
Cmax	12-16 hours
Protein Binding	99.7% protein bound (fingolimod and fingolimod-phosphate)
Elimination	After oral administration, about 81% of the dose is slowly excreted in the urine as inactive metabolites. Fingolimod and fingolimod-phosphate are not excreted intact in urine but are the major components in the feces with amounts of each representing less than 2.5% of the dose.
Half-Life	6-9 days
Metabolism	Fingolimod is primarily metabolized via human CYP4F2 with a minor contribution of CYP2D6, 2E1, 3A4, and 4F12.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

- Disability
- Clinical exacerbation/Relapse
- Withdrawals due to adverse effects
- Serious adverse events

Study Primary Endpoints:

- Annualized relapse rate (ARR)

Evidence Table

Ref./Study Design	Drug Regimens	Patient Population	N	Duration	Efficacy Results	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR / NNH[3]	Quality Rating; Comments
FREEDOMS [1]									
Kappos L, Radue EW, O'Connor P, et al RCT,DB, PC, Phase III	F1: Fingolimod 0.5mg QD F2: Fingolimod 1.25mg QD P: Placebo	Median age: 37.1 yrs Female: 69.9% With relapsing-remitting MS Median disease duration: 6.7 yrs Mean EDSS score: 2.4 #of relapses in previou year: 1.5; #of relapses in previous two yrs: 2.1; Approx. 59% of patients had no history of disease-modifying treatment Exclusion criteria: active infection, macular edema, diabetes, immune suppression, or clinically significant systemic disease	N= 1272 F1: 429 F2: 425 P:418	24 months	Annualized relapse rate over 24 months: F1: 0.18 (0.15 – 0.22) F2: 0.16 (0.13 – 0.19) P: 0.4 (0.34 – 0.47) P value: < 0.001 for both groups Progression of Disability (%): F1: 17.7% P: 24.2% RR 0.73 (0.56 to 0.95) P=0.02 F2: 16.6% P: 24.2% RR 0.68 (0.50-0.93) P=0.02 Relapse free at 24 months : F1: 70.4% (66.0 – 74.8) F2: 74.7% (70.4 – 78.9) P: 45.6% (40.7 – 50.6) HR vs. placebo: F1: 0.48 95% CI (0.39-0.61) p < 0.001 F2: 0.38 95% CI (0.3-0.48) p < 0.001	N/A ARR/NNT 6.6%/15 ARR/NNT 7.6%/13 ARR/NNT 24.8%/4 ARR/NNT 29.1%/3	Withdrawals due to AE: F1: 15 (3.5%) F2: 31 (7.2%) P: 24 (5.7%) Total Withdrawals: F1: 80 (18.8%) F2: 131 (30.5%) P: 115 (27.5%) RR 0.7 95% CI 0.5-0.9 (F1 vs P) P=0.002 RR 1.2 95% CI 0.9-1.4 (F2 vs P) P=0.3 Any serious AE: F1: 43 (10.1%) F2: 51 (11.9%) P: 56(13.4%)	NS N/A NS	Fair • More than 10% lost from time of randomization to study completion between groups • Although baseline characteristics of groups are similar, the adequacy of allocation and randomization is unclear • Safety analyses showed dose related toxicity, including bradycardia and AV block on the first dose, macular edema, LFTs increases and pulmonary toxicity Due to its MOA, there is potentia for increased risk of serious infections and neoplasms. The trial excluded pts with pre-existing DM, heart conduction disorders or pulmonary disease. To address the known ADES and to further evaluate serious ADEs, REMS is in place for post-market monitoring. • >10% overall attrition between groups

Author

TRANSFORMS [2]									
Cohen JA, Barkhof F, Comi G, et al. RCT,DB, PC, PG Phase III	F1: Fingolimod 0.5mg QD F2: Fingolimod 1.25mg QD A: interferon beta-1a 30 µg weekly	Median age: 36.2 yrs Female: 67.3% Median disease duration: 5.9 yrs Mean EDSS score: 2.2 Approx. 49% had received prior interferon beta therapy; 14% received glatiramer acetate previously. Exclusions: Patients with a documented relapse or corticosteroid treatment within 30 days before randomization, active infection, macular edema, immunosuppression (either drug- or disease-induced), clinically significant coexisting systemic disease	N= 1292 F1: 431 F2: 426 A: 435	12 months	Annualized relapse rate (n/95% CI) : F1: 0.16 (0.12-0.21) F2: 0.20 (0.16- 0.26) A: 0.33 (0.26-0.42) P<0.001 (F1 vs. A and F2 vs. A) *Pts who had no previous disease-modify therapy:* F1: 0.15 (0.10-0.23) F2: 0.17 (0.11-0.25) A: 0.31 (0.22-0.41) *Pts who had previous disease-modify therapy:* F1: 0.26 (0.19– 0.34) F2: 0.33 (0.26 -0.42) A: 0.53 (0.43 – 0.65) Patients with no disability progression(%) : F1: 94.1 (91.8 – 96.3) F2: 93.3 (90.9 – 95.8) A: 92.1 (89.4 – 94.7) P=0.25 (F1 vs. INF) P=0.5 (F2 vs. INF) Relapse free /95% CI: F1: 354 (82.5%) (79.0 – 86.3) F2: 338 (80.5%) (75.9 – 83.7) A: 302 (70.1%) (64.8 – 73.8) RR 1.2 95% CI 1.1-1.3 (F1 vs. IFN) RR 1.1 95% CI 1.0-1.2 (F2 vs. IFN) P<0.001 (both groups vs. IFN)	N/A NS NS NS ARR: F1: 12.4% F2: 10.4% NNT: F1: 8.3 F2:10	Withdrawals due to adverse events: F1: 16 (3.7%) F2: 32 (7.6%) A: 12 (2.8%) RR 2.7 95% CI (1.3-5.5): F2 vs A P=0.002 Total Withdrawals: F1: 62 (14.8%) F2: 44(10.3%) A: 51 (11.8%) Any serious event: F1: 30 (7.0%) F2: 45(10.7%) A: 25 (5.8%)	ARI/NNT: 4.8%/21 (NS for F1) NS	Fair. • Around 50% of patients in trial had used interferon prior to enrollment. Despite the double dummy design, patients with prior experience with interferon may have more likely to have guessed which treatment they were on, due to previous experience with ADEs. • The success of blinding patients or neurologist was not evaluated • The rates of progression reported in this trial were much lower those found previous disease modifying drugs trials where beta interferon groups at years ranged from 11.4% to 26.6% and in placebo groups from 20.3% to 36.4%[3]. • Unclear if randomization metho adequate • >10% overall attrition

Author

TRANSFORMS Extension Study [4]									
Khatri B, Barkhof F, Comi G, et al. RCT,DB, PC, PG	F1: Fingolimod 0.5mg QD F2: Fingolimod 1.25mg QD F1N: Fingolimod 0.5mg QD F2N: Fingolimod 1.25mg QD *F1N and F2N are patients who recv'd interferon beta-1a in TRANSFORMS study.	1027 patients in TRANSFORMS study entered additional 12 months extension study. All patients who completed the core TRANSFORMS study were eligible for extension	N= 1027 F1: 356 F2: 330 F1N: 167 F2N: 174	12 months	Annualized relapse rate 95% CI(1 end point) : 0-12 months: F1: 0.12 (0.08-0.17) F2: 0.15 (0.1-0.21) F1N: 0.31 (0.22-0.43) F2N: 0.29 (0.20– 0.40) 13-24 months: F1: 0.11 (0.08-0.16); p* = 0.8 F2: 0.11 (0.08– 0.16); p=0.12 F1N: 0.22 (0.15-0.31); p=0.049 F2N: 0.18 (0.12-0.27); p=0.024 *p-value months 13-24 versus months 0-12	ARR: F1N: 0.01 F2N: 0.04 NNT: F1N:100 F2N:25	Discontinuations Due to adverse effects: F1: 9 (2.5%) F2: 11 (3.3%) F1N: 6(3.6%) F2N: 11 (6.3%) Infectious events: F1N (0-12mo): 97 (58%) F1N (13-24): 91 (54%) F2N (0-12): 88 (51%) F2N (13-24): 91 (52%) Any serious AE: F1N (0-12mo): 10 (6%) F1N (13-24): 8 (5%) F2N (0-12): 8 (5%) F2N (13-24): 21 (12%)	NA	Poor • Patient and investigators blindin was lost due to study design. • Norvatis collected and analyzed the data. • The study authors acknowledge the extension study has no placebo or active comparator group. The benefits after the switching cannot conclusively shown to be solely due to fingolimod. This also applies to risks associated with fingolimod. • Authors also noted the conclusions of study are based o a large number of analyses without adjustment for multiple comparisons. • Patients who withdrew from the TRANSFORMS study did not ente extension study, the findings of this study should be interpreted cautiously. • Overall rate of attrition of 15%

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

Author

Clinical Findings –

The FREEDOMS trial was a 2-year, double-blind Phase II study. The primary endpoint was the annualized relapse rate and the secondary endpoint was the time to disability progression. The ARR was 0.18 in the fingolimod 0.5mg, 0.16 in the 1.25 mg fingolimod group, and 0.40 in the placebo group ($p<0.001$ for both doses versus placebo).[2] Both treatment experienced and treatment naïve patients demonstrated significant reductions in annual relapse rate. Fingolimod reduced the risk of disability progression, confirmed after 3 months, over the 24-month study period (hazard ratios [HR], 0.70 for fingolimod 0.5 mg and 0.68 for fingolimod 1.25 mg).[2]

The TRANSFORMS trial evaluated two strengths of fingolimod to an active comparator, interferon beta-1a (Avonex). The most recent systematic review conducted by the Oregon EPC Drug Effectiveness Review Project (DERP) concluded that there was fair evidence that interferon beta-1a (Avonex) is less effective than interferon beta 1a SC (Rebif) and interferon beta-1b (Betaseron) in preventing in patients with RRMS, and that there is few differences in effectiveness or direct evidence is lacking for other outcomes.[7] The TRANSFORMS trial was large, relative to other trials of drugs to treat MS, enrolling 1292 patients.[3,5] The ARR was significantly lower in both groups receiving fingolimod (0.2 in the 1.25mg group, 0.16 in the 0.5mg group, 0.33 in the IFN-B1a group; $p<0.001$).[3] Other measures of relapse also showed both fingolimod doses to be superior. However, the numbers needed to treat for the proportion relapse-free with fingolimod compared with interferon beta-1a at 1 year were not very small (8.3 and 10).[5] Disability progression was not different significantly between fingolimod and interferon beta-1a . The benefit of fingolimod over interferon beta-1a was greater in the subgroup of patients who had prior exposure to a DMT (difference in 0.20 to 0.27 relapses) than in patients who had no exposure (0.13 to 0.16 relapses). A post hoc analysis of the TRANSFORMS trial showed that the rate of outpatient steroid use was higher in the interferon group (11.2%, 13.1%, and 18.3% for fingolimod 0.5 mg, 1.25mg, and IFN beta-1a respectively) and the rate of hospitalization was lowest in the 0.5mg fingolimod group and highest in the interferon group (1.9% vs. 7%; $p=0.001$).[5] In the TRANSFORMS trial, two fatal infections occurred. The most common adverse reactions to treatment with fingolimod include influenza virus infections, headaches, diarrhea and elevated liver enzyme activity. Higher rates of pyrexia (RR 4.26), influenza-like illness (RR 10.55), were found with interferon beta-1a, while a higher rate of increased alanine aminotransferase (RR 3.52) was found with fingolimod.[5] Other measures of relapse (relapse-free, proportion with multiple relapses, and the time to first relapse) also showed fingolimod doses to be superior but progression of disease was not different between the treatments after one year. The benefit of fingolimod over interferon beta-1a was greater in the subgroup of patients who had prior exposure to a disease-modifying drug than in patients who had no prior exposure, although not statistically significant. Overall, there were no differences in the rate of discontinuation over 1 year, including for both lack of efficacy and due to adverse events.

In the TRANSFORMS 12-month extension trial, patients originally assigned to receive fingolimod in the TRANSFORMS study continued, and patients receiving interferon were re-randomized to receive fingolimod 0.5 mg or 1.25 mg.[4] This extension study lost the inherent placebo or active comparator control group when switching patients and all patients were aware that they were receiving fingolimod making it essentially open-label. Therefore, it is difficult to draw conclusions from the analysis. Patient's who withdrew from the core TRANSFORMS study were also excluded from this analysis. Patients who received interferon beta-1a in the core study (months 1-12) had relative reductions in ARR during months 13-24 of 30% after switching to 0.5mg fingolimod (ARR ratio 0.7, 95% CI 0.49-1.00, $p=0.49$) and 36% after switching to 1.25mg (0.64, 95% CI 0.43-0.94, $p=0.024$).[4]

Author

There was also a small (n=277) placebo-controlled trial that only last 6 months that used MRI findings as the primary outcome, and the clinical relevance is uncertain. In addition, this trial used doses higher than was ultimately approved by the US FDA (5mg once daily and 1.25 mg once daily). Therefore this study was not included in our evidence table or critical appraisal process.[5,12]

DRUG SAFETY[1]

Serious: No absolute contraindications have been determined.

Warnings:

- Bradyarrhythmia and Atrioventricular Blocks: All patients should be observed for 6 hours after the first dose for signs and symptoms of bradycardia.
- Increased risk of infections due to a dose dependent reduction in peripheral lymphocyte count
- Macular edema
- Elevations in liver enzymes

Tolerability: In the FREEDOMS trial 14.2% of patients in the 1.25 mg fingolimod group, 7.5% in the 0.5 mg fingolimod group, and 7.7% in the placebo group discontinued therapy. Major reasons included bradycardia, macular edema, elevated liver enzymes, and mild hypertension. In the TRANSFORMS trial 10% of patients receiving fingolimod 1.25 mg, 5.6% receiving fingolimod 0.5 mg, and 3.7% receiving interferon beta 1a discontinued study treatment. Main adverse events due to discontinuation included bradycardia and atrioventricular block after the first dose.

Pregnancy/Lactation rating: Pregnancy Category C

Dose Index (efficacy/toxic): No cases of overdosage have been reported. However, single doses up to 80-fold the recommended dose (0.5 mg) resulted in no clinically significant adverse reactions. At 40 mg, 5 of 6 subjects reported mild chest tightness or discomfort which was clinically consistent with small airway reactivity.

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

NME Drug Name	Lexi-Comp	USP Online	First DataBank	ISMP	Clinical Judgment
Fingolimod	None	None	None	None	None
Gilenya	None	None	None	None	Glatiramer Injection

Author

Common Drug-Related Adverse Events [1]		
Adverse Events (%)	**Fingolimod 0.5 mg daily (%)**	**Placebo (%)**
Number of Patients	425	418
Infections		
Influenza Viral Infections	13	10
Herpes Viral Infections	9	8
Bronchitis	8	4
Sinusitis	7	5
Cardiovascular Disorders		
Bradycardia	4	1
Abdominal Pain		
Macular edema	0.7	0
Gastrointestinal		
Diarrhea	12	7
Laboratory Tests		
ALT/AST increased	14	5
Increased blood triglycerides	3	1
Musculoskeletal Disorders		
Back pain	12	7
Nervous System Disorders		
Headache	25	23
Dizziness	7	6
Paresthesia	5	4
Migraine	5	1
Psychiatric Disorders		
Depression	8	7
Skin and Subcutaneous Tissue Disorders		
Alopecia	4	2
Pruritis	3	1

Author

DOSE & AVAILABILITY[1]:

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
0.5 mg	Tab	PO	Daily	The blood level of some metabolites is increased in severe renal impairment. The toxicity of these metabolites has not been explored.	Patients with severe hepatic impairment should be monitored for adverse reactions.	Safety and effectiveness have not been established	GILENYA should be used with caution in patients aged 65 years and over, reflecting the greater frequency of decreased hepatic, or renal, function and of concomitant disease or other drug therapy.	With or without food. Patients should be observed for 6 hours after the initial dose to monitor for signs and symptoms of bradycardia.

ALLERGIES/INTERACTIONS[1]

Drug-Drug: Ketoconazole can increase fingolimod blood levels by 1.7-fold when coadministered. The risk of adverse effects may be increased.

Heart rate lowering drugs: Experience with GILENYA in patients receiving concurrent therapy with beta blockers is limited. These patients should be carefully monitored during initiation of therapy.

Vaccines: Vaccination can be less effective during and for up to 2 months after discontinuation of treatment with fingolimod.

Author

REFERENCES

1. Gilenya. Prescribing Information. Novartis Pharmaceuticals Corp; Available at: http://www.pharma.us.novartis.com/product/pi/pdf/gilenya.pdf.

2. Kappos L, Radue E-W, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N. Engl. J. Med.* 2010;362(5):387-401.

3. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N. Engl. J. Med.* 2010;362(5):402-415.

4. Khatri B, Barkhof F, Comi G, et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. *Lancet Neurol.* 2011;10(6):520-529.

5. McDonagh M. Disease-modifying drugs for multiple sclerosis: Single drug addendum: Fingolimod. Final original report. Available at: http://derp.ohsu.edu/about/final-document-display.cfm. Accessed January 30, 2012.

6. Commissioner O of the. Safety Alerts for Human Medical Products - Gilenya (fingolimod): Drug Safety Communication - Safety Review of a Reported Death After the First Dose. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm284355.htm. Accessed January 30, 2012.

7. Smith B, Carson S, Fu R, et al. Drug Class Review: Disease-modifying Drugs for Multiple Sclerosis. Update 1. Available at: http://derp.ohsu.edu/about/final-products.cfm. Accessed January 24, 2012.

8. Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002;58(2):169-178.

9. Miller RM, Happe LE, Meyer KL, Spear RJ. Approaches to the management of agents used for the treatment of multiple sclerosis: consensus statements from a panel of u.s. Managed care pharmacists and physicians. *J Manag Care Pharm*. 2012;18(1):54-62.

10. Center for Drug Evaluation and Research. Application Number: 22-527. Summary Review.

11. David OJ, Kovarik JM, Schmouder RL. Clinical pharmacokinetics of fingolimod. *Clin Pharmacokinet*. 2012;51(1):15-28.

12. Kappos L, Antel J, Comi G, et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N. Engl. J. Med.* 2006;355(11):1124-1140.

13. Oregon Evidence-Based Practice Center. Drug Effectiveness Review Project: Systematic Review Methods and Procedures. Available at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/upload/DERP_METHODS_WEB_Final_January-2011-2.pdf.

Author

Appendix 1:

Strength of Evidence Grades and Definitions Used[13]:

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit the estimation of an effect.

Methods to assess quality of trials[13]

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?	
• Yes	Use of the term "randomized" alone is not sufficient for a judgment of "Yes". Explicit description of method for sequence generation must be provided. Adequate approaches include: Computer-generated random numbers, random numbers tables
• No	Randomization was either not attempted or was based on an inferior approach (e.g., alternation, case record number, birth date, or day of week)
• Unclear	Insufficient detail provided to make a judgment of yes or no.
2. Was the treatment allocation concealed?	
• Yes	Adequate approaches to concealment of randomization: Centralized or pharmacy-controlled randomization, serially-numbered identical containers, on-site computer based system with a randomization sequence that is not readable until allocation *Note: If a trial did not use adequate allocation concealment methods, the highest rating it can receive is "Fair".*
• No	Inferior approaches to concealment of randomization: Use of alternation, case record number, birth date, or day of week, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
• Unclear	No details about allocation methods. A statement that "allocation was concealed" is not sufficient; details must be provided.
3. Were groups similar at baseline in terms of prognostic factors?	
• Yes	Parallel design: No clinically important differences Crossover design: Comparison of baseline characteristics must be made based on order of randomization. *Note: Determine beforehand which prognostic factors are important to consider. A statistically significant difference does not automatically constitute a clinically important difference.*
• No	Clinically important differences
• Unclear	Statement of "no differences at baseline", but data not reported; or data not reported by group, or no mention at all of baseline characteristics. For crossover design, only reported baseline characteristics of the overall group.
4. Were eligibility criteria specified?	
• Yes	Eligibility criteria were specified a priori.
• No	Criteria not reported or description of enrolled patients only.
5. Were outcome assessors blinded to treatment allocation?	

Author

6. Was the care provider blinded? **7. Was the patient blinded?**	
• Yes	Explicit statement(s) that outcome assessors/care provider/patient were blinded. Double-dummy studies and use of identically-appearing treatments are also considered sufficient blinding methods for patients and care providers.
• No	No blinding used, open-label
• Unclear, described as double-blind	Study described as double-blind but no details provided.
• Not reported	No information about blinding
8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?	
• Yes	All patients that were randomized were included in the analysis. Specify if imputation methods (e.g., last-observation carried forward) were used. OR Exclusion of 5% of patients or less is acceptable, given that the reasons for exclusion are not related to outcome (e.g., did not take study medication) and that the exclusions would not be expected to have an important impact on the effect size
• No	Exclusion of greater than 5% of patients from analysis OR less than 5%, with reasons that may affect the outcome (e.g., adverse events, lack of efficacy) or reasons that may be due to bias (e.g., investigator decision)
• Unclear	Numbers analyzed are not reported
9. Did the study maintain comparable groups?	
• Yes	No attrition. OR, the groups analyzed remained similar in terms of their baseline prognostic factors.
• No	Groups analyzed had clinically important differences in important baseline prognostic factors
• Unclear	There was attrition, but insufficient information to determine if groups analyzed had clinically important differences in important baseline prognostic factors
10. Were levels of crossovers (≤ 5%), nonadherence (≤ 20%), and contamination (≤ 5%) acceptable?	
• Yes	Levels of crossovers, adherence and contamination were below specified cut-offs.
• No	Levels or crossovers, adherence, and contamination were above specified cut-offs.
• Unclear	Insufficient information provided to determine the level of crossovers, adherence and contamination.
11. Was the rate of overall attrition and the difference between groups in attrition within acceptable levels?	
Overall attrition: There is no empirical evidence to support establishment of a specific level of attrition that is universally considered "important". The level of attrition considered important will vary by review and should be determined a priori by the review teams. Attrition refers to discontinuation for ANY reason, including lost to follow-up, lack of efficacy, adverse events, investigator decision, protocol violation, consent withdrawal, etc.	
• Yes	The overall attrition rate was below the level that was established by the review team.
• No	The overall attrition rate was above the level that was established by the review team.
• Unclear	Insufficient information provided to determine the level of attrition
Differential attrition	
• Yes	The absolute difference between groups in rate of attrition was below 10%.
• No	The difference between groups in the overall attrition rate or in the rate of attrition for a specific reason (e.g., adverse events, protocol violations, etc.) was 10% or more.
• Unclear	Insufficient information provided to determine the level of attrition

Oregon State University
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

Month/Year of Review: March 2012
Generic Name: Dalfampridine
Brand Name: (Manufacturer): Ampyra™
Class: Potassium Channel Blocker for MS symptoms

End date of literature search: January 3, 2012
Manufacturer: Acorda Therapeutics, Inc
Dossier received: Yes
Comparator Therapies: None

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.

Summary:
FAM, also known as fampridine and 4-aminopyridine, is the first symptomatic therapy approved for MS patients with impaired walking mobility. MS is a chronic, progressive, immune-mediated disorder that destroys axonal myelin sheaths, resulting in neurodegeneration and the accumulation of neurologic deficits over time. Symptoms that arise are myriad but may include impaired walking mobility. Nearly 50 percent of those with MS will require the use of a walking aid within 15 to 25 years of diagnosis.

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.

Efficacy: 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 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.

Though statistical significance for the endpoint was not achieved, researchers used post-hoc analysis to create a novel primary endpoint, referred to as "response to treatment," for the two phase 3 trials. This endpoint, which has not been validated, defines a responder as one who has a walking speed for at least three visits during the trials' double-blind treatment period was faster than the maximum speed in five non-treatment visits.

Using "response to treatment" as the primary efficacy endpoint, the two phase 3 studies compared FAM 10 mg bid to placebo and used the change in 12-item MS walking scale (MSWS-12) between baseline and treatment's end to address validity and clinical significance. The MSWS-12 assessed MS patients' perspectives on their ambulatory disability. Both studies achieved statistical significance for the endpoint (NNT 3–4), and researchers found a statistically significant decrease in MSWS-12 score from baseline for responders compared to non-responders, independent of treatment group.

However, FDA analysis showed that at the end of the double-blind (DB) treatment period for phase 3 study MS-F203 the difference in walking speed between responders and non-responders over 25 feet was 1.75 seconds (s) (1.99 s for placebo-treated responders versus non-responders and 1.60 s FAM for responders versus non-responders) and for phase 3 study MS-F204 was 1.71 s (1.54 s for placebo-treated responders versus noon-responders and 2.15 s for FAM responders versus non-responders).

Neither phase 3 study directly addressed what impact being a responder would have on the quality of life of MS patients or their activities of daily living, health, or homecare requirements. No information was available concerning distances walked beyond 25 feet. The studies also were unable to address how one would use FAM in practice, given that only a subset of patients were deemed responders and no method exists to identify potential responders prior to treatment.

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 fampridine 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.

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 a walking disability that requires 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.

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 information is available for distances beyond 25 feet.

   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.

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.

The following scenarios could result in a patient potentially having a seizure: (1) FAM could be prescribed to patients who have not had their renal function checked and to patients who may be prone to seizures; (2) patients may inadvertently take two doses at once or less than 12 hours apart or may cut, crush, or chew tablets; and (3) the dosage form could fail and "dump" on occasion. FAM also could present an as yet unidentified risk to patients with decreased seizure threshold due to alcohol use, brain damage, or concomitant use of drugs that lower the seizure threshold.

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 (NNH25) 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:

Should criteria be developed to restrict FAM's use, the following should be included: FAM should be limited to those who (1) have a walking disability that requires 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.

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.[3, 4]

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.[5]

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]

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.[6]

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.[7] Both direct and indirect costs rise continuously with each stepwise increase in disability as measured by the Expanded Disability Status Scale (EDSS).[8]

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)-β1b (Betaseron), IFN-β1a (Avonex), IFN-β1a (Rebif), glatiramer acetate (Copaxone), natalizumab (Tysabri), and mitoxantrone (Novantrone).[3, 4] 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.[3–5] 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.[9–11] An EDSS of 4.0 and 6.0 typically would correspond to limited walking ability and to the need for unilateral support for walking.[12]

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).[9]

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.[13] Four feet per second is normal walking speed.[14]

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.[10, 14, 15] 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.[15]

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.[13] 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.[17]

CLINICAL PHARMACOLOGY[1]

FAM is a broad spectrum potassium channel blocker whose mechanism of action has yet to be fully elucidated. FAM has been shown in animal studies to increase the conduction of action potentials in demyelinated axons.

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[1]	Drug Regimens[1]	Patient Population[1,2]	N*	Duration[1]	Efficacy Results[3] (CI, p-values)	ARR/NNT[3, 4]	Safety Results (CI, p-values)	ARR/NNH[3,4]	Quality Rating/Comments[5]
MS-F203									Fair
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 T25FW 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 Patient characteristics: PLA, FAM total, FAM responders, FAM non-responders Age (mean yrs): 50.9, 51.5, 51.4, 51.6 Female (%): 60, 71, 76, 69 White (%): 93, 93, 91, 93 MS course (%)	224 72	Treatment period: 14 weeks Phases: 1. Screening 2. SB placebo run-in, beginning 1 week after screening: 2 weeks (visits 0 and 1, separated by 1 week) 3. DB treatment period, beginning 3 weeks after screening: 14 weeks (visits 2 and 3, separated by 2 weeks, and visits 4, 5, and 6, separated by 4 weeks) 4. Non-treatment follow-up, beginning 17 weeks after screening: 4 weeks (visits 7 and 8, separated by 2 weeks)	Timed walk responders (TWR): 1. FAM: 35% [p<0.0001; OR 4.75; CI: 2.08 to 10.86] 2. PLA: 8% 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] Mean change from baseline in walking speed during treatment period: FAM TWR: 0.51 ft/s [CI: 0.41 to 0.61] FAM TWNR: 0.16 ft/s [CI: 0.11 to 0.21] PLA (TWR + TWNR): 0.1 ft/s [CI: 0.03 to 0.17]	27 / 4	Seizure: 1. FAM: 0.4% (n=1) 2. PLA: 0% Withdrew due to adverse events: 1. FAM: 4.8% 2. PLA: 0%	0.4 / NA 4.8 / 21	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 T25FW 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 T25FW 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

		Relapsing-remitting: 29, 27, 19, 31 Primary progressive: 19, 14, 14, 13 Secondary progressive: 49, 55, 62, 51 Progressive relapsing: 3, 4, 5, 4 Treatment w/ interferon or glatiramer (%): 71, 66, 65, 67 MS duration (mean yrs): 12.7, 13.4, 14.1, 13.1 EDSS score (mean): 5.8, 5.8, 5.8, 5.7 T25FW (feet/s): 2.1, 2.1, 2.1, 2.0 LEMMT score: 4, 4.1, 4, 4.1 Ashworth score: 1, 1, 0.9, 0.9 MSWS-12 score: 68.5, 70.7, 70.3, 70.1 SGI score: 4.7, 4.6, 4.6, 4.6							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 from which patients drawn not described
MS-F204									Fair
Goodman 39 center 5/07–2/08 Phase III MC, DB, PC, RCT	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 LEMMT 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	119 118	Treatment period: 9 weeks Phases: 1. Pre-screening:1 week 2. SB placebo run-in, beginning 1 week after screening: 2 weeks (visits 0 and 1, separated by 1 week) 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: –6.84 [CI: –9.57 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	Seizure: 1. FAM: 0% 2. PLA: 0.84% (n=1) Withdrawals due to adverse events: 1. FAM: 3.3% 2. PLA: 3.4%	NA NA	• Internal and external validity issues similar to MS-F203, as the two studies principally differed only as follows: shorter duration of DB treatment period (9 weeks v. 14 weeks); 1:1 randomization to active drug and placebo; and an additional visit at the end of the treatment period to obtain data on efficacy and drug plasma concentration near the dosing interval's end. • The FAM group has a higher baseline MSWS-12 score (p=0.006)
MS-F202									Poor
Goodman 24 center	1. FAM 10 mg BID	**Inclusion criteria:** • Aged 18–70	51	Treatment period: 12 weeks	Mean percent change in walking speed during	NA NA	Seizure: FAM 10 mg: 0%	NA	Primary endpoint statistical significance not achieved.

Phase II 2/03–12/03 MC, DB, PC, RCT	2. FAM 15 mg BID 3. FAM 20 mg BID 4. PLA	• 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 10 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 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, 4.56, 4.25	50 57 47	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 weeks) 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)	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 27 / 4 28 / 4 30 / 3	2. 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%	NA 0.04 / NA NA NA 0.07 / NA	**Internal validity concerns** • Did not indicate what % of patients were on immunomodulators and what immunomodulators they were on • Did not state what concomitant medications or non-pharmacologic therapies patients were using that may have affected mobility • Allowed changes in dosing of concomitant medications when necessary • Used modified ITT **External validity concerns** • Ambulatory deficits in MS caused by multiple factors; unclear which affected by FAM • Clinical significance of the primary endpoint unclear, e.g., impact on activities of daily living, number of hospitalizations, home care needs, quality of life • Setting from which patients drawn not described • No progressive relapsing patients in the study • Patients predominantly Caucasian • Setting from which patients drawn not described

[1]Study design abbreviations: DB = double-blind, RCT = randomized trial, PC = placebo-controlled, FAM = fampradine, PLA = placebo
[2]MS disability tests: T25FW: timed 25-foot walk (maximum time allowed to complete is 180 s, or 0.14 ft/s), EDSS: expanded disability status scale, MSFC: MS functional composite, 9-HPT: 9-hole peg test, PASAT: paced auditory serial addition test, LEMMT: lower extremity manual muscle test, MSWS-12: 12-item MS walking scale, SGI: subject global impression (assesses physical wellbeing, 1=terrible to 7=delighted), CGI: clinical global impression (1=not ill to 7=extremely ill)
[3]Results abbreviations: ARR = absolute risk reduction, TWR: timed walk responders, TWNR, timed walk non-responders, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval.
[4]NNT/NNH are reported only for statistically significant results
[5]Quality Rating: (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
[6]Modified 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.

Summary of Findings

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, 19] 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.[18] (See Clinical Efficacy Evidence Table)

Study MS-F202 was a dose comparison trial of sustained-release FAM that randomized 206 patients 1:1:1:1 to receive FAM 10 mg bid, FAM 15 mg bid, FAM 20 mg bid, or placebo. 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 8–60 seconds (s) at screening. The study population had an average EDSS >5.64. The primary efficacy endpoint was mean percent change in walking speed during treatment using the T25FW.[18]

Statistical significance for the primary endpoint was not achieved for MS-F202. Therefore, 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.[18]

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).[18] 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]

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 second."[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 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 homecare 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.

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)

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 6 months and 405 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 trails, 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.

Sherri J. Willard Argyres

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 dalfamprindine	Delavirdine Desipramine	None		None	None
LA/SA for Ampyra	Anakinra	None		None	None

Sherri J. Willard Argyres

ADVERSE REACTIONS[1]

In clinical trials, the most commonly observed adverse reactions—incidence ≥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	RENAL ADJ	HEPATIC ADJ	Pediatric 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*				• 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.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	96%
Cmax	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/INTERACTIONS[1]

Drug-Drug: None

Food-Drug: None

Allergy/Cross Reactive Substances: None

Sherri J. Willard Argyres

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. Courtney AM, Treadaway K, Remington G et al. Multiple Sclerosis. *Med Clin North Am.* 2009; 93(2): 451–476.
4. 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).
5. Snook EM, Moyl RW. Effect of exercise training on walking mobility in multiple sclerosis: a meta-analysis. *Neurorehabil neural repair.* 2009; 23: 108–116.
6. Noseworthy JH, Lucchinetti C, Rodriguez M et al. Multiple sclerosis. *NEJM.* 2000; 343(13): 938–952.
7. Kobelt G, Berg J, Atherly D et al. Costs and quality of life in multiple sclerosis. *Neurology.* 2006; 66:1696–1702.
8. 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.
9. Filippini G, Munari L, Incorvaia B et al. Interferons in relapsing remitting multiple sclerosis: a systematic review. *Lancet.* 2003; 361: 545–552.
10. Mitsikostas DD. Methodology of clinical trials in multiple sclerosis. *Neurol Sci.* 2006; 27: S362–S364.
11. 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.
12. Pozzilli C and Prosperini L. Clinical markers of therapeutic response to disease modifying drugs. *Neurol Sci.* 2008; 29:S211–S213.
13. 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.
14. 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).
15. 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.
16. 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.
17. Hobart JC, Riazi A, Lamping DL et al. Measuring the impact of MS on walking ability: The 12-Item MS Walking Scale (MSWS-12). *Neurology.* 2003; 60: 31–36.
18. Goodman AD, Brown TR, Krupp LB et al. Dose comparison trial of sustained-release fampridine in multiple sclerosis. *Neurology.* 2008; 71: 1134–1141.
19. 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.
20. Van Dieman 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.

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

Class Update: Atypical Antipsychotic Medications

Month/Year of Review: March 2012
New Product for review: Lurasidone (Latuda®)
Manufacturer: Sunovion Pharmaceuticals
Last Oregon Review: Dec 2010 (Oregon HRC)

Dossier received: Yes

Source Document: DERP

Table 1. Current Voluntary PDL Preferred/Non-Preferred Atypical Antipsychotics

Current Preferred Agents:	Current Non-Preferred Agents:
Clozapine (Clozaril®)	Abilify® tablet/solution/Discmelt®/IM
Geodon® capsule/IM	Fanapt® tablet
Risperidone (Risperdal®) tablet/solution--generic	Invega® tablet
Risperidone Tab RAPDIS	Invega Sustenna®
Seroquel® (therapeutic doses) tablet/XR tablet	Risperdal Consta®
	Olanzapine (Zyprexa®) tablet--generic
	Saphris® SL tablet
	Zyprexa Relprevv®
	Zyprexa Zydis®

Reason for Review:
The Oregon Evidence-based Practice Center drug effectiveness review project (DERP) published an update to the drug class review on atypical antispychotics.[1] This was reviewed by the Oregon Health Resources Commission in December 2010 and their conclusions are listed in Appendix 1.[2] Since the last OR review, however, the Agency for Healthcare Research and Quality (AHRQ) has release an update report on the off-label use of atypical antipsychotics[3], a new atypical antipsychotic, lurasidone (Latuda®), has been FDA-approved,[4] and various systematic reviews through the Cochrane Library were done to evaluate and compare atypical antipsychotics in patients with schizophrenia.[5-9] The evidence-based practice guidelines endorsed by the American Psychiatric Association have not been updated since 2002 for the treatment of bipolar affective disorder and 2004 for the treatment of schizophrenia. This update will summarize the results from the AHRQ systematic review regarding the off-label use of atypical antipsychotics, evaluate the effectiveness, safety, and place in therapy for lurasidone, and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines.

Issues:

- Is there any new evidence of effectiveness or harms that will support atypical antipsychotic management strategies or changes?
- Is there any evidence that lurasidone is more effective or safer than currently available medications in the PDL drug class including in subgroups of patients?
- What recommendations for management of the atypical antipsychotic class can be made?

Conclusions:

- No trials have been done evaluating the newest agents (asenapine, iloperidone, paliperidone, and lurasidone) for any off-label uses.
- Benefits and harms vary among atypical antipsychotics and direct comparisons of different agents for off-label conditions are rare.
- There is low quality evidence that lurasidone is safe and effective based on short-term placebo controlled trials in improving the general mental state. There is insufficient evidence to determine comparative effectiveness of lurasidone with other atypical antipsychotics.
- There is insufficient evidence to determine how maintenance lurasidone affects other clinical important outcomes in patients with schizophrenia including quality of life, improvement in social functioning, hospitalization, mortality, or adherence.
- From a recent AHRQ systematic review, there was moderate to high level of evidence available to support the following off-label use of the listed atypical antipsychotics.[3]
  - Generalized anxiety disorder: quetiapine
  - Dementia (overall): aripiprazole, risperidone
  - Dementia (psychosis): risperidone
  - Dementia (agitation): olanzapine, risperidone
  - Depression (selective serotonin reuptake inhibitor (SSRI)/ selective serotonin-norepinephrine reuptake inhibitor (SNRI) augmentation): aripiprazole, quetiapine, risperidone
  - Depression (monotherapy): quetiapine
  - Obsessive Compulsive Disorder (SSRI augmentation): risperidone
  - Post Traumatic Stress Disorder (PTSD): risperidone

Recommendations:

1. No changes are recommended for the atypical antipsychotic preferred drug class list based on safety and efficacy. Costs should be reviewed in executive session.
2. Based upon findings from the AHRQ report on off-label antipsychotics, it is recommended to maintain the current dose limit for quetiapine (limits doses <150mg for >3 months) to prevent off-label use.
3. Based on the lack of long-term comparative effectiveness data, recommend listing lurasidone a non-preferred agent on the voluntary PDL.
4. Due to the need for voluntary compliance with the PDL for this drug class, it is recommended that educational outreach interventions be considered in the management strategy.
   i. As one example, academic detailing can be used to promote appropriate utilization and minimize inappropriate off-label use.

Background:

Antipsychotic medications are approved by the U.S. FDA for treatment of schizophrenia and bipolar disorder and are divided into the older, conventional antipsychotics and the second generation atypical antipsychotics. There are currently ten different atypical antipsychotics available and approved by the FDA. Some offer a variety of dosage forms (e.g. orally disintegrating tablets or long-acting injectables) and many have an assortment of approved indications (ranging from the irritability associated with autistic disorder in children and adolescents to the maintenance treatment for schizophrenia in adults), as well as are commonly used off-label for various psychiatric conditions.[3] Appendix 2 lists FDA approved indications for the atypical antipsychotics. No consistent differences in efficacy have been demonstrated between the available agents. Side effect profiles between the agents do vary and is often an important factor in treatment selection. These side effects may include extrapyramidal symptoms, autonomic effects, increased prolactin levels, metabolic effects, and cardiac risks including increased risk of ventricular arrhythmias.

Methods:
The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, the Department of Veteran Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality 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.

Comparative Effectiveness Reviews:

AHRQ Off-Label Use of Atypical Antipsychotics: An Update (September 2011)

The AHRQ report performed a systemic review on the efficacy and safety of atypical antipsychotics for use in conditions lacking FDA approval.[3] These conditions include anxiety, attention deficit hyperactivity disorder (ADHD), dementia and severe geriatric agitation, major depressive disorder (MDD), eating disorders, insomnia, OCD, PTSD, personality disorders, substance abuse, and Tourette's syndrome. Lurasidone was not included in this review.

Key Questions and Conclusions:

1. What are the leading off-label uses of atypical antipsychotics in utilization studies? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

- Atypicals have been studied as off-label treatment for the following conditions: ADHD, anxiety, dementia in elderly patients, depression, eating disorders, insomnia, obsessive compulsive disorder (OCD), personality disorder, PTSD, substance use disorders, and Tourette's syndrome.
- Off-label use of atypical antipsychotics in various settings has increased rapidly since their introduction in the 1990s; risperidone, quetiapine, and olanzapine are the most common atypicals prescribed for off-label use.
- One recent study indicated that the 2005 regulatory warning from the FDA and Health Canada was associated with decreases in the overall use of atypical antipsychotics, especially among elderly dementia patients. Use of atypicals in the elderly is much higher in long-term care settings than in the community.
- Atypicals are frequently prescribed to treat PTSD in the U.S. Department of Veterans Affairs health system.
- At least 90 percent of antipsychotics prescribed to children are atypical, rather than conventional antipsychotics. The majority of use is off-label.
- No off-label use of the newly approved atypicals (asenapine, iloperidone, and paliperidone) was reported in the utilization literature.

2. What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics, for off-label indications?

- Moderate to high evidence for efficacy for the following off-label indications and atypical antipsychotics:
  - Generalized anxiety disorder: quetiapine
  - Dementia (overall): aripiprazole, risperidone
  - Dementia (psychosis): risperidone
  - Dementia (agitation): olanzapine, risperidone
  - Depression (SSRI/SRNI augmentation): aripiprazole, quetiapine, risperidone
  - Depression (monotherapy): quetiapine
  - Obsessive Compulsive Disorder (SSRI augmentation): risperidone
  - PTSD: risperidone

- Moderate to high evidence for inefficacy for the following off-label indications and atypical antipsychotics:
  - Eating Disorders: olanzapine
  - Substance Abuse (alcohol): aripiprazole
  - MDD (monotherapy): olanzapine

- A complete summary of strength of efficacy by drug and conditions is available in Appendix 3.

3. What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

- There are insufficient data regarding efficacy, effectiveness, and harms to determine what subset of the population would potentially benefit from off-label uses of atypicals.

4. What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

- In elderly patients, adverse effects included an increased risk of death (NNH 87), stroke (NNH 53 for risperidone), extrapyramidal symptoms (NNH 10 for olanzapine, 20 for risperidone), and urinary symptoms.
- In nonelderly adults, adverse events included weight gain (especially with olanzapine), fatigue, sedation, akithisia (for aripiprazole), and extrapyramidal symptoms.
- In elderly patients, a metaanalysis found a small but statistically significant difference in the risk of death for atypicals compared to placebo and found no difference between drugs in the class.

5. What is the effective dose and time limit for off-label indications?

- There are too few studies comparing doses of atypical antipsychotic medications to draw a conclusion about a minimum dose needed.
    - Most trials used flexible dosing, resulting in patients taking a wide range of doses.
    - According the meta-analysis conducted by AHRQ, using the percentage of remitters and responders according to the Montgomery-Asperg Depression Rating Scale (MADRS) as an outcome, 150 mg quetiapine daily augmentation has equal efficacy as augmentation with 300 mg for patients with MDD who respond inadequately to SSRIs.
    - More trials examining different doses of other atypicals for MDD are needed as are dosage trials for treating conditions such as OCD, PTSD, and anxiety disorder.
- Though there is some trial data regarding duration of treatment in PTSD, eating disorders, and borderline personality disorder, the outcome of treatment appears to be the same regardless of reported follow-up time.

Cochrane Reviews:

Five systematic reviews were also identified from the Cochrane Library evaluating quetiapine, olanzapine, risperidone, clozapine, and ziprasidone versus other atypical antipsychotics for schizophrenia.[5-9] It was clear across all of the reviews that it remains difficult to draw strong conclusions due to the high rates of attrition in these groups (risperidone 46.9%, olanzapine 49.2%, ziprasidone 59.1%, quetiapine 57.6%). Differences in efficacy were small and most often seen in general mental state. Most differences are seen in side effects and toleratibility profiles between the different medications.

Other conclusions from these reviews include:

- Olanzapine may be a more efficacious drug in improving the general mental state than some other atypical antipsychotics (aripiprazole, risperidone, quetiapine, and ziprasidone), but this small superiority in efficacy needs to be considered that it can be associated with more weight gain and metabolic problems than other medications in the class, except clozapine.
- Ziprasidone may be a slightly less efficacious antipsychotic drug based on the Positive and Negative Syndrome Scale (PANSS) than olanzapine (4 RCTs, n=1291, MD 8.32 CI 5.64 to 10.99) and risperidone (3 RCTs, n=1016, MD 3.91 CI 0.27 to 7.55). Its main advantage is the low propensity to induce weight gain and associated adverse effects.
- Risperidone seems to produce somewhat more extrapyramidal side effects and clearly more prolactin increase than most other second generation antipsychotics.
- Risperidone improved the general mental state (PANSS score) slightly less than olanzapine (15 RCTs, n = 2390, MD 1.94 CI 0.58 to 3.31), but slightly more than quetiapine (9 RCTs, n = 1953, MD -3.09 CI -5.16 to -1.01) and ziprasidone (3 RCTs, n =1016, MD -3.91 CI -7.55 to -0.27).
- Clozapine differs more clearly in adverse effects from other second generation antipsychotics and the side-effect profile could be key in the selection of treatment depending on the clinical situation and patient's preferences. Data on other important outcomes such as cognitive functioning, quality of life, death or service use are currently largely missing, making further large and well-designed trials necessary
- Efficacy data favored olanzapine and risperidone compared with quetiapine (PANSS total score versus olanzapine: 10 RCTs, n=1449, WMD 3.66 CI 1.93 to 5.39; versus risperidone: 9 RCTs, n=1953, WMD 3.09 CI 1.01 to 5.16), but clinical meaning is unclear. There were no clear mental state differences when quetiapine was compared with clozapine or ziprasidone.
- Most data that has been reported within existing comparisons of quetiapine are of very limited value because of assumptions and biases within them. There is much scope for further research into the effects of this widely used drug.

Another recent Cochrane Review attempted to assess the effects of atypical antipsychotics in people who are diagnosed with both schizophrenia and depression and concluded that there is insufficient evidence to make any definitive conclusions or recommendations. Only three studies were included in their review and evaluation.[10]

New Drug Review[11,12]

FDA approved indications: Lurasidone is an atypical antipsychotic agent indicated for the treatment of patients with schizophrenia.

Clinical Trial Data:[12]

Efficacy: The efficacy of lurasidone was established in four short term (six-week), randomized, placebo-controlled studies in 1307 adults with schizophrenia and who were hospitalized for an acute exacerbation and had a duration of illness for at least one year.[12] Table 2 provides a summary of the evidence findings for the two published and peer-reviewed studies.[13,14] The remaining two have not been published or peer-reviewed and were not included because they could not be assessed for quality or risk of bias. There are no head-to-head comparative trials comparing lurasidone with any other atypicals. Among the measures used to deem effectiveness were Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale derived (BPRSd), and Clinical Global Impression severity scale (CGI-S). These are all validated measures. Endpoints were measured at the end of week six. All studies had a high discontinuation rates (34%-65.8%).

In one fair-quality study (n=180) phase II study, lurasidone 80 mg daily was found to be superior to placebo in the mean change inf BPRSd total score and CGI-S.[14] The mean change was -8.9 and -4.2 for the 80mg and placebo groups (p= 0.018). A total of 99 (55%) patients completed the study. The proportion of subjects experiencing ≥1 AE was not significantly higher in the lurasidone group (76.7%) than in the placebo group (68.9%). In another fair-quality randomized controlled trial (n=473), patients were randomized to an active control of olanzapine 15mg, lurasidone 40 mg, 120 mg, or placebo. A total of 298 subjects (62%) completed the double-blind study phase. All three active arms were superior to placebo on the PANSS total score and CGI-S.[13] The mean change in the PANSS total score was -25.7, -23.6, -28.7 and -16 for the 40mg, 120mg, olanzapine and placebo groups respectively and the difference from placebo in mean change was significant in the lurasidone 40mg group and the lurasidone 120mg group (p= 0.002 and 0.022 respectively). There was no improved efficacy with the 120mg dose compared to 40mg dose, and an increased risk of adverse events.

Two other randomized short term trials were evaluated by the FDA for the approval of lurasidone. In one study, a total of 488 participants were randomized to lurasidone 80mg, lurasidone 160 mg, placebo, or quetiapine XR 600mg as an active comparator. The difference from placebo in the mean change in the PANSS total score from baseline to week 6 was significant in the lurasidone 80 mg group (-11.9, p<0.001) and the lurasidone 160 mg group (-16.2, p<0.001). A randomized study (n=489) evaluated lurasidone 40, 80, and 120 mg daily compared to placebo.[12] Only the 80 mg daily dose demonstrated superiority to placebo in the primary endpoint of PANSS total score and CGI-S. The 120 mg daily dose did not have additional benefit over lower daily doses. The mean change in the PANSS score was -19.2, -23.4, -20.5, -17 in the 40mg, 80mg, 120mg and placebo groups respectively (p=0.591, 0.034, and 0.391) .[12] A third published study assessing performance and interview-based cognitive change in lurasidone versus ziprasidone is also available, but because it does not measures common efficacy endpoints it is not included in the following evidence table.[15] There was a fifth study (049) that failed to distinguish either lurasidone (at any of 3 doses: 20, 40, or 80 mg/day) or haloperidol (10 mg/day) from placebo and was not further reviewed by the FDA.

Safety: Commonly observed adverse effects (incidence ≥5% and at least twice the rate of placebo) include: somnolence, akathisia, nausea, parkinsonism, and agitation. Electrocardiogram changes exceeding 500 milliseconds were not reported. In short-term trials, weight gain, fasting glucose, and lipid levels appear to be similar to placebo. The mean change in fasting glucose was 1.4 mg/dL in the lurasidone group, 0.6 mg/dL in the placebo group and 9 mg/dL in the olanzapine group. Mean increases in TC, LDL, and TC was not noted in the lurasidone group. Latuda has the same warnings and precautions as other atypical antipsychotics such as increased mortality in the elderly, neuroleptic malignant syndrome, tardive dyskinesia, and metabolic side effects. Mean increases in weight was 0.75 kg in the lurasidone group, 0.26 kg for placebo and 4.1 kg for olanzapine.[4]

Consideration in Subpopulations:
Pediatrics: Several atypical are approved for use in pediatrics. Lurasidone has not been studied in patients less than 18 years of age.
Geriatrics: Older patients may be more likely to experience adverse effects due to lower renal and hepatic function. All atypical have a warning of increased risk of death in elderly patients with dementia-related psychosis.
Gender, race, ethnicity: Subgroup analyses for these 4 studies based on gender and race generally showed consistency in the results across these subgroups.[12] There is no known difference in clinical efficacy or safety based on gender, race, or ethnicity.

COMPARATIVE CLINICAL EFFICACY:

Relevant Endpoints in schizophrenia:

- Mortality
- Quality of Life
- Functional Capacity
- Hospitalization
- Efficacy as measured by symptom response
- Withdrawals due to adverse events and time to withdrawal
- Major adverse events

Study Primary Endpoints:

- Meltzer et al: Positive and Negative Syndrome Scale (PANSS)
- Nakamura et al: Brief Psychiatric Rating Scale (BPRSd)

Table 2. Lurasidone Comparative Evidence Table

Ref./ Study Design	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR/ NNH[3]	Quality Rating[4]; Comments
1.Meltzer, et al. Prospective, multicenter, DB, PG study Lurasidone vs Placebo Olanzapine vs Placebo	1. Lurasidone 40mg 2. Lurasidone 120mg 3. Olanzapine 15mg 4. Placebo All dosed QD	Recently admitted inpatients with schizophrenia with an acute exacerbation of psychotic sx illness duration of at least 1 year and to have been hospitalized for ≤2 weeks for an acute exacerbation of psychotic symptoms	478	6-weeks	<u>PANSS total score (change from baseline to week 6):</u> Lurasidone 40mg = -25.7 Placebo = -16.0 p-value = 0.002 Lurasidone 120mg = -23.6 Placebo = -16.0 p-value = 0.022 Olanzapine 15mg = -28.7 Placebo = -16.0 p-value <0.001	N/A	<u>Discontinuations due to adverse events:</u> Lur 40mg : 8 (6.7%) Lur 120mg: 14 (11.8%) Olan 15mg: 8 (6.5%) Placebo 10 (8.6%)	N/A	Fair; *Placebo controlled, not head-to-head* *No dose-response relationship was observed between 40mg and 120mg of lurasidone* *Manufacturer sponsored trial* *Short-term trial* *Rates of Attrition:* *32%-45% lurasidone* *39% placebo*
2.Nakamura, et al. DB, PC, RCT	1. Lurasidone 80mg 2. Placebo	Age 18-64 yrs, hospitalized for an acute exacerbation of schizophrenia Minimum illness duration of at least 1 year 75.6% male Mean age 39.7	N=90 N=90	6-weeks	<u>BPRSd (change from baseline to week 6):</u> Lurasidone 80mg = -8.9 (CI= -11.5 to -6.2) Placebo = -4.2 (CI = -6.9 to -1.5) p-value = 0.0118 PANSS (change from baseline) Lurasidone: -14.1 Placebo: -5.5 P=0.004	N/A N/A	Discontinuations due to adverse events: Lur 80mg : 6 (6.7%) Placebo: 1(1.1%) P=0.118 Severe Adverse Events: Lur 80mg: 7 (7.8%) Placebo: 5 (5.6%)	NS NS	Fair; Unknown methods for allocation concealment *CIs appear to cross for efficacy measure BPRSd* *Manufacturer sponsored trial* *Short-term trial* *High rates of Attrition:* *48% placebo* *42% lurasidone*

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

Table 3. Lurasidone Dose & Availability

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
40mg	Tab	PO	Daily	Max 40mg/d (CrCl 10-50 ml/min)	Max 40mg/d Child-Pugh Class B or C	Not Established	None	Should be given with food
80mg	Tab	PO	Daily					

Pharmacology

Lurasidone is a benzoisothiazol derivative thought to work through a combination of central Dopamine Type 2 (D2) and serotonin Type 2 (5HT2A) receptor antagonism.

Table 4. Lurasidone Pharmacokinetics

Parameter	Result
Oral Bioavailability	9-19% (increased w/food)
Cmax	1-3 hours
Protein Binding	~99%
Elimination	Feces 80% Urine 9%
Half-Life	18 hours
Metabolism	CYP3A4 2 active; 2 inactive metabolites

ADVERSE EFFECTS:[4] Adverse reactions observed in >2% of patients and greater incidence than placebo treated patients

	Icatibant (N=1004)	***Placebo (N=455)***
System Organ Class	***Subjects (%)***	***Subjects (%)***
Gastrointestinal Disorders		
Nausea	*12*	*6*
Vomiting	*6*	*8*
Dyspepsia	*8*	*6*
Nervous System Disorders		
Somnolence	*22*	*10*
Akathisia	*15*	*3*
Parkinsonism	*11*	*5*
Dystonia	*5*	*1*
Dizziness	*5*	*3*
Psychiatric Disorders		
Insomnia	*8*	*7*
Agitation	*6*	*3*
Anxiety	*6*	*3*
Restlessness	*3*	*2*

Appendix 1

Previous Conclusions by DERP[1,2]:

Schizophrenia:

1. No consistent differences in efficacy were found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, Iloperidone, asenapine or aripiprazole in shorter-term trials of inpatients or outpatients.
2. There is insufficient evidence to draw conclusions regarding the impact of medications in this class on suicide death.
3. There is no evidence of a clinically meaningful difference in rates of rehospitalization for the included drugs.
4. Good quality evidence shows olanzapine is superior to quetiapine for reduction in relapse rate. Evidence for olanzapine vs. risperdone was mixed for relapse rate. No evidence was found for the other included drugs
5. There was no evidence to differentiate between drugs in this class for quality of life. Olanzapine, quetiapine, risperdone, ziprasidone and clozapine were the only drugs compared.
6. In a single 12 month study (n=108) no difference was seen between clozapine and risperdone for social functioning. There is insufficient evidence to draw conclusions about differences between quetiapine, risperidone, clozapine, and extended release palinperidone for social functioning.
7. There is insufficient evidence to draw conclusions regarding the impact of this class of drugs on:
    - Employment, Global assessment of functioning, Violent behavior, Rates of discontinuation or time to discontinuation, Inpatient outcome, Aggressive behavior, Length of stay, Time to onset of efficacy, Nursing burden in inpatient setting, Comparative differences in extrapyramidal symptoms, Metabolic syndrome, Subgroups of race, age, and gender
8. There was consistent evidence that showed no difference for medications in this class for response rates. Asenapine and iloperidone had no published studies.
9. One good quality study of first episode schizophrenia (n=400) found no statistically significant differences in overall discontinuation rates (primary outcome) or symptom response for olanzipine, immediate release quetiapine, and risperidone.
10. Weight gain was 6 to 13 pounds greater with olanzapine than the other atypical antipsychotics over periods of 1.5 to 18 months of treatment.
11. There was no evidence of clinically meaningful differences in rates of sexual dysfunction for the included drugs.
12. Evidence indicates that clozapine is more sedating than risperidone and olanzapine.

Bipolar Disorder

1. There is insufficient evidence to determine a clinically meaningful difference between drugs in this class for bipolar disorder.
2. The strength of evidence for efficacy and comparative difference between drugs in this category is low.

Major Depressive Disorder

1. No atypical antipsychotic had evidence of providing a significant long-term benefit when used as an adjunctive treatment for augmentation of antidepressant therapy in adults with treatment resistant depression.

Dementia

1. There was no consistent evidence that any atypical antipsychotic was superior to haloperidol for treating behavioral and psychological symptoms of dementia.
2. There were no significant differences between drugs or between drug and placebo on a variety of evaluation scales.
3. The incidence of Parkinsonism is higher with olanzapine and risperidone compared to immediate release quetiapine and placebo in patients with dementia.

Children with Pervasive Developmental Disorder or Disruptive Behavior Disorder

1. There is insufficient evidence to draw conclusions regarding the impact of medications in this class on patients with pervasive developmental disorder or disruptive behavior disorder.
2. The conclusions that could be drawn from these reviews were limited by the small numbers of available trials and lack of long-term follow-up data.

Serious Harms

1. While clozapine has been shown to be associated with an increased risk of seizures (2.9% and 4.2% in two separate studies) and agranulocytosis (13 studies reported incidence of 0-2.4%), differences among the drugs in other serious harms have not been clearly shown.

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

Appendix 2:[17]

FDA Approved Indications for Atypical Antipsychotics

Indication	*Abilify*	*Risperdal*	*Seroquel*	*Seroquel XR*	*Zyprexa*	*Geodon*	*Invega*	*Fanapt*	*Saphris*
Acute Treatment of Schizophrenia in Adults	X	X	X	X	X	X	X	X	X
Maintenance Treatment for Schizophrenia in Adults	X	X		X	X	X	X		
Acute Treatment of Schizophrenia in Adolescents (13-17 yrs)	X	X	X		X=				
Acute Treatment of Bipolar Mania in Adults	X	X	X	X	X	X			X
Acute Treatment of Bipolar Mania in Adults—Adjunct to Lithium/Valproate	X	X	X	X	X				
Acute Treatment of Bipolar Mania in Pediatric Patients (10-17 yrs)	X	X			X=				
Acute Treatment of Bipolar Mania in Pediatric Patients (10-17 yrs)—Adjunct to Lithium/Valproate	X								
Maintenance Treatment of Bipolar Mania in Adults	X				X				
Maintenance Treatment of Bipolar Mania in Adults—Adjunct to Lithium/Valproate			X	X		X			
Acute Treatment of Agitation Associated with Schizophrenia in Adults*	X				X	X			
Treatment of Depressive Episodes Associated with Bipolar Disorder in Adults			X	X					
Irritability Associated with Autistic Disorder in Children and Adolescents (5-16 yrs)	X	X							
Acute Treatment of Depressive Episodes Associated with Bipolar Disorder in Combination with Fluoxetine					X				
Acute Treatment of Treatment Resistant Depression in Adults in Combination with Fluoxetine					X				
Adjunctive Therapy to Antidepressants for Acute Treatment of Major Depressive Disorder in Adults	X			X					
Acute Treatment of Schizoaffective Disorder as Monotherapy							X		
Acute Treatment of Schizoaffective Disorder—Adjunct to Mood Stabilizers and/or Antidepressants							X		

=Zyprexa label suggests trial of other drugs first in adolescents
*Injectable formulations for IM use only

Oregon State University
College of Pharmacy

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

Appendix 3: Summary of Strength of Evidence of Efficacy By Drug and Condition[3]

	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Generalized Anxiety Disorder	0	-	++	-	-
Social Phobia	0	+	-	0	0
ADHD (no co-occurring disorders)	0	0	0	+	0
ADHD (bipolar children)	-	0	0	0	0
ADHD (mentally retarded children)	0	0	0	+	0
Dementia (overall)	++	+	+	++	0
Dementia (psychosis)	+	+/-	+/-	++	0
Dementia (agitation)	+	++	+/-	++	0
Depression (SSRI/SNRI augmentation)	++	+	++	++	+
Depression (monotherapy)	0	-	++	0	0
Eating Disorders	0	--	-	0	0
Insomnia	0	0	-	0	0
Obsessive Compulsive Disorder (SSRI augmentation)	0	+	--	++	-
Obsessive Compulsive Disorder (citalopram augmentation)	0	0	+	+	0
Personality Disorder (borderline)	+	+/-	+	0	-
Personality Disorder (schizotypal)	0	0	0	+/-	0
PTSD	0	+/-	+	++	0
Substance Abuse (alcohol)	--	-	-	0	0
Substance Abuse (cocaine)	0	-	0	-	0
Substance Abuse (methamphetamine)	-	0	0	0	0
Substance Abuse (methadone clients)	0	0	0	-	0
Tourette's Syndrome	0	0	0	+	-

Key: **) (+=low or very low evidence of efficacy) (+/-=mixed results) (-=low or very low evidence of inefficacy)** (--=moderate or high evidence of inefficacy) **(0=no trials)**

REFERENCES:

1. McDonagh MS, Peterson K, Carson S, Fu R, Thakurta S. Drug class review: Atypical antipsychotic drugs. Update 3. Available at: http://derp.ohsu.edu/about/final-document-display.cfm. Accessed December 20, 2011.

2. Health Resources Commission. Atypical Antipsychotic Drugs. December 2010. Available at: http://www.oregon.gov/OHA/pharmacy/therapeutics/ebr.shtml

3. Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43. (Prepared by the Southern California/RAND Evidence-based Practice Center under Contract No. HHSA290-2007-10062-1.) AHRQ Publication No. 11-EHC087-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed January 11, 2012.

4. Latuda Prescribing Information. Sunovion Pharmaceuticals Inc. Available at: http://www.latuda.com/LatudaPrescribingInformation.pdf

5. Komossa, K., Rummel-Kluge, C., Hunger, H., Schmid, F., Schwarz, S., Duggan, L., et al. (2010). Olanzapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*, Issue 3.

6. Komossa, K., Rummel-Kluge, C., Schmid, F., Hunger, H., Schwarz, S., Srisurapanont Manit, K. W., et al. (2010). Quetiapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*, Issue 1.

7. Komossa, K., Rummel-Kluge, C., Schwarz, S., Schmid, F., Hunger, H., Kissling, W., et al. (2011). Risperidone versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*, Issue 1.

8. Lobos, C.A., Komossa, K., Rummel-Kluge, C., Hunger, H., Schmid, F., Schwarz, S., et al. (2010). Clozapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*, Issue 12.

9. Komossa K, Rummel-Kluge C, Hunger H, et al. (2010). Ziprasidone versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*, Issue 12.

10. Furtado VA, Srihari V, Kumar A. (2012). Atypical antipsychotics for people with both schizophrenia and depression. *Cochrane Database of Systematic Reviews*, Issue 1.

11.(4.) Latuda Hospital Formulary Kit. Sunovion. 2011

12. (5.) FDA Center for Drug Evaluation and Research. Application Number: 200603 (lurasidone). Summary Review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/200603Orig1s000SumR.pdf. Accessed: January 3, 2012.

13.Meltzer HY, Cucchiaro J, Silva R, et al. Lurasidone in the treatment of schizophrenia: A randomized, double-blind, placebo- and olanzapine-controlled study. Am J Psychiatry. 2011; 168:957-967.

14. Nakamura M, Ogasa M, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: A double-bline, placebo-controlled trial. J Clin Psychiatry. 2009; 70:829-836.

15. Harvey PD, Ogasa M, Cucchiaro J, et al. Performance and interview-based assessments of cognitive change in a randomized, double-blind comparison of lurasidone vs. ziprasidone. Schizophrenia Research. 2011; 127:188-194.

16. Hamer A. Atypical Antipsychotic Drug Class Review Summary of Findings. The Oregon State Drug Review. 2011;1(1). Available at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/newsletter/osdr_articles/volume1/osdr_v1_i1.pdf. Accessed: January 3, 2012.

17. Hamer A. Answers to frequently asked questions about atypical antipsychotics. DUR Board Newsletter. 2010;12(3). Available at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/newsletter/articles/volume12/durv12i3.pdf. Accessed: January 3, 2012.

Oregon State University
College of Pharmacy

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

Month/Year of Review: March 2012
PDL Class: Statins & combos

Date of Last Review: February 2010
Source Document: HRC Report

Current Preferred Agents:
Atorvastatin (Lipitor®)
Simvastatin
Lovastatin
Pravastatin

Current Non-Preferred Agents:
Fluvasatin, Fluvastin XL
Rosuvastatin (Crestor®)
Lovastatin (Altoprev® ER)
Pitavastatin (Livalo®)
Niacin/Lovastatin (Advicor®)
Ezetimibe/Simvastatin (Vytorin®)

Previous Conclusions (February 2010):[1]

Adults

- Evidence supports the ability of atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin to improve coronary heart disease clinical outcomes.
- Atorvastatin, pravastatin and simvastatin have been shown to reduce strokes.
- While these drugs improve clinical outcomes the absolute risk reduction is small.
- Fair to good strength evidence demonstrates that when statins are provided in doses that are approximately equipotent, a similar percent reduction in low-density lipoprotein cholesterol can be achieved, along with comparable increases in high-density lipoprotein cholesterol.
- In adult patients with no known coronary heart disease there were still no head to head trials of statins or fixed dose combination products containing a statin (and another lipid lowering drug) for health outcomes.
- There are no clinical outcome studies for fixed dose combination products containing a statin and another lipid lowering agent.
- No evidence supports differences between Statins in adverse effects in sub-populations by race and ethnicity, age, gender or comorbidity.
- Niacin containing fixed dose combination products have a higher rate of discontinuation due to flushing.
- Studies in patients with diabetes did not have higher rates of adverse events.
- Potential for interactions with CYP 3A4 inhibitors (atorvastatin, lovastatin, and simvastatin).
- Potential for interaction with CYP 2C9 inhibitors (fluvastatin).
- Statin-fibrate combination increases risk of musculoskeletal-related adverse events compared with monotherapy.

Children

- Trials of statins (simvastatin, atorvastatin, lovastatin, pravastatin, and rosuvastatin) have been conducted primarily in children with familial hypercholesterolemia and other familial dyslipidemias in trials of less than one year duration.
- The comparison of the fixed dose combination product ezetimibe/simvastatin vs. simvastatin demonstrated a 54% reduction in low-density lipoprotein for the combination vs. 38% for simvastatin alone.
- Studies of statins in children have not been conducted with long enough follow-up to assess for outcomes related to cardiovascular mortality and morbidity.
- No trials have evaluated statins in children with diabetes or obesity.
- There is insufficient data to determine rates of adverse events or harms in children.

Reason for Review:

Since the last OR review in 2010 pitavastatin (Livalo®) was FDA approved to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol. Also,new safety alerts including new restrictions, contraindications and dose limitations for simvastatin were released by the FDA to reduce the risk of muscle injury. This update will examine the place in therapy for pitavastatin, and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

Issues:

- Is there any new comparative evidence showing a significant difference between statins in their ability to reduce the risk of nonfatal myocardial infarcation, coronary heart disease, mortality, stroke, or hospitalization?
- Is there any reliable data that pitavastatin is safer or more effective than other lipid-lowering agents?
- Is there any differences in effectiveness or harms in subpopulations between pitavastatin and other currently available statins?

Conclusions:

Reductions in cardiovascular and cerebrovascular risk are not unique to any specific statin and have been demonstrated with many of the available medications. Decreases in the risk for acute coronary syndromes, coronary procedures, strokes, and other coronary outcomes have been demonstrated. There is no comparative effectiveness data that the most recent FDA-approved agent, pitavastatin, is more effective or safer than other lipid-lowering agents for managing the risk of cardiovascular events or death in patients with hypercholesterolemia. In June 2011 the FDA issued a safety warning regarding the highest dose of simvastatin. New dosing restrictions warrant further management to avoid muscle injury associated with simvastatin 80mg and associated drug drug interaction and simvastatin 80mg should not be initiated in new patients.

Recommendations:

1. Make pitavastatin a non-preferred statin medication on the PDL due to lack of long term clinical outcomes data and no apparent advantages over currently available statins.
2. Due to the increased risk of muscle damage associated with simvastatin 80mg, recommend implementing a prospective dose limit.

Methods:

A MEDLINE Ovid search was conducted using all statins including: hyperlipidemia, hypercholesterolemia, cardiovascular disease, hydroxyl-3-methyglutaryl coenzyme A (HMG COA) reductase inhibitors, statin, Zocor, Lipitor, Mevacor, Pravachol, Lescol, Livalo, and Crestor. The search was limited to randomized controlled trials and meta-analysis, English language, and to studies conducted in humans from February 2010 to present. 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 and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The Food and Drug Administration (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.

New Systematic Reviews:

There were several systematic reviews published within this class review period that focused on various sub-populations.[2-4] See Appendix A for details of selected review abstracts.

- In July 2010, the Cochrane Collaboration[2] produced a review of evidence-based literature to assess the effectiveness and safety of statins in children with familial hypercholesterolemia. The search included randomized and controlled clinical trials up to March 11, 2010 for patients up to 18 years of age comparing a statin to a placebo or diet alone. There were 19 potentially eligible studies of which they included eight randomized placebo-controlled trials (897 participants). The authors concluded that statin treatment is an efficient lipid-lowering therapy in children with familial hypercholesterolemia. Statins reduced the mean LDL at all time points and clinical adverse events were similar in both groups. It seems to be safe in the short term but long-term safety is unknown. Children treated with statins should be carefully followed up by their pediatricians. Large long-term randomized controlled comparative trials are needed to establish the long-term safety of statins in children.

- A meta-analysis published in November 2011 by Tonelli M et al.[4] evaluated the efficacy of statins for primary prevention in people at low cardiovascular risk defined as observed an observed 10-year risk of less than 20% for cardiovascular-related death or nonfatal myocardial infarction. The review concluded that Statins were found to be efficacious in preventing death and cardiovascular morbidity in people at low cardiovascular risk based on 29 trials. Reductions in relative risk for all cause mortality were similar to those seen in patients with a history of coronary artery disease and significantly lower among patients receiving a statin than among placebo (pooled

RR 0.90, 95% confidence interval [CI] 0.84-0.97, I^2=2.0%; NNT = 239) Patients in the statin group were also significantly less likely to have a nonfatal myocardial infarcation (RR 0.64, 95% CI 0.49 to 0.84; NNT = 153) and nonfatal stroke (RR 0.81, 95% CI 0.68 to 0.96; NNT = 335). The trials were individually assessed for a risk of bias and were found to exhibit a moderate risk.

New Guidelines:

There were no new guidelines regarding statin use during this class review period. In May 2010, the Canadian Agency for Drugs and Technologies in Health (CADTH) released a guideline review on Statin administration following acute myocardial infarctions based on a limited literature search on key health technology assessments resources.[6] The overall findings include the following:

- High-dose statins, defined as those aimed at reducing LDL level below 70mg/dL, significantly reduce the risk of mortality or major cardiovascular event compared to a standard lipid lowering regimens.
- The five systemic reviews estimated the high-dose statins reduced the risk of mortality by 19-28% over less intensive lipid-lower regimens, with mean follow-up durations of one to two years.
- One systemic review estimated that the survival benefit of intensive statin treatment after an acute coronary episode was seen as early as four months after the event, reaching statistical significance at 12 months.
- One of the systemic reviews defined "intensive statin therapy" as atorvastatin 80mg/day, simvastatin 80mg/day or rosuvastatin 20-40mg/day.
- All identified guidelines recommend the administration of statins following acute coronary episodes (including MI), with most specifying long-term therapy; however, there were differences regarding recommended dosage.
- A New Zealand guideline recommends starting all patients on the equivalent of 20-40mg/day of simvastatin after MI, whereas three others recommended intensive statin therapy defined as equivalent of simvastatin 80mg/day.
- The Scottish Intercollegiate Guideline Network guideline for coronary heart disease recommends a stepwise approach: patients with cardiovascular events should be started on simvastatin 40mg/day, stepping up to atorvastatin 20, 40, and finally 80mg/day if LDL-C level targets were not met. LDL-C treatment targets also varied between guidelines, ranging from less than 70mg/dL to less than 116mg/dL.

New Randomized Controlled Trials (RCT):

The MEDLINE search retrieved 88 full citations. After a review of citations and abstracts, 27 studies were identified for assessment. After review for relevant patient populations, interventions, and outcomes, twelve new randomized control trials (RCT) were identified, excluding the study supporting approval of Livalo® (Appendix B). Eleven of these studies compared the different statins or a statin in combination with ezetimibe (Zetia®) or fenofibrate with various dosing strategies to achieve the treatment goal. None of these studies evaluated comparative effectiveness in long term cardiovascular outcomes.

New FDA Indications:
None identified.

New FDA safety alerts:

Medication	Alert Date	FDA Alert
Simvastatin (Zocor®) Ezetimibe/ Simvastatin (Vytorin®)	06/08/2011	**New restrictions, contraindications and dose limitations to reduce the risk of muscle injury:** **Revised Contraindications:** Posaconazole, gemfibrozil, cyclosporine and Danazol are added as new drugs to be contraindicated with simvastatin. **New restrictions including dose limitations:** • Do not exceed 10mg simvastatin with amiodarone, verapamil and diltiazem. (Note: These drugs are contraindicated with Simcor as Simcor is only available with 20mg and 40mg of simvastatin.) • Do not exceed 20mg simvastatin daily with amlodipine and ranolazine. • Simvastatin 80mg should only be used in patients who have been taking this dose for 12 months or more and have not experienced any muscle toxicity. It should not be prescribed to new patients. • *12/15/2011 update*: Simvastatin dose limitation has been increased from 10mg to 20mg when con-administered with amiodarone.
Ezetimibe/ Simvastatin (Vytorin®)	October 2011	**Warnings and precautions** **Myopathy/Rhabdomyolysis:** Vytorin therapy should be discontinued if marked elevated CPK levels occur or myopathy suspected. **Liver Enzymes:** There have rare post marketing reports of fatal and non-fetal hepatic failure on patients taking statins, including simvastatin. **Adverse Reactions:** **Post-marketing experience:** There have been rare post marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated... **Patient counseling information:** **Liver enzymes:** ...All patients treated with Vytorin should be advised to report promptly any symptoms that may indicate liver injury, including... **Patient package insert:** **"What are the possible side effects of Vytorin?"...:** Your doctor should do blood tests to check your liver before you start taking Vytorin and if you have any...

New FDA-approved drugs:
Pitavastatin (Livalo®)

Clinical Findings:
Pitavastatin is the 7th HMG CoA reductase inhibitor approved by the FDA. It has been available in several countries for many years and various previous studies are available describing the use of pitavastatin. However, the studies were mainly done in foreign countries (e.g., Japan, South Korea). Data cannot necessary be extrapolated to U. S population as many sub-populations and different ethnicities can respond differently to HMGs. Studies performed in the Western countries which allowed it to gain FDA approval only evaluated its efficacy based on the intermediate outcome of decreasing serum LDL. In a dose-ranging study[23] (n = 251) pitavastatin 1 mg, 2 mg and 4mg each given once daily in those with primary hyperlipidemia, led to LDL-C reductions of -32%, -36%, and -43%, respectively, at week 12. Comparative data are available with pitavastatin vs. other HMGs. Pitavastatin was compared to other statins in non-inferiority trials and found to be effective in lowering LDL. One pitavastatin vs. atorvastatin (Lipitor®) trial[23] (n = 817) found that at 12 weeks pitavastatin 2 mg QD and atorvastatin 10 mg QD, has similar LDL-C lowering capacity (-38%); pitavastatin 4 mg QD and atorvastatin 20 mg QD were also similar (LDL-C reductions of -45% and -44%, respectively). In another similar trial[20] (n = 843), the LDL-C reductions with pitavastatin 2 mg QD and simvastatin 20 mg QD (Zocor®) were similar (-39% and -35%, respectively); the respective percentages for pitavastatin 4 mg QD and simvastatin 40 mg QD were -44% and -43%. Other trials[21, 22] are available, but none of the pivotal data compared atorvastatin or simvastatin utilized the 80 mg maximum dose.

Clinical Pharmacology[23]: Pitavastatin is a HMG-CoA reductase inhibitor, which is a rate-determining enzyme involved with biosynthesis of cholesterol, in a manner of competition with the substrate so that it inhibits cholesterol synthesis in the liver. As a result, the expression of LDL-receptors followed by the uptake of LDL from blood to liver is accelerated and then the plasma TC decreases. Further, the sustained inhibition of cholesterol synthesis in the liver decreases levels of very low density lipoproteins. It is indicated for patients with primary hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total-C, LDL-C, apo B, TG, and to increase HDL-C.

Drug Safety[23]:

Contraindications: Known hypersensitivity to the components of pitavastatin. Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels. Do not administer pitavastatin to women who are pregnant or may become pregnant. Pitavastatin should not be given to nursing mothers and in those receiving cyclosporine. Pitavastatin is contraindicated in those with active liver disease.

Warnings/Precautions:

Skeletal muscle effects: Pitavastatin should be prescribed with caution in those with predisposing factors for myopathy. Such factors include advanced age (aged > 65 years), renal impairment, and inadequately treated hypothyroidism. The risk of myopathy may be increased with concurrent administration of fibrates or lipid-modifying doses of niacin. Use pitavastatin with caution in patients with impaired renal function, in elderly patients, or when used concomitantly with fibrates or lipid-modifying doses of niacin. Discontinue pitavastatin if markedly elevated creatine kinase (CK) levels occur or myopathy is diagnosed or suspected.

Liver enzyme abnormalities and monitoring: Increases in serum transaminases (asparatate aminotranferase [AST]/serum glutamic-oxaloacetic transaminase, or alanine aminotranferase [ALT]/serum glutamic-pyruvic transaminase) have been reported with HMGs, including pitavastatin. In most instances, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. In placebo-controlled, Phase 2 studies, ALT > 3 times the upper limit of normal was not observed in the placebo, pitavastatin 1 mg or Livalo 2 mg groups. One out of 202 patients (0.5%) given pitavastatin 4 mg had ALT > 3 times the upper limit of normal. Liver enzyme tests should be performed before and 12 weeks after both therapy initiation and dose increases; monitor periodically thereafter (e.g., semiannually).

Geriatrics: Of the 2,800 patients randomized to pitavastatin 1 mg to 4 mg in controlled clinical studies, 1,209 (43%) were aged > 65 years. No significant differences in efficacy or safety were noted between elderly patients and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

Clinical Efficacy:

Relevant Endpoints: LDL- lowering and HDL- raising ability

Reduction in nonfatal myocardial infarcation

Coronary Artery Disease, stroke, and mortality

Withdrawals due to adverse events;

Serious adverse events

Study Endpoints: LDL reduction

Evidence Table

Ref./Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy; Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR / NNH[3]	Quality Rating[4]; Comments
1. Ose L et al[20] MC, prospective RCT, DB, DD PG	1. Pitavastatin (P) 2mg 2. Pitavastatin (P) 4mg 3. Simvastatin (S) 20mg 4. Simvastatin (S) 40mg	Men and non-pregnant, non-lactating women aged 18-75 years of age with primary hyper-cholesterolemia or combined dyslipidemia	P2: 307 P4: 319 S20: 107 S40: 110	12 weeks	• Endpoint mean % LDL change (SD): P2 : -39 (14.6); S20: -35 (15.5) P4: -44 (14.5); S40: -42.8 (15.8 • Adjusted mean difference (95% CI): P2 vs. S20: 4.1 (0.8-7.3); p = 0.014 (noninferiority) P4 vs. S40: 1.1 (-2.1- 4.3); p=0.509 (noninferiority) • Target attained according NCEP criteria (n %): P2: 215 (70.0); S20: 69 (64.5) CI: -16.0 - 4.9; P = 0.297 (noninferiority) P4: 253 (79.6); S40: 86 (78.2) CI: -10.3 - 7.5; P = 0.762 (noninferiority) • Target attained according to EAS criteria (n %): P2: 183 (59.6); S20: 52 (48.6) CI: -22.0 to -0.1; P = 0.049 (noninferiority) P4: 239 (75.2); S40: 83 (75.5) CI: -9.0 - 9.6; P = 0.950 (noninferiority)	NA	• Any ADEs (n %): P2: 110 (35.4) S20: 36 (33.6) P4: 103 (32.2) S40: 30 (27.3) • Any serious ADEs (n %): P2: 3 (1.0) S20: 2 (1.9) P4: 4 (1.3) S40: 2 (1.8) • Any treatment-related ADEs (n %): P2: 52 (16.7) S20: 15 (14.0) P4: 42 (13.1) S40: 9 (8.2) • DC due to ADEs (n %): P2: 13 (4.2) S20: 3 (2.8) P4: 8 (2.5) S40: 1 (0.9) *CI and p values were not reported.	NA	Fair • The chosen simvastatin doses of 20mg and 40mg were based on assumption they ar expected to be equipotent and they are the most commonly prescribed. • Patients with significant CV disease such as MI, CAD or PAD, bypass graft surgery were excluded in the study. • Female is majority gender cross all study groups and concurrent HRT, oral contraceptives are allowed; however if the baseline concurrent medication uses are comparable is unknown. • The study design used 3:1 ratio, made it less powerful t detect ADEs in the simvastati groups; therefore unable to directly compare ADEs between pitavastatin and simvastatin. • Clinical outcomes such as mortality, CV mortality or CV mordality were not reported

2.Gumprech J et al[21] RCT, DB, DD PG	1. Pitavastatin (P) 4mg 2. Atorvastatin (A) 20mg 3.Atorvastatin (A) 40mg	18 -75 years with type 2 diabetes with HbA1C ≤ 7.5% on either oral or insulin therapy	Core study: P4: 279 A20: 139 Extension study: P4: 141 A20:64 A40: 7	Core study 12 weeks Extension Study: 44 weeks	• Endpoint mean % LDL change (n, mean ±SD) at week 12: P4: 274, -40.8±19.6 A20: 136, -43.3±16.4 CI: -2.33 (- 6.18 to 1.52) • Endpoint mean % LDL change n, mean ±SD at week 16: P4: 141, -43.0±18.6 A20 or A40: 71, -42.9±20.3 CI: 0.11 (-5.23 to 5.44) • Endpoint mean % LDL change n, mean ±SD (CI) at week 44: P4: 141; -41.0±19.1 A20 or A40: 71, -41.4±21.2 CI: -0.02 (-5.46 to 5.41)	NA	• Any ADEs (n %): P4: 100 (36.4) A20: 54 (39.4) • Any serious ADEs (n %): P4: 4 (1.5) A20: 4 (2.9) • DC due to ADEs (n %): P4: 7 (2.5) A20: 5 (3.6)	NA	Fair • Patients completing the core study could continue on stud drugs if lipid targets not reached by wk8 for further 4 wks (extension study); however it is not statistically powered • The atorvastatin group had a slightly longer mean duration o f dyslipidemia and more pts had a duration of DM at least 5 yrs compared with pitavastatin group. • P value was not reported for endpoint analyses. • Clinical outcomes such as mortality, CV mortality or CV mordality were not reported
3.Eriksson M[22] RCT, DB, DD PG	1. Pitavastatin (P) 4mg 2. Simvastatin (S) 40mg	18-75 y/o with ≥ of the following CV risk factors: smoking; BP ≥ 140/90 or on BP tx; HDL ≤40mg/dL; family hx of CHD in a male or female 1st degree relative < 55 or <65 respectively; age >45 in men or > 55 in women. An HDL>60 mg/dL was considered to offset 1 risk factor	P4: 233 S40: 119	12 weeks	• Endpoint mean % LDL change n, mean ±SD: P4: 233, -44.0±12.8 S40: 119, -43.8±14.4 CI: 0.31 (-2.47 to 3.09) P = 0.829 (noninferiority) • Selected 2ndary endpoint mean % LDL change n, mean ±SD: HDL-C: P4: 223, 6.8±12.6 S40: 118, 4.5±12.1 CI: -2.30 (-4.91 to 0.30); P: 0.083 TG: P4: 223, -19.8±21.3 S40: 118, -14.8±29.7 CI: 5.23 (0.15 to 10.30) P = 0.044	NA	• Any ADEs (n %): P4: 119 (51.1) S40: 60 (50.4) • Any serious ADEs (n %): P4: 4 (1.7) S40: 5 (4.29) • DC due to ADEs (n %): P4: 9 (3.9) S40: 6 (5.0) • Tx related ADEs (n %): P4: 33 (14.2) S40: 26 (21.8)		Fair • More than 2/3 of the patients in each group fell into moderate NCEP risk category • There were slightly more pts in simvastatin group on a CCB than pitavastatin • Short term study • Clinical outcomes such as mortality, CV mortality or CV mordality were not reported.

[1]**Study design abbreviations:** DB = double-blind, DD = double dummy, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR =absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

Common Drug-Related Adverse Events and Drug Interactions:[23]

Adverse events: The most frequent adverse reactions (rate ≥ 2.0% in at least one marketed dose) were myalgia, back pain, diarrhea, constipation and pain in extremity.

Drug interactions: Livalo is metabolized by glucuronidation via liver UGTs with subsequent formation of pitavastatin lactone. There is only minimal metabolism by the cytochrome P450 system (marginally metabolized by CYP2C9 and to a lesser extent by CYP2C8). Pitavastatin is associated with some drug-drug interactions or monitoring recommendations. Coadministration of cyclosporine with pitavastatin is contraindicated. Protease inhibitors, such as lopinavir, ritonavir, rifampin, and erythromycin increase the level of pitavastatin. Concurrent use of fibrates and niacin should be cautiously due to increased risk of skeletal muscle effects.

DOSE & AVAILABILITY:

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
1mg	Tablet	Oral	Once daily	CrCl 30-59: start 1mg, max. 2mg/day; CrCl 10-29: not defined.	None.	Not established	None	Pitavastatin can be taken with or without food at any time of the day. Doses greater than 4mg daily were associated with an increased risk of severe myopathy; do not exceed 4mg daily.
2mg	Tablet	Oral	Once daily					
4mg	Tablet	Oral	Once daily					

PHARMACOKINETICS

Parameter	Result
Oral Bioavailability	51% for oral solution. High fat meal (50% fat content) decreases C_{max} by 43%, not AUC.
C_{max}	1 hour
Protein Binding	99%
Elimination	15% in urine and 79% in feces
Half-Life	12 hours
Metabolism	Primarily by glucuron-idation via liver UGTs. Marginally by CYP2C9, and to a lesser extent by CYP2C8

References:

1. Health Resource Commisions-2010-02-statin.pdf. Available at http://www.oregon.gov/OHA/pharmacy/therapeutics/docs/hrc-2010-02-statin.pdf?ga=t. Accessed January 29, 2012.

2. Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Strandberg T, Tonstad S, Gylling H. Statins for children with familial hypercholesterolemia. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD006401. DOI: 10.1002/14651858.CD006401.pub2. Accessed January 29, 2012.

3. CADTH. Statin Therapy in Adults with Diabetes: Clinical Efficacy. 13 September 2011. Available at: http://www.cadth.ca/media/pdf/htis/ sept-2011/RB0419_Statins_final.pdf. Accessed January 29, 2012.

4. Marcello Tonelli et al., "Efficacy of statins for primary prevention in people at low cardiovascular risk: a meta-analysis," *CMAJ: Canadian Medical Association Journal = Journal De l'Association Medicale Canadienne* 183, no. 16 (November 8, 2011): E1189-1202.

5. Comparative Effectiveness of Rosuvastatin versus Other Statins: A Review of Clinical Effectiveness.pdf. http://www.cadth.ca/ media/pdf/this/feb-2011/L0247-Rosuvastatin_final.pdf. Accessed January 29, 2012.

6. CADTH. Statin Adminsitration Following Acute Myocardial Infarction: Guidelines. 11 May 2010. Available at: http://www.cadth.ca /media/pdf/k0185_statins_post-mi_treatment_htis1-5.pdf. Accessed January 30, 2012.

7. Bardini, Gianluca, Carlo B Giorda, Antonio E Pontiroli, Cristina Le Grazie, and Carlo M Rotella. "Ezetimibe + Simvastatin Versus Doubling the Dose of Simvastatin in High Cardiovascular Risk Diabetics: a Multicenter, Randomized Trial (the LEAD Study)." *Cardiovascular Diabetology* 9 (2010): 20.

8. Conard, S, H Bays, L A Leiter, S Bird, J Lin, M E Hanson, A Shah, and A M Tershakovec. "Ezetimibe Added to Atorvastatin Compared with Doubling the Atorvastatin Dose in Patients at High Risk for Coronary Heart Disease with Diabetes Mellitus, Metabolic Syndrome or Neither." *Diabetes, Obesity & Metabolism* 12, no. 3 (March 2010): 210-218.

9. Ur, Ehud, Anatoly Langer, Simon W Rabkin, Cristina-Dana Calciu, and Lawrence A Leiter. "Achieving Cholesterol Targets by Individualizing Starting Doses of Statin According to Baseline Low-density Lipoprotein Cholesterol and Coronary Artery Disease Risk Category: The CANadians Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (CanACTFAST) Study." *The Canadian Journal of Cardiology* 26, no. 2 (February 2010): 80-86.

10. Park, Jong-Seon, Young-Jo Kim, Ji-Yong Choi, Yoon-Nyun Kim, Teck-Jong Hong, Dong-Soo Kim, Ki-Young Kim, et al. "Comparative Study of Low Doses of Rosuvastatin and Atorvastatin on Lipid and Glycemic Control in Patients with Metabolic Syndrome and Hypercholesterolemia." *The Korean Journal of Internal Medicine* 25, no. 1 (March 2010): 27-35.

11. Yoon, Hyung Sik, Sung Ho Kim, Jeong Kyung Kim, Sang Hun Ko, Jae Ee Ko, Soo Jin Park, Moon Gi Park, Jae Hwan Lee, and Min Soo Hyon. "Comparison of Effects of Morning Versus Evening Administration of Ezetimibe/simvastatin on Serum Cholesterol in Patients with Primary Hypercholesterolemia." *The Annals of Pharmacotherapy* 45, no. 7–8 (July 2011): 841-849.

12. Averna, Maurizio, Augusto Zaninelli, Cristina Le Grazie, and Gian Franco Gensini. "Ezetimibe/simvastatin 10/20 Mg Versus Simvastatin 40 Mg in Coronary Heart Disease Patients." *Journal of Clinical Lipidology* 4, no. 4 (August 2010): 272-278.

13. Farnier, Michel, Armin Steinmetz, Kjetil Retterstøl, and Albert Császár. "Fixed-dose Combination Fenofibrate/pravastatin 160/40 Mg Versus Simvastatin 20 Mg Monotherapy in Adults with Type 2 Diabetes and Mixed Hyperlipidemia Uncontrolled with Simvastatin 20 Mg: a Double-blind, Randomized Comparative Study." *Clinical Therapeutics* 33, no. 1 (January 2011): 1-12.

14. Zieve, Franklin, Nanette K Wenger, Ori Ben-Yehuda, Christian Constance, Steven Bird, Raymond Lee, Mary E Hanson, Charlotte Jones-Burton, and Andrew M Tershakovec. "Safety and Efficacy of Ezetimibe Added to Atorvastatin Versus up Titration of Atorvastatin to 40 Mg in Patients > or = 65 Years of Age (from the ZETia in the ELDerly [ZETELD] Study)." *The American Journal of Cardiology* 105, no. 5 (March 1, 2010): 656-663.

15. Foody, JoAnne M, W Virgil Brown, Franklin Zieve, Adeniyi J Adewale, Doreen Flaim, Robert S Lowe, Charlotte Jones-Burton, and Andrew M Tershakovec. "Safety and Efficacy of Ezetimibe/simvastatin Combination Versus Atorvastatin Alone in Adults ≥65 Years of Age with Hypercholesterolemia and with or at Moderately High/high Risk for Coronary Heart Disease (the VYTELD Study)." *The American Journal of Cardiology* 106, no. 9 (November 1, 2010): 1255-1263.

16. Bulbulia, R, L Bowman, K Wallendszus, S Parish, J Armitage, R Peto, and R Collins. "Effects on 11-year Mortality and Morbidity of Lowering LDL Cholesterol with Simvastatin for About 5 Years in 20,536 High-risk Individuals: a Randomised Controlled Trial." *Lancet* 378, no. 9808 (December 10, 2011): 2013-2020.

17. McCormack, T, P Harvey, R Gaunt, V Allgar, R Chipperfield, and P Robinson. "Incremental Cholesterol Reduction with Ezetimibe/simvastatin, Atorvastatin and Rosuvastatin in UK General Practice (IN-PRACTICE): Randomised Controlled Trial of Achievement of Joint British Societies (JBS-2) Cholesterol Targets." *International Journal of Clinical Practice* 64, no. 8 (July 2010): 1052-1061.

18. Armitage, Jane, Louise Bowman, Karl Wallendszus, Richard Bulbulia, Kazem Rahimi, Richard Haynes, Sarah Parish, Richard Peto, and Rory Collins. "Intensive Lowering of LDL Cholesterol with 80 Mg Versus 20 Mg Simvastatin Daily in 12,064 Survivors of Myocardial Infarction: a Double-blind Randomised Trial." *Lancet* 376, no. 9753 (November 13, 2010): 1658-1669.

19. Budinski D, Ameson V, Hounslow N, Gratsiansky N. Pitavastatin compared with atorvastatin in primary hypercholesterolemia or combined dyslipidemia. *Clin Lipidol.* 2009;4(3):291-302.

20. Ose, Leiv, Dragos Budinski, Neil Hounslow, and Valerie Arneson. "Comparison of Pitavastatin with Simvastatin in Primary Hypercholesterolaemia or Combined Dyslipidaemia." *Current Medical Research and Opinion* 25, no. 11 (November 2009): 2755-2764.

21. Gumprecht, J, M Gosho, D Budinski, and N Hounslow. "Comparative Long-term Efficacy and Tolerability of Pitavastatin 4 Mg and Atorvastatin 20-40 Mg in Patients with Type 2 Diabetes Mellitus and Combined (mixed) Dyslipidaemia." *Diabetes, Obesity & Metabolism* 13, no. 11 (November 2011): 1047-1055.

22. Eriksson, Mats, Dragos Budinski, and Neil Hounslow. "Comparative Efficacy of Pitavastatin and Simvastatin in High-risk Patients: a Randomized Controlled Trial." *Advances in Therapy* 28, no. 9 (September 2011): 811-823.

23. Livalo® tablets [package insert]. Montgomery, AL: Kowa Pharmaceuticals (by Pantheon, Inc, Cincinnati, OH); August 2009.

Appendix A: Abstract of new Systematic Review

1. **Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Strandberg T, Tonstad S, Gylling H. Statins for children with familial hypercholesterolemia. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD006401. DOI: 10.1002/14651858.CD006401.pub2.**

Abstract

Background: Familial hypercholesterolemia is one of the most common inherited metabolic diseases; the average worldwide prevalence of heterozygous familial hypercholesterolemia is about 1 in 500. Diagnosis of familial hypercholesterolemia in children is based on two measurements of low-density lipoprotein cholesterol level above 4.0 mmol/L or a DNA-based analysis. Coronary stenosis has been detected in men with familial hypercholesterolemia as young as 17 years old and in women with familial hypercholesterolemia at 25 years of age. Atherosclerosis and its clinical complications occur prematurely, especially in men, thus lifelong hypolipidemic measures, started in childhood, are needed to reduce the risk of cardiovascular diseases. In children with familial hypercholesterolemia, diet has been the main mode of treatment. Anion exchange resins, such as cholestyramine and colestipol, have also been found to be effective but are generally considered unpalatable and therefore poorly tolerated. Since the 1990s statin trials have been carried out among children with familial hypercholesterolemia (aged 7 to 17 years), and statins reduced their serum low-density lipoprotein cholesterol levels by 23% to 40%. The safety of statins among children is not well known even though statins seem to be safe and well-tolerated in adults.

Objectives: To assess the effectiveness and safety of statins in children with familial hypercholesterolemia.

Search methods: Relevant trials were identified from the Group's Inborn Errors and Metabolism Trials Register and Medline. Date of most recent search: 11 March 2010

Selection criteria: Randomized and controlled clinical trials including participants up to 18 years old comparing a statin to placebo or to diet alone.

Data collection and analysis: Two authors independently assessed studies for inclusion and extracted data.

Main results: We found 19 potentially eligible studies of which we included eight randomized placebo-controlled trials (897 participants). Statins reduced the mean low-density lipoprotein cholesterol concentration at all time points. There was no difference between serum aspartate and alanine aminotranferase or creatine kinase concentrations at any time-point. The risks of myopathy and clinical adverse events were also similar in both groups. In one study simvastatin was shown to improve flow-mediated dilation of the brachial artery, and in another study treatment with pravastatin for two years induced a significant regression in carotid intima-media thickness.

Authors' conclusions: Statin treatment is an efficient lipid-lowering therapy in children with familial hypercholesterolemia. It seems to be safe in the short term but long-term safety is unknown. Children treated with statins should be carefully followed up by their pediatricians. Large long-term randomized controlled trials are needed to establish the long-term safety of statins in children.

2. **Efficacy of statins for primary prevention in people at low cardiovascular risk: a meta-analysis.**
Tonelli M, Lloyd A, Clement F, Conly J, Husereau D, Hemmelgarn B, Klarenbach S, McAlister FA, Wiebe N, Manns B; Alberta Kidney Disease Network. CMAJ. 2011 Nov 8;183(16):E1189-202. Epub 2011 Oct 11.

Abstract
Background: Statins were initially used to improve cardiovascular outcomes in people with established coronary artery disease, but recently their use has become more common in people at low cardiovascular risk. We did a systematic review of randomized trials to assess the efficacy and harms of statins in these individuals.

Methods: We searched MEDLINE and EMBASE (to Jan. 28, 2011), registries of health technology assessments and clinical trials, and reference lists of relevant reviews. We included trials that randomly assigned participants at low cardiovascular risk to receive a statin versus a placebo or no statin. We defined low risk as an observed 10-year risk of less than 20% for cardiovascular-related death or nonfatal myocardial infarction, but we explored other definitions in sensitivity analyses.

Results: We identified 29 eligible trials involving a total of 80,711 participants. All-cause mortality was significantly lower among patients receiving a statin than among controls (relative risk [RR] 0.90, 95% confidence interval [CI] 0.84-0.97) for trials with a 10-year risk of cardiovascular disease < 20% [primary analysis] and 0.83, 95% CI 0.73-0.94, for trials with 10-year risk < 10% [sensitivity analysis]). Patients in the statin group were also significantly less likely than controls to have nonfatal myocardial infarction (RR 0.64, 95% CI 0.49-0.84) and nonfatal stroke (RR 0.81, 95% CI 0.68-0.96). Neither metaregression nor stratified analyses suggested statistically significant differences in efficacy between high-and low-potency statins, or larger reductions in cholesterol.

Interpretation: Statins were found to be efficacious in preventing death and cardiovascular morbidity in people at low cardiovascular risk. Reductions in relative risk were similar to those seen in patients with a history of coronary artery disease.

Appendix B: Abstracts of new randomized controlled trials

1. **Ezetimibe + simvastatin versus doubling the dose of simvastatin in high cardiovascular risk diabetics: a multicenter, randomized trial (the LEAD study). Bardini G, Giorda CB, Pontiroli AE, Le Grazie C, Rotella CM. Cardiovasc Diabetol. 2010 May 21;9:20.**

Abstract

Background: The primary goal of therapy in patients with hypercholesterolemia and coronary heart disease (CHD) is reducing low-density lipoprotein cholesterol (LDL-C). This was a multicenter, randomized, double-blind, double-dummy study in patients with type 2 diabetes mellitus (T2DM).

Methods: Adult patients with T2DM and CHD (N = 93) on a stable dose of simvastatin 20 mg with LDL-C >or= 2.6 mmol/L (100 mg/dL) and <or= 4.1 mmol/L (160 mg/dL) were randomized to ezetimibe 10 mg plus simvastatin 20 mg (EZ + simva 10/20 mg) or simvastatin 40 mg for 6 weeks. Percent change in LDL-C, high-density lipoprotein cholesterol, and triglycerides was assessed.

Results: EZ + simva 10/20 mg produced a significantly greater change from treated baseline compared with simvastatin 40 mg in LDL-C (-32.2% vs -20.8%; $p < 0.01$) and total cholesterol (-20.6% vs -13.2%; $p < 0.01$). A greater proportion of patients achieved LDL-C < 2.6 mmol/L with EZ + simva 10/20 mg than with simvastatin 40 mg, but this was not statistically significant (78.4% vs 60%; odds ratio = 2.81; $p = 0.052$). Changes in high-density lipoprotein cholesterol and triglycerides were similar between treatments. Both treatments were generally well-tolerated.

Conclusions: These results demonstrate that EZ + simva 10/20 mg may provide a superior alternative for LDL-C lowering vs doubling the dose of simvastatin to 40 mg in hyperlipidemic patients with T2DM and CHD. In addition, the combination therapy may provide an alternative treatment for patients who require further LDL-C reduction than they can achieve with simvastatin 20 mg alone.

2. **Ezetimibe added to atorvastatin compared with doubling the atorvastatin dose in patients at high risk for coronary heart disease with diabetes mellitus, metabolic syndrome or neither. Conard S, Bays H, Leiter LA, Bird S, Lin J, Hanson ME, Shah A, Tershakovec AM. Diabetes Obes Metab. 2010 Mar;12(3):210-8.**

Abstract

Aim: Type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) are both associated with increased risk for atherosderotic coronary heart disease (CHD). Thus, it is useful to know the relative efficacy of lipid-altering drugs in these patient populations.

Methods: A double-blind, parallel group trial of adult patients with hypercholesterolaemia at high-CHD risk receiving atorvastatin 40 mg/day compared atorvastatin 40 mg plus ezetimibe 10 mg (ezetimibe) vs. doubling atorvastatin to 80 mg. This post hoc analysis reports lipid efficacy results in patients grouped by diagnosis of T2DM, MetS without T2DM or neither. Per cent change from baseline at week 6 was assessed for LDL-C, total cholesterol, HDL-C , non-HDL-C , Apo A-I, Apo B and triglycerides. Safety was monitored through clinical and laboratory adverse events (AEs).

Results: Compared with doubling atorvastatin, atorvastatin plus ezetimibe resulted in greater reductions in LDL-C, triglycerides, Apo B, non-HDL-C, total cholesterol and lipid ratios in the T2DM, MetS and neither groups. Treatment effects were of similar magnitude across patient groups with both treatments, except triglycerides, which were slightly greater in the T2DM and MetS groups vs. neither group. Changes in HDL-C , Apo A-I and high sensitivity C-reactive protein (hs-CRP) were comparable for both treatments in all three groups. Safety and tolerability profiles were generally similar between treatments and across patient groups, as were the incidence of liver and musde AEs.

Conclusions: Compared with doubling atorvastatin to 80 mg, addition of ezetimibe to atorvastatin 40 mg produced greater improvements in multiple lipid parameters in high-CHD risk patients with T2DM, MetS or neither, consistent with the significantly greater changes observed in the full study cohort (dinical trial # NCT00276484).

3. **Achieving cholesterol targets by individualizing starting doses of statin according to baseline low-density lipoprotein cholesterol and coronary artery disease risk category: the CANadians Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (CanACTFAST) study. Ur E, Langer A, Rabkin SW, Calciu CD, Leiter LA; CanACTFAST Study Investigators. Can J Cardiol. 2010 Feb;26(2): 80-6.**

Abstract

Background: Despite an increasing body of evidence on the benefit of lowering elevated levels of low-density lipoprotein cholesterol (LDL-C), there is still considerable concern that patients are not achieving target LDL-C levels.

Objectives: The CANadians Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (CanACTFAST) trial tested whether an algorithm-based statin dosing approach would enable patients to achieve LDL-C and total cholesterol/high-density lipoprotein cholesterol (TC/HDL-C) ratio targets quickly.

Methods: Subjects requiring statin therapy, but with an LDL-C level of 5.7 mmol/L or lower, and triglycerides of 6.8 mmol/L or lower at screening participated in the 12-week study, which had two open-label, six-week phases: a treatment period during which patients received 10 mg, 20 mg, 40 mg or 80 mg of atorvastatin based on an algorithm incorporating baseline LDL-C value and cardiovascular risk; and patients who achieved both LDL-C and TC/HDL-C ratio targets at six weeks continued on the same atorvastatin dose. Patients who did not achieve both targets received dose uptitration using a single-step titration regimen. The primary efficacy outcome was the proportion of patients achieving target LDL-C levels after 12 weeks.

Results: Of 2016 subjects screened at 88 Canadian sites, 1258 were assigned to a study drug (1101 were statin-free and 157 were statin-treated at baseline). The proportion of subjects who achieved LDL-C targets after 12 weeks of treatment was 86% (95% CI 84% to 88%) for statin-free patients and 54% (95% CI 46% to 61%) for statin-treated patients. Overall, 1003 subjects (80%; 95% CI 78% to 82%) achieved both lipid targets.

Conclusions: Algorithm-based statin dosing enables patients to achieve LDL-C and TC/HDL-C ratio targets quickly, with either no titration or a single titration.

4. **Comparative study of low doses of rosuvastatin and atorvastatin on lipid and glycemic control in patients with metabolic syndrome and hypercholesterolemia. Park JS, Kim YJ, Choi JY, Kim YN, Hong TJ, Kim DS, Kim KY, Jeong MH, Chae JK, Oh SK, Seong IW. Korean J Intern Med. 2010 Mar;25(1):27-35. Epub 2010 Feb 26.**

Abstract

Background/Aims: This multicenter, open-labeled, randomized trial was performed to compare the effects of rosuvastatin 10 mg and atorvastatin 10 mg on lipid and glycemic control in Korean patients with nondiabetic metabolic syndrome.

Methods: In total, 351 patients who met the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria for metabolic syndrome with low-density lipoprotein cholesterol (LDL-C) levels > or = 130 mg/dL were randomized to receive either rosuvastatin 10 mg (n = 173) or atorvastatin 10 mg (n = 178) for over 6 weeks.

Results: After 6 weeks of treatment, greater reductions in total cholesterol (- 35.94 +/- 11.38 vs. - 30.07 +/- 10.46%, $p < 0.001$), LDL-C (48.04 +/- 14.45 vs. 39.52 +/- 14.42%, $p < 0.001$), non-high-density lipoprotein cholesterol (- 42.93 +/- 13.15 vs. - 35.52 +/- 11.76%, $p < 0.001$), and apolipoprotein-B (- 38.7 +/- 18.85 vs. - 32.57 +/- 17.56%, $p = 0.002$) levels were observed in the rosuvastatin group as compared to the atorvastatin group. Overall, the percentage of patients attaining the NCEP ATP III goal was higher with rosuvastatin as compared to atorvastatin (87.64 vs. 69.88%, $p < 0.001$). Changes in glucose and insulin levels, and homeostasis model assessment of insulin resistance index were not significantly different between the two groups. The safety and tolerability of the two agents were similar.

Conclusions: Rosuvastatin 10 mg was more effective than atorvastatin 10 mg in achieving NCEP ATP III LDL-C goals in patients with nondiabetic metabolic syndrome, especially in those with lower NCEP ATP III target level goals.

5. **Comparison of effects of morning versus evening administration of ezetimibe/simvastatin on serum cholesterol in patients with primary hypercholesterolemia. Yoon HS, Kim SH, Kim JK, Ko SH, Ko JE, Park SJ, Park MG, Lee JH, Hyon MS. Ann Pharmacother. 2011 Sep;45(9):1172.**

Abstract

Background: Ezetimibe, a first-in-its-class inhibitor of cholesterol absorption, is an effective agent for combined use with statins to achieve low-density lipoprotein cholesterol (LDL-C) goals. Ezetimibe in combination with simvastatin as a single-tablet formulation has proven to be highly effective in reducing serum LDL-C through the dual inhibition of cholesterol absorption and biosynthesis. The effect of time of administration on efficacy of this combination therapy has not been evaluated.

Objective: To compare the effects of morning versus evening administration of ezetimibe/simvastatin on serum cholesterol levels of patients with primary hypercholesterolemia.

Methods: In this multicenter, open-label, randomized, 2-sequence, 2-period crossover study, patients with primary hypercholesterolemia randomly received ezetimibe/simvastatin 10 mg/20 mg once daily, either in the morning (within 1 hour of breakfast) or in the evening (within 1 hour of dinner) for 6 weeks.

Results: Data on 171 patients (87 in the morning administration group and 84 in the evening administration group) were analyzed. A significant reduction ($p \leq 0.001$) in the total cholesterol, triglyceride, high-density lipoprotein cholesterol, LDL-C, apo-lipoprotein B, and high-sensitivity C-reactive protein (hs-CRP) from baseline was achieved after each treatment. Noninferiority of morning administration versus evening administration was shown in the percentage reduction of the LDL-C level from baseline (difference, -1.62%; 90% CI -4.94 to 1.70). No significant difference was found between groups with respect to the percentage of changes in other lipid parameters from baseline. Furthermore, there was no significant difference in the percentage of change in hs-CRP as an antiinflammatory marker between the morning and evening administration groups. The frequency of adverse events was similar between groups.

Conclusions: Morning administration of ezetimibe/simvastatin 10 mg/20 mg is noninferior to evening administration with respect to LDL-C-lowering ability.

6. **Ezetimibe/simvastatin 10/20 mg versus simvastatin 40 mg in coronary heart disease patients. Averna M, Zaninelli A, Le Grazie C, Gensini GF. J Clin Lipidol. 2010 Jul-Aug;4(4):272-8. Epub 2010 Jun 1.**

Abstract

Background: Reducing low-density lipoprotein cholesterol (LDL-C) is the primary goal of therapy in patients with hypercholesterolemia and coronary heart disease (CHD).

Methods: This double blind placebo-controlled study enrolled patients 18 to 75 years of age with primary hypercholesterolemia and established CHD who were taking a stable daily dose of simvastatin 20 mg. Patients were randomized to ezetimibe/simvastatin 10/20 mg (eze/simva; n = 56) or simvastatin 40 mg (simva; n = 56) for 6 weeks. Percent change from baseline in LDL-C, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were assessed by use of the Student t test. The percent of patients achieving LDL-C less than 100 mg/dL (<2.6 mmol/L) or less than 80 mg/dL (<2.0 mmol/L) was analyzed via logistic regression with terms for treatment, baseline LDL-C, age, and gender.

Results: Baseline characteristics were similar between groups. Treatment with eze/simva combination resulted in significantly greater reductions in LDL-C, total cholesterol, and triglycerides versus doubling the dose of simva to 40 mg (all P < .01). Significantly more patients achieved LDL-C less than 100 mg/dL (<2.6 mmol/L) and less than 80 mg/dL (<2.0 mmol/L) with ezetimibe/simvastatin versus doubling the dose of simva to 40 mg (73.2% vs 25.0%; P < .001) for simvastatin. Changes in HDL-C were similar between treatments. Both treatments were generally well tolerated.

Conclusion: In high-risk CHD patients with hypercholesterolemia, treatment with eze/simva combination resulted in significantly greater reductions in LDL-C, total cholesterol and triglycerides, as well as greater achievement of recommended LDL-C targets, compared with doubling the simvastatin dose to 40 mg over the 6-week period. (Clinical trial registration number: NCT00423579).

7. **Fixed-dose combination fenofibrate/pravastatin 160/40 mg versus simvastatin 20 mg monotherapy in adults with type 2 diabetes and mixed hyperlipidemia uncontrolled with simvastatin 20 mg: a double-blind, randomized comparative study. Farnier M, Steinmetz A, Retterstøl K, Császár A. Clin Ther. 2011 Jan;33(1):1-12.**

Abstract

Background: Patients with type 2 diabetes mellitus and mixed hyperlipidemia have an increased cardiovascular risk and may not achieve recommended LDL-C and non-HDL-C goals on statin monotherapy. This study was designed to obtain regulatory approval of a fenofibrate/pravastatin 160/40 mg fixed-dose combination (FDC) capsule.

Objective: The aim of this study was to compare the efficacy and tolerability of this FDC and simvastatin 20 mg in patients with type 2 diabetes.

Methods: This multicenter, randomized, double-blind, parallel-arm study was conducted in patients with type 2 diabetes and mixed hyperlipidemia, without cardiovascular disease, and who were not at lipid goals with simvastatin 20 mg monotherapy. After a 6-week run-in period during which patients received simvastatin 20 mg, those with non-HDL-C concentrations ≥130 mg/dL or LDL-C concentrations ≥100 mg/dL and triglyceride concentrations 150 to 600 mg/dL were enrolled. Eligible patients were randomly assigned to receive 12-week treatment with fenofibrate/pravastatin 160/40 mg FDC or simvastatin 20 mg once daily, followed by a 12-week open-label tolerability-assessment period during which all patients received the FDC. The primary efficacy outcome was the mean percentage change in non-HDL-C after 12 weeks. Secondary efficacy outcomes included changes in other lipid and lipoprotein parameters, fibrinogen, and high-sensitivity C-reactive protein. Tolerability was assessed based on the prevalence of adverse events and abnormal laboratory data in each treatment group.

Results: A total of 291 patients were randomized to receive fenofibrate/pravastatin (n= 145) or simvastatin (n = 146). The mean (SD) age of the participants was 56.6 (8.9) years, 48.1% were men, and the body mass index was 31.3 (4.6) kg/m(2). The FDC was associated with a significantly greater reduction in non-HDL-C (primary end point) compared with simvastatin monotherapy (-12.9% [1.8] vs -6.8% [1.8]; P = 0.008). Triglyceride (-28.6% [3.7] vs +5.0% [3.6]; P < 0.001), fibrinogen (-11.5% [1.6] vs +0.3% [1.6]; P < 0.001), and HDL-C (+6.3% [1.3] vs +1.8% [1.3]; P = 0.008) concentrations also were significantly improved with the FDC compared with simvastatin monotherapy. The proportions of patients who achieved the LDL-C target (<100 mg/dL) were not significantly different between the 2 groups. The proportion of patients who achieved the combined end point of non-HDL-C <130 mg/dL and LDL-C <100 mg/dL was significantly greater with fenofibrate/pravastatin compared with simvastatin monotherapy (41 [28.5%] vs 26 [17.9%]; P < 0.05). The prevalences of patients who experienced ≥1 adverse event were not statistically different between the fenofibrate/pravastatin and simvastatin groups (17.2% vs 15.1%). However, compared with simvastatin monotherapy, the combination treatment was associated with significantly greater increases in alanine aminotransferase (+9.6% vs +1.5%; P = 0.03 between groups), creatinine (+13.7% vs +6.8%; P = 0.002 between groups), and homocysteine (+36.5% vs +1.6%; P < 0.001 between groups) concentrations.

Conclusions: In this selected population of adults with type 2 diabetes, the fenofibrate/pravastatin 160/40 mg FDC was associated with significantly greater changes from baseline in non-HDL-C, triglyceride, and HDL-C concentrations compared with simvastatin 20 mg. Both treatments were well tolerated.

8. **Safety and efficacy of ezetimibe added to atorvastatin versus up titration of atorvastatin to 40 mg in Patients > or = 65 years of age (from the ZETia in the ELDerly [ZETELD] study). Zieve F, Wenger NK, Ben-Yehuda O, Constance C, Bird S, Lee R, Hanson ME, Jones-Burton C, Tershakovec AM. Am J Cardiol. 2010 Mar 1;105(5):656-63. Epub 2009 Dec 24.**

Abstract

Few clinical studies have focused on the efficacy of lipid-lowering therapies in patients > or = 65 years of age. The percentage of change from baseline in low-density lipoprotein (LDL) cholesterol and the percentage of patients achieving prespecified LDL cholesterol levels after 12 weeks of ezetimibe 10 mg plus atorvastatin versus up titration of atorvastatin were assessed in subjects > or = 65 years old with hyperlipidemia and at high risk of coronary heart disease. After stabilization of atorvastatin 10-mg therapy, 1,053 patients, > or = 65 years old, at high risk of coronary heart disease, with and without atherosclerotic vascular disease and a LDL cholesterol level that was not <70 or <100 mg/dl, respectively, were randomized to receive ezetimibe added to atorvastatin 10 mg for 12 weeks versus up titration to atorvastatin 20 mg for 6 weeks followed by up titration to atorvastatin 40 mg for an additional 6 weeks. Ezetimibe added to

atorvastatin 10 mg resulted in significantly greater changes at week 6 in LDL cholesterol (p <0.001), significantly more patients with atherosclerotic vascular disease achieving a LDL cholesterol level of <70 mg/dl (p <0.001), and significantly more patients without atherosclerotic vascular disease achieving a LDL cholesterol level of <100 mg/dl (p <0.001) at weeks 6 and 12 compared to atorvastatin 20 mg or atorvastatin 40 mg. In addition, ezetimibe plus atorvastatin 10 mg resulted in significantly greater changes at week 6 in total cholesterol, triglycerides, non-high-density lipoprotein (HDL) cholesterol, apolipoprotein B (all p <0.001), and HDL cholesterol (p = 0.021) compared with atorvastatin 20 mg and significantly greater changes at week 12 in LDL cholesterol, non-HDL cholesterol, apolipoprotein A-I (p = 0.001), total cholesterol, apolipoprotein B (p <0.030), and HDL cholesterol (p <0.001) compared with atorvastatin 40 mg. Both treatments were generally well tolerated, with comparable safety profiles. In conclusion, adding ezetimibe to atorvastatin 10 mg produced significantly greater favorable changes in most lipids at 6 and 12 weeks and significantly greater attainment of prespecified LDL cholesterol levels than doubling or quadrupling the atorvastatin dose in patients > or =65 years old at high risk for coronary heart disease.

9. **Safety and efficacy of ezetimibe/simvastatin combination versus atorvastatin alone in adults ≥65 years of age with hypercholesterolemia and with or at moderately high/high risk for coronary heart disease (the VYTELD study). Foody JM, Brown WV, Zieve F, Adewale AJ, Flaim D, Lowe RS, Jones-Burton C, Tershakovec AM. Am J Cardiol. 2010 Nov 1;106(9):1255-63.**

Abstract

Higher than 80% of coronary heart disease-related mortality occurs in patients ≥65 years of age. Guidelines recommend low-density lipoprotein (LDL) cholesterol targets for these at-risk patients; however, few clinical studies have evaluated lipid-lowering strategies specifically in older adults. This multicenter, 12-week, randomized, double-blind, parallel-group trial evaluated the efficacy and safety of the usual starting dose of ezetimibe/simvastatin (10/20 mg) versus atorvastatin 10 or 20 mg and the next higher dose of ezetimibe/simvastatin (10/40 mg) versus atorvastatin 40 mg in 1,289 hypercholesterolemic patients ≥65 years of age with or without cardiovascular disease. Patients randomized to ezetimibe/simvastatin had greater percent decreases in LDL cholesterol (-54.2% for 10/20 mg vs -39.5% and -46.6% for atorvastatin 10 and 20 mg, respectively; -59.1% for 10/40 mg vs -50.8% for atorvastatin 40 mg; p <0.001 for all comparisons) and the number attaining LDL cholesterol <70 mg/dl (51.3% for 10/20 mg, 68.2% for 10/40 mg) and <100 mg/dl (83.6% for 10/20 mg; 90.3% for 10/40 mg) was significantly larger compared to those receiving atorvastatin for all prespecified dose comparisons (p <0.05 to <0.001). A significantly larger percentage of high-risk patients achieved LDL cholesterol <70 mg/dl on ezetimibe/simvastatin 10/20 mg (54.3%) versus atorvastatin 10 mg (10.9%, p <0.001) or 20 mg (28.9%, p <0.001) and ezetimibe/simvastatin 10/40 mg (69.2%) versus atorvastatin 40 mg (38.2%, p <0.001), and a significantly larger percentage of intermediate-risk patients achieved LDL cholesterol <100 mg/dl on ezetimibe/simvastatin 10/20 mg (82.1%) versus atorvastatin 10 mg (59.3%, p <0.05). Improvements in non-high-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and lipoprotein ratios were significantly greater with ezetimibe/simvastatin than atorvastatin for all comparisons (p <0.01 to <0.001). High-density lipoprotein cholesterol and triglyceride results were variable. All treatments were generally well tolerated. In conclusion, ezetimibe/simvastatin provided significantly greater improvements in key lipid parameters and higher attainment of LDL cholesterol targets than atorvastatin, with comparable tolerability.

10. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. Heart Protection Study Collaborative Group, Bulbulia R, Bowman L, Wallendszus K, Parish S, Armitage J, Peto R, Collins R. Lancet. 2011 Dec 10;378(9808):2013-20. Epub 2011 Nov 22.

Abstract

Background: Findings of large randomised trials have shown that lowering LDL cholesterol with statins reduces vascular morbidity and mortality rapidly, but limited evidence exists about the long-term efficacy and safety of statin treatment. The aim of the extended follow-up of the Heart Protection Study (HPS) is to assess long-term efficacy and safety of lowering LDL cholesterol with statins, and here we report cause-specific mortality and major morbidity in the in-trial and post-trial periods.

Methods: 20,536 patients at high risk of vascular and non-vascular outcomes were allocated either 40 mg simvastatin daily or placebo, using minimised randomisation. Mean in-trial follow-up was 5·3 years (SD 1·2), and post-trial follow-up of surviving patients yielded a mean total duration of 11·0 years (SD 0·6). The primary outcome of the long-term follow-up of HPS was first post-randomisation major vascular event, and analysis was by intention to treat. This trial is registered with ISRCTN, number 48489393.

Findings: During the in-trial period, allocation to simvastatin yielded an average reduction in LDL cholesterol of 1·0 mmol/L and a proportional decrease in major vascular events of 23% (95% CI 19-28; p<0·0001), with significant divergence each year after the first. During the post-trial period (when statin use and lipid concentrations were similar in both groups), no further significant reductions were noted in either major vascular events (risk ratio [RR] 0·95 [0·89-1·02]) or vascular mortality (0·98 [0·90-1·07]). During the combined in-trial and post-trial periods, no significant differences were recorded in cancer incidence at all sites (0·98 [0·92-1·05]) or any particular site, or in mortality attributed to cancer (1·01 [0·92-1·11]) or to non-vascular causes (0·96 [0·89-1·03]).

Interpretation: More prolonged LDL-lowering statin treatment produces larger absolute reductions in vascular events. Moreover, even after study treatment stopped in HPS, benefits persisted for at least 5 years without any evidence of emerging hazards. These findings provide further support for the prompt initiation and long-term continuation of statin treatment.

11. **Incremental cholesterol reduction with ezetimibe/simvastatin, atorvastatin and rosuvastatin in UK General Practice (IN-PRACTICE): randomised controlled trial of achievement of Joint British Societies (JBS-2) cholesterol targets. McCormack T, Harvey P, Gaunt R, Allgar V, Chipperfield R, Robinson P; IN-PRACTICE study. Int J Clin Pract. 2010 Jul;64(8):1052-61. Epub 2010 May 12.**

Abstract

Aim: The aim of this study was to compare ezetimibe/simvastatin combination therapy with intensified statin monotherapy as alternative treatment strategies to achieve the Joint British Societies (JBS)-2 and National Institute for Health and Clinical Excellence low-density-lipoprotein cholesterol (LDL-C) target of < 2 mmol/l for secondary prevention or JBS-2 LDL-C target of < 2 mmol/l for primary prevention in high-risk patients who have failed to reach target with simvastatin 40 mg.

Methods: This is a prospective, double-blind study conducted in 34 UK primary care centres; 1748 patients with established cardiovascular disease (CVD), diabetes or high risk of CVD who had been taking simvastatin 40 mg for > or = 6 weeks were screened and 786 (45%) with fasting LDL-C > or = 2.0 mmol/l (and < 4.2 mmol/l) at screening and after a further 6-week run-in period on simvastatin 40 mg were randomised to ezetimibe/simvastatin 10/40 mg (as a combination tablet; n = 261), atorvastatin 40 mg (n = 263) or rosuvastatin 5 mg (n = 73) or 10 mg (n = 189) once daily for 6 weeks. Rosuvastatin dose was based on UK prescribing instructions. The primary outcome measure was the proportion of patients achieving LDL-C < 2 mmol/l at the end of the study.

Results: The percentage of patients (adjusted for baseline differences) achieving LDL-C < 2 mmol/l was 69.4% with ezetimibe/simvastatin 10/40 mg, compared with 33.5% for atorvastatin 40 mg [odds ratio 4.5 (95% CI: 3.0-6.8); p < 0.001] and 14.3% for rosuvastatin 5 or 10 mg [odds ratio 13.6 (95% CI: 8.6-21.6); p < 0.001]. Similar results were observed for achievement of total cholesterol < 4.0 mmol/l. All study treatments were well tolerated.

Conclusion: Approximately 45% of patients screened had not achieved LDL-C < 2 mmol/l after > or = 12 weeks of treatment with simvastatin 40 mg. In this group, treatment with ezetimibe/simvastatin 10/40 mg achieved target LDL-C levels in a significantly higher proportion of patients during a 6-week period than switching to either atorvastatin 40 mg or rosuvastatin 5-10 mg.

12. **Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage J, Bowman L, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, Parish S, Peto R, Collins R. Lancet. 2010 Nov 13;376(9753):1658-69. Epub 2010 Nov 8.**

Abstract

Background: Lowering of LDL cholesterol reduces major vascular events, but whether more intensive therapy safely produces extra benefits is uncertain. We aimed to establish efficacy and safety of more intensive statin treatment in patients at high cardiovascular risk.

Methods: We undertook a double-blind randomised trial in 12,064 men and women aged 18-80 years with a history of myocardial infarction. Participants were either currently on or had clear indication for statin therapy, and had a total cholesterol concentration of at least 3·5 mmol/L if already on a statin or 4·5 mmol/L if not. Randomisation to either 80 mg or 20 mg simvastatin daily was done centrally using a minimisation algorithm. Participants were assessed at 2, 4, 8, and 12 months after randomisation and then every 6 months until final follow-up. The primary endpoint was major vascular events, defined as coronary death, myocardial infarction, stroke, or arterial revascularisation. Analysis was by intention to treat. This study is registered, number ISRCTN74348595.

Findings: 6031 participants were allocated 80 mg simvastatin daily, and 6033 allocated 20 mg simvastatin daily. During a mean follow-up of 6·7 (SD 1·5) years, allocation to 80 mg simvastatin produced an average 0·35 (SE 0·01) mmol/L greater reduction in LDL cholesterol compared with allocation to 20 mg. Major vascular events occurred in 1477 (24·5%) participants allocated 80 mg simvastatin versus 1553 (25·7%) of those allocated 20 mg, corresponding to a 6% proportional reduction (risk ratio 0·94, 95% CI 0·88-1·01; p=0·10). There were no apparent differences in numbers of haemorrhagic strokes (24 [0·4%] vs 25 [0·4%]) or deaths attributed to vascular (565 [9·4%] vs 572 [9·5%]) or non-vascular (399 [6·6%] vs 398 [6·6%]) causes. Compared with two (0·03%) cases of myopathy in patients taking 20 mg simvastatin daily, there were 53 (0·9%) cases in the 80 mg group.

Interpretation: The 6% (SE 3·5%) reduction in major vascular events with a further 0·35 mmol/L reduction in LDL cholesterol in our trial is consistent with previous trials. Myopathy was increased with 80 mg simvastatin daily, but intensive lowering of LDL cholesterol can be achieved safely with other regimens.

Oregon State University
College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | Fax 503-947-1119

Month/Year of Review: March 2012
End date of literature search: January 2012
Generic Name: Icatibant
Brand Name (Manufacturer): Firazyr (Shire)
PDL Class: None
Dossier received: Yes
Comparator Therapies:
C1 esterase inhibitor replacement (Berinert) –Treatment of acute abdominal, facial, or laryngeal attacks in adult and adolescent patients.
Ecallantide (Kalbitor) –Treatment of acute attacks of hereditary angioedema in patients 16 years of age and older.

FDA Approved Indications: [1] Treatment of acute attacks of hereditary angioedema in adults 18 years of age or older.

Summary:[4-7]
Icatibant (Firazyr) is the first available self-administered treatment for acute attacks of hereditary angioedema (HAE) in adults.

Efficacy: Four phase 3 clinical trials have been conducted with icatibant. FAST-1 and FAST-2 were multicenter, double-blind, randomized controlled trials, which compared icatibant to placebo and tranexamic acid, respectively. Based on potential design flaws, data from these trials was insufficient to warrant FDA approval, so FAST-3, a randomized, placebo controlled trial was conducted to further evaluate the efficacy and safety of icatibant. In FAST-3, treatment with icatibant resulted in a statistically significant reduction in time to a 50% decrease in symptoms when compared to placebo, and validated the efficacy of icatibant seen in previous phase 3 trials. All studies used primary endpoints that evaluated the time to a pre-specified reduction in symptoms; there are no studies available that evaluate the time to complete resolution of symptoms as a primary outcome.

Safety: Icatibant has a mild safety profile, with no reports of anaphylaxis as seen with ecallantide (Kalbitor®); the vast majority of icatibant-treated patients experienced injection-site reactions which were self-limiting. Icatibant has the advantage over alternative medications for acute HAE, in that it is a subcutaneous injection that can be self-administered, the safety of which was supported in the open-label FAST-4 trial. Across all phase 3 trials, 1,076 icatibant doses were given to 225 patients for 987 attacks.

Conclusion:
- There is moderate quality evidence that icatibant is superior to placebo in reducing time to onset of symptom relief in patients having acute attacks of HAE.
- There is moderate quality of evidence that icatibant is relatively safe with the most common adverse event being injection site reactions.

Generic Name: Icatibant Review Date:

Recommendations:
Recommend including with utilization restrictions including dose limits, age restrictions to patients > 17 y/o, and documented diagnosis of Hereditary Angioedema.

Background/current landscape:

Hereditary Angioedema (HAE) is a rare autosomal dominant disorder that affects an estimated 1 in 10,000 to 50,000 individuals worldwide. Patients with HAE lack functional C1 esterase inhibitor, which can lead to elevated bradykinin, a key mediator of symptoms in hereditary angioedema. There are two major types of HAE. Type 1 is caused by decreased production of C1-INH and is the cause of 80-85% of all HAE cases. Type II HAE is caused by the functional deficiency of C1-INH.[7] HAE manifests as unpredictable episodes of subcutaneous or submucosal swelling of various organs. These often occur in the gastrointestinal tract, the skin, or more seriously in the upper respiratory tract. Attacks are unpredictable in their frequency; they may be induced by stress, but often times have no identifiable trigger. Attacks generally last 48-96 hours, but may last for more than a week, and are potentially life-threatening.[5]

There are several treatment options available for patients who need long-term HAE prophylaxis.[8] The antifibrinolytic agent, tranexamic acid, has been used for this purpose, but is not used in the United States due to the potential carcinogenic effects and limited supporting evidence. Several androgenic steroids have been used for chronic treatment of HAE, however Danazol is the only agent that is approved and marketed in the US for preventing attacks of angioedema. More recently, Cinryze, a human plasma-derived C1-inhibitor was approved for routine prophylaxis of HAE attacks, but can be very costly at $5,016.89 per dose and is typically administered by IV infusion every 3 or 4 days.[7-9]

In 2009, two different agents were approved for the acute treatment of HAE. Kalbitor (ecallantide), an inhibitor of human plasma kallikrein, carries a Boxed Warning for serious hypersensitivity reactions, therefore the SQ injections must be administered by a health care professional.[3] Berinert, a C1 esterase inhibitor, was originally approved only for the treatment of acute abdominal or facial attacks of HAE in adult and adolescent patients. In late 2011, the FDA approved a label expansion that includes an indication to treat life-threatening laryngeal HAE attacks as well as self-administration of the IV infusion after proper training.[2]

Icatibant is the third agent approved for the acute treatment of HAE with a unique mechanism of action. FDA approval was originally denied after the submission of two phase 3 studies (FAST-1 and FAST-2) as efficacy data was not convincing and the use of tranexamic acid as a comparator in one of the trials was potentially inappropriate. FDA approval was granted after the completion of a third phase 3 (FAST-3) study and an open-label trial [FAST-4 or EASSI (Evaluation of the Safety of Subcutaneous Icatibant)] intended to evaluate the safety of self-administered injections.[6,9]

CLINICAL PHARMACOLOGY:[1]

HAE is caused by the absence of dysfunction of C1-esterase inhibitor (C1-INH), which regulates the production of bradykinin through a proteolytic cascade. Icatibant is a bradykinin B2 receptor antagonist and alleviates HAE symptoms of excess bradykinin (swelling, inflammation, and pain) by preventing the binding of bradykinin to this receptor.

Generic Name: Icatibant

Review Date:

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1. Total symptom resolution
2. Time to symptom resolution

Primary Endpoints:

1. Time to onset of symptom relief based on a pre-specified reduction in Visual Assessment Scores (VAS).

   FAST-1 and FAST-2: VAS score based on primary symptom (0-100mm)

   FAST-3: Composite VAS score based on 3 or 5 (for laryngeal attacks) symptoms

Evidence Table

<table>
<tr><th>Ref./ Study Design[1]</th><th>Drug Regimens</th><th>Patient Population</th><th>N</th><th>Efficacy Results (CI, p-values)</th><th>Safety Results^ (CI, p-values)</th><th>Quality Rating[4]; Comments</th></tr>
<tr>
<td>Ref. 4 (FAST-1)

Multicenter, DB, RCT, PC with open-label extension</td>
<td>1. Single 30 mg SQ dose of icatibant . Patients who required multiple doses were switched to the open-label extension (n=27)

2. Placebo (n=29)</td>
<td>Diagnosis of Type I or II HAE with a confirmed C1-INH deficiency.

Patients with angioedema that was not hereditary angioedema, serious concomitant illness and pregnancy or lactation were excluded.

Cutaneous Attacks:
Icatibant: 14
Placebo: 13

Abdominal Attacks:
Icatibant: 13
Placebo:16</td>
<td>56</td>
<td>
<table>
<tr><th></th><th>Icatibant Median (IQR)</th><th>Placebo) Median (IQR)</th><th>P value</th></tr>
<tr><td>Time to clinically significant relief of the index symptom (h)</td><td>2.5 (1.1-6.0)</td><td>4.6 (1.8-10.2)</td><td>0.14</td></tr>
<tr><td colspan="4">Secondary Endpoints</td></tr>
<tr><td>Time to first symptom improvement according to patient (h)</td><td>0.8 (0.5-2.0)</td><td>16.9 (3.2-NA)</td><td><0.001</td></tr>
<tr><td>Time to first symptom improvement according to investigator (h)</td><td>1.0 (0.8-2.0)</td><td>5.7 (2.0-11.2)</td><td><0.001</td></tr>
<tr><td>Time to almost complete symptom relief (h)</td><td>8.5 (2.5-31.5)</td><td>19.4 (10.2-55.7)</td><td>0.08</td></tr>
<tr><td>Clinically significant relief of the index symptom at 4 hr after start of study drug - % (95% CI)</td><td>67 (46-84)</td><td>46 (28-66)</td><td>0.18</td></tr>
<tr><td colspan="4">Use of Rescue Medications [no. (%)]</td></tr>
<tr><td>After 12 hours</td><td>3 (11)</td><td>13 (45)</td><td>NA</td></tr>
<tr><td>After 48 hours</td><td>6 (22)</td><td>15 (52)</td><td>NA</td></tr>
</table>
• NA denotes not available, CI confidence interval, IQR interquartile range

*ARR/NNT not available with data
</td>
<td>Any Adverse Event:
Icatibant: 12(44%)
Placebo: 19(66%)

Drug-related adverse event:
Icatibant: 4(15%)
Placebo: 1(3%)

Serious adverse event:
Icatibant: 0
Placebo: 0

Injection-site reaction:
Icatibant: 26(96%)
Placebo: 8(28%)</td>
<td>Fair

The author suggests that the definition of the primary outcome and the use of rescue medications in the placebo group may have contributed to the non-significant result.

The author indicates the study may have been underpowered to detect a clinically significant endpoint.

The majority of the patients experienced injection site reactions, which may have affected blinding.

Validity of the primary endpoint has not been studied. It is difficult to gauge what is considered clinically significant using this endpoint.

Patients with laryngeal attacks automatically entered into the open-label extension and were not randomized for analysis.</td>
</tr>
</table>

Generic Name: Icatibant

Review Date:

Ref 4. (FAST-2) Multicenter, DB, RCT, double-dummy design with open-label extension	1. Single 30 mg SQ dose of icatibant . Patients who required multiple doses were switched to the open-label extension (n=36) 2. Tranexamic acid (TA): 1 gram three times daily over two days (n=38)	Diagnosis of Type I or II HAE with a confirmed C1-INH deficiency. Patients with angioedema that was not hereditary angioedema, serious concomitant illness and pregnancy or lactation were excluded. Cutaneous Attacks: Icatibant: 24 TA: 23 Abdominal Attacks: Icatibant: 12 TA:15	74		Icatibant Median (IQR)	Placebo) Median (IQR)	P value
				Time to clinically significant relief of the index symptom (h)	2.0 (1.0-3.5)	12.0 (3.5-25.4)	<0.001
				Secondary Endpoints			
				Time to first symptom improvement according to patient (h)	0.8 (0.4-1.4)	7.9 (1.1-NA)	<0.001
				Time to first symptom improvement according to investigator (h)	1.5 (0.7-3.0)	6.9 (4.0-13.8)	<0.001
				Time to almost complete symptom relief (h)	10.0 (2.8-23.2)	51.0 (12.0-79.5)	<0.001
				Clinically significant relief of the index symptom at 4 hr after start of study drug - % (95% CI)	80 (63-92)	31 (16-48)	<0.001
				Use of Rescue Medications [no. (%)]			
				After 12 hours	0 (0)	5 (13)	NA
				After 48 hours	6 (17)	11 (29)	NA
				• NA denotes not available, CI confidence interval, IQR interquartile range *ARR/NNT not available with data			
Any Adverse Event: Icatibant: 19(53%) TA: 16(42%) Drug-related adverse event: Icatibant: 5(14%) TA: 4(11%) Serious adverse event: Icatibant: 4(11%) TA: 1(3%) Injection-site reaction: Icatibant: 35(97%) TA: 10(26%)	Poor The majority of the patients experienced injection site reactions, which may have affected blinding. TA is associated with nausea, vomiting, diarrhea, and color vision disturbance which may have affected blinding. Validity of the primary endpoint has not been studied. It is difficult to gauge what is considered clinically significant using this endpoint. This study used tranexamic acid as the active comparator. This is not an accepted treatment for acute HAE. This comparator choice partially contributed to the FDA's initial rejection for approval. Patients with laryngeal attacks automatically entered into the open-label extension and were no randomized for analysis.						

Generic Name: Icatibant

Review Date:

<table>
<tr>
<td>Ref 5.(FAST-3)

Multicenter, DB, RCT, PC with open-label extension</td>
<td>Patients with abdominal or cutaneous attacks:

1. Single 30 mg SQ dose of icatibant (n=43)

2. Placebo (n=45)

Patients with laryngeal attacks:
Mild to Moderate (blinded):
1. Open-label icatibant (blinded) (n=3)
2. Placebo (n=2)

Severe: Open-label icatibant (n=5)</td>
<td>Diagnosis of Type I or II HAE with a confirmed C1-INH deficiency.

Subjects presenting within 12 hours of onset with cutaneous, abdominal or mild/moderate laryngeal attacks were randomized 1:1 to icatibant or placebo. Subjects with Severe symptoms were randomized to open-label icatibant.</td>
<td>93</td>
<td>
<table>
<tr><td colspan="4">Non-laryngeal ITT Population</td></tr>
<tr><td></td><td>Icatibant</td><td>Placebo</td><td>P value</td></tr>
<tr><td>Time to onset of symptom relief (h) (50% reduction from pretreatment VAS-3 score)</td><td>2.0 (1.5, 3.0)</td><td>19.8 (6.1,26.3)</td><td><0.001</td></tr>
<tr><td>Time to onset of primary symptom relief (h) (a reduction for single primary VAS symptom)</td><td>1.5 (1.0, 2.0)</td><td>18.5 (3.6, 23.9)</td><td><0.001</td></tr>
<tr><td>Time to subject-assessed initial symptom relief, (h)</td><td>0.8 (0.5,1.0)</td><td>3.5 (1.9,5.4)</td><td><0.001</td></tr>
<tr><td>Time to investigator-assessed initial symptom relief (h)</td><td>0.8 (0.6,1.3)</td><td>3.4 (2.6,6.0)</td><td><0.001</td></tr>
<tr><td>Time to almost complete symptom relief (h) (Defined as the earliest of 3 consecutive VAS <10 mm)</td><td>8.0 (5.0,42.5)</td><td>36.0 (29.0,50.9)</td><td>0.012</td></tr>
<tr><td>Use of rescue medications at any time during the attack and up to 5 days post-treatment</td><td>3 (7%)</td><td>18 (40%)</td><td>NA</td></tr>
<tr><td colspan="4">Laryngeal ITT Population</td></tr>
<tr><td></td><td>Icatibant (blinded)</td><td>Placebo (blinded)</td><td>Icatibant (OLE)</td></tr>
<tr><td>Time to onset of primary symptom relief (h) (50% reduction from VAS-5 score)</td><td>2.5 (1.3, 3.0)</td><td>3.2 (1.0, 5.4)</td><td>2.3(1.5,4.0)</td></tr>
<tr><td>Time to onset of primary symptom release (h)</td><td>2.5 (1.3, 3.0)</td><td>2.7 (1.0, 4.4)</td><td>2.3(1.7,4.0)</td></tr>
<tr><td>Time to subject-assessed initial symptom relief, (h)</td><td>1.0 (0.6, 2.5)</td><td>2.1 (0.5, 3.9)</td><td>0.2(0.1,-)</td></tr>
<tr><td>Time to investigator-assessed initial symptom relief (h)</td><td>1.0 (0.6, 2.5)</td><td>2.2 (0.5, 3.9)</td><td>0.5(0.2,1.5)</td></tr>
<tr><td>Time to almost complete symptom relief (h) (Defined as the earliest of 3 consecutive VAS <10 mm)</td><td>6.0 (3.5, 44.8)</td><td>4.0 (1.5, 6.4)</td><td>4.5(2.2,47.5)</td></tr>
<tr><td>Use of rescue medications at any time during the attack and up to 5 days post-treatment</td><td>1(33%)</td><td>1(50%)</td><td>0</td></tr>
</table>
</td>
<td>Subjects with ≥1 drug-related AE
Icatibant: 5 (10.9)
Placebo: 3 (6.5)

Subjects with ≥1 serious AE
Icatibant: 0
Placebo: 3 (6.5)

Subjects who died because of an AE
Icatibant: 0
Placebo: 1 (2.2)

Subjects with ≥1 therapy-related sever AE
Icatibant: 2 (4.4)
Placebo: 0

There were no AE in the open-label icatibant patients (n=6)</td>
<td>Good

The study used a different primary outcome than the previous two studies, accounting for reduction in 3-5 symptoms depending on type of attack.

All patients treated with icatibant experienced an injection site reaction which may have affected blinding.

Small sample sizes of patients experiencing laryngeal attacks preclude a statistical analysis. However results from the laryngeal ITT population are consistent with the non-laryngeal population.

Results from this study are consistent with results from previous phase 3 studies.</td>
</tr>
</table>

Generic Name: Icatibant

Review Date:

Ref 6,7.(FAST-4 or EASSI) Multicenter, self-administration trial, open label Study is not yet published.	1. Self-administration of one 30 mg SQ dose for an attack. Health care professionals administered second and third doses if needed.	Patients who had a history of at least 1 dose of icatibant that was administered by a health care professional and had received proper training on subcutaneous injections.	56	<table><tr><th>Efficacy Results</th><th>Patients administering icatibant</th></tr><tr><td>Time (h) to 50% reduction in symptoms [median (CI)]</td><td>2.6 (2.0-4.0)</td></tr><tr><td>Time (h) to onset of primary symptom relief [median (CI)]</td><td>2.0 (1.3-2.0)</td></tr><tr><td>Resolution of symptoms at 48 hours post dose per patient [# of patients (%)]</td><td>48 (86%)</td></tr><tr><td>Self administration preferable to clinic administration, per patient [# of pts (%)]</td><td>53 (95%)</td></tr><tr><td>Easy or very easy to self-inject, per patient [# of pts (%)]</td><td>49 (88%)</td></tr><tr><td>Convenient or very convenient to carry medication for self-injection, per patient (# of pts (%)]</td><td>46 (82%)</td></tr><tr><td>Rescue medication use [# of pts (%)]</td><td>11 (20%)</td></tr></table>	Any Adverse event: 18 (32%) Severe adverse event: 4 (7%) Worsening or new HAE attack 13 (23%) 2 patients required an additional dose of icatibant for an acute attack 95% experienced an injection site reaction	Fair Trial was done to evaluate safety of self-injection. From a safety standpoint the trial had a good study design. Despite the open-label study design and lack of a comparator, efficacy endpoints are consistent with those seen in previous phase 3 studies.

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
[5]**Study design abbreviations:** VAS = visual analogue scale

Clinical Findings –

Data from the multicenter, randomized, double-blind, controlled FAST-1 and FAST-2 trials were published simultaneously in 2010. The FAST-1 study compared icatibant to placebo, while FAST-2 compared icatibant to tranexamic acid; both looked at the primary endpoint of time to onset of clinically significant relief of the primary (or index) symptom. Patients who had a severe HAE attack that required more than one study dose were moved to open-label extension studies. All patients who had potentially life-threatening laryngeal angioedema were placed in the open-label studies, excluding them from randomized trials.

FAST-1 randomized 56 subjects and found that a single 30 mg icatibant dose showed index symptom relief in 2.5 hours compared to 4.6 hours with placebo ($p=0.14$). Although icatibant was not statistically different from placebo for the primary endpoint, it was statistically superior to placebo for secondary efficacy endpoints including time to first symptom improvement (evaluated by patient and also by investigator), and time to complete relief of symptoms. Complete relief of symptoms was defined as a score of 0-10mm on the VAS at three consecutive time points. The author notes that there was numerically higher use of rescue medications (significance not reported) in patients in the placebo group which may have contributed to the non-significant difference between icatibant and placebo for the primary endpoint. Furthermore, the definition of the primary endpoint may have also contributed to the non-significant outcome, as post-hoc analyses indicate that the time to symptom improvement is statistically different when a composite score of three symptoms are evaluated.

FAST-2 randomized 74 subjects to either one 30 mg dose of icatibant or tranexamic acid 1 gram three times daily for two days. Subjects receiving icatibant found primary symptom relief in 2 hours versus 12 hours with tranexamic acid, a difference that was statistically significant ($p<0.001$). Similar to FAST-1, icatibant was statistically superior for all secondary endpoints, when compared to tranexamic acid. The validity of these results is compromised by the choice of the active comparator, as tranexamic acid is not approved for use in acute HAE attacks due to lack of studies showing benefit. In both FAST-1 and FAST-2, many patients receiving icatibant may have experienced injection-site reactions, which could potentially affect the blinding of the studies. Patients with laryngeal attacks were automatically entered into the open-label extension phase and were therefore not randomized for analysis. Impact of icatibant in this patient population cannot be assessed using these trials.

The most common adverse events seen in FAST-1 and FAST-2 were recurrent or worsening angioedema and injection site reactions. In the FAST-1 trial 5 patients had side effects attributed to the study drug which were injection-site pain, abnormal results on a liver-function test, dizziness, and nasal congestion. In the FAST-2 trial, 5 patients experienced drug-related adverse events which consisted of abdominal pain, nausea, and worsening of an acute attack of angioedema, asthenia, injection-site reactions, and rash. None of the serious adverse events in FAST-2 were attributed to the study drug. No patient discontinued either study due to an adverse event.

To address the insufficient efficacy data seen in the first 2 trials, a third study was conducted. FAST-3 was a randomized, multicenter, double-blind, placebo controlled trial which compared a single 30 mg dose of icatibant to placebo in patients with cutaneous, abdominal and laryngeal attacks. The study used a different primary outcome than previous trials: time to onset of symptom relief, based on a three-symptom composite VAS of skin swelling, skin pain, and abdominal pain. The median time to onset of VAS-3 symptom relief was 2 hours in icatibant subjects versus 19.8 hours with

placebo (p<0.001). Icatibant also resulted in a shorter time to relief of symptoms defined by multiple secondary endpoints when compared to placebo. Use of rescue medications was minimal, with 3 (7%) patients receiving a rescue medication in the icatibant group and 18 (40%) in the placebo group. For patients with laryngeal attacks, the primary outcome was similar, but based on a five-symptom composite VAS. Laryngeal attacks were infrequent, resulting in small sample sizes, precluding a statistical analysis. Nonetheless, the times to onset of symptom relief were fairly consistent with the non-laryngeal ITT group, which supports the efficacy of icatibant in this patient population. Overall, the primary endpoint was consistent with the primary endpoints seen in FAST-1 and FAST-2, although the primary endpoints were defined differently and cannot be directly compared.

The most frequently reported adverse event was worsening or recurrence of HAE attack, which occurred in 5 (10.9%) patients in the icatibant group and 10 (21.7%) patients in the placebo group. Injection site reactions occurred in all icatibant-treated subjects; no icatibant-treated patients withdrew from the trial due to an adverse event.

In the previous three trials, icatibant was administered by a health care professional. To evaluate the safety of patient-administration, a fourth trial known as FAST-4 (or EASSI), an open-label, trial was conducted. The trial addressed safety in 56 patients self-administering icatibant during an acute attack. Health care professionals demonstrated to patients how to use the subcutaneous injection, and all patients in the study had received a dose of icatibant prior. Health care professionals administered second and/or third doses if needed. Self-administration of the icatibant was not overseen by investigators, but subjects were asked to keep a diary to capture data related to the safety and efficacy of self-administered icatibant. Results showed that 32% of patients reported adverse events, 7% reported serious adverse events, and 23% reported worsening or new HAE attacks. The majority of patients experienced injection site reactions, the severity of which decreased over time and by 10 hours, no patients had any symptoms considered to be severe. Efficacy endpoints were also recorded with a median primary symptom relief time of 2 hours and a median 50% reduction of symptoms time of 2.6 hours. These results were similar to previous phase 3 trials, when icatibant was administered by a health care professional.

Across all phase 3 trials, 1,076 icatibant doses were given to 225 patients for 987 attacks. FAST-3 and FAST-4 provided the FDA with enough evidence to approve icatibant in November of 2011 as a self-administered subcutaneous injection for acute HAE.

DRUG SAFETY:[1]

Serious (REMS, Black Box Warnings, Contraindications):

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Patients with laryngeal symptoms should seek medical attention immediately in an appropriate health care facility after administration of Firazyr.[1]

Studies in rats and dogs showed that repeated exposure resulted in a dose-related reduction in circulating sex hormone levels and the repeated use of icatibant reversibly delayed sexual maturation. There was no effect on male mice fertility at doses up to 80.8 mg/kg/day and rats up to 10 mg/kg/day.

Tolerability

There were no patients who dropped out of phase 3 studies due to adverse effects of icatibant.

Pregnancy/Lactation rating:

Pregnancy category C. There is no clinical data for the exposure of icatibant on human pregnancies. The package insert suggests only using icatibant in pregnant women if the benefit justifies the potential risk for the fetus (e.g. for treatment of potentially life threatening laryngeal attacks). There was no teratogenicity in rats at doses up to 25 mg/kg/day and rabbits up to 10 mg/kg/day, but it did cause delayed parturition. Because of the antagonism of bradykinin, at high doses, the implantation process and subsequent uterine stability in early pregnancy can be effected.[1]

Icatibant is excreted in the milk of lactating rats at concentrations similar to those in maternal blood. In a study of rat pups, no effects were seen. Since it is unknown whether icatibant is excreted in human breast milk, the recommendation is to avoid breastfeeding for 12 hours after treatment.

Unanswered safety questions:

No long term studies to evaluate the carcinogenic potential of icatibant have been conducted.

Toxicity: A dose of 3.2 mg/kg intravenously (~8 times therapeutic dose) caused transient erythema, itching, or hypotension in healthy subjects. None required therapeutic intervention.

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 (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	First Databank	ISMP	Clinical Judgment
LA/SA for [generic]	None			None	
LA/SA for [brand]	None			None	

ADVERSE EFFECTS:[1] Adverse reactions observed in >1% of patients with acute attacks of HAE and at a higher rate with icatibant versus placebo in placebo-controlled trials.[a]

	Icatibant (N=77)	***Placebo (N=75)***
System Organ Class Preferred Term	***Subjects (%)***	***Subjects (%)***
General disorders and administration site conditions		
Injection site reaction[b]	*75 (97)*	*25 (33)*
Pyrexia	*3 (4)*	*0*
Investigations		
Transaminase increased	*3 (4)*	*0*
Nervous system disorders		
Dizziness	*2 (3)*	*1 (1)*

[a]*Events occurring within 14 days of study drug administration*
[b]*Injection site bruising, Injection site hematoma, Injection site burning, Injection site erythema, Injection site hypoesthesia, Injection site irritation, Injection site numbness, Injection site edema, Injection site pain, Injection site pressure sensation, Injection site pruritus, Injection site swelling, Injection site urticaria, and Injection site warmth*

DOSE & AVAILABILITY:[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
30 mg	Solution	SQ	Once. May be repeated every 6 hours. Max: 3 doses in 24 hours.	No	No	Only approved for patients ≥18 years old	Age-related decrease in renal function results in a 50-60% higher exposure (age 75-80). No dose adjustments recommended.	For laryngeal attacks, patients should seek medical attention after treatment with icatibant.

PHARMACOKINETICS:[1,10]

Parameter	Result
Bioavailability	97%
Tmax	0.75 hours
Distribution	20.3-37.7 L
Protein Binding	44%
Elimination	Plasma clearance: 15-20 l/h independent of dose. Excreted primarily in urine; with ~10% excreted as active drug in urine.
Half-Life	1-2 hours
Metabolism	Proteolytic enzymes

ALLERGIES/INTERACTIONS:[1]

Drug-Drug:

Drug interactions involving CYP450 are not expected. An interaction with ACE inhibitors has not but studied, however ACE inhibitor administration in HAE patients is contraindicated due to potential increase in bradykinin levels.1

Food-Drug:

None reported

Allergy/Cross Reactive Substances:

Four patients tested positive for ant-icatibant antibodies after receiving repeated treatment with icatibant in clinical trials. Three of the patients had subsequent tests which were negative. No association between anti-icatibant antibodies and efficacy was observed.

REFERENCES

1. Firazyr [package insert]. Lexington, MA: Shire Orphan therapies, Inc; August 2011.
2. Berinert [package insert]. Kankakee, IL: CSL Behring LLC; December 2011.
3. Kalbitor [package insert]. Cambridge, MA: Dyax Corp.; December 2009.
4. Cicardi M, A Banerji, F Bracho et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med 2010;363:532-41.
5. Lumry WR, HH Li, RJ Levy et al. Randomized placebo-controlled trial of the bradykinin B2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. Ann Allergy Asthma Immunol 2001;107:529-37.
6. Center for Drug Evaluation and Research. FDA Summary Review: Application Number 022150Orig1s000. Accessed 12/20/2011 at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022150Orig1s000SumR.pdf
7. AMCP Dossier. Firazyr (icatibant injection). Shire Human Genetic Therapies, Inc.
8. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol 2010;6:24.
9. Limb S, et al. FDA briefing document: NDA 022-150: Firazyr (icatibant) injection for the treatment of acute attacks of hereditary angioedema (HAE) in patients 18 years of age and older. June 23, 2011.
10. Lexi-Comp online. Icatibant. Accessed 1/10/2012 at http://online.lexi.com

Oregon State University
College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | Fax 503-947-1119

Class Update: Attention Deficit Hyperactivity Disorder (ADHD)

EXECUTIVE SUMMARY:

Month/Year of Review: February 2012

Reason for Review:
The Oregon Evidence-based Practice Center (EPC) for the Drug Effectiveness Review Project (DERP) produced an updated report for the Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder which was published in December of 2011[1]. The full report can be found on the Evidence-based Practice Center website: http://derp.ohsu.edu/about/final-document-display.cfm. This report will be evaluated and summarized for any potential Oregon Health Plan policy decisions. Refer to the full reports for details on methods, search strategy, inclusion criteria, outcomes included, and methods for grading the evidence.

Summary:
Recent years have seen an increase in the use of non-stimulant pharmacological treatments for Attention Deficit Hyperactivity Disorder (ADHD) including antipsychotics, antidepressants, atomoxetine, clonidine and guanfacine. The Oregon Health Plan (OHP) uses formulary controls of a Preferred Drug List (PDL) and Prior Authorization (PA) criteria. Many mental health medications are exempt from the use of PA criteria, and may only be controlled by the PDL.[2] Previous class reviews only included stimulant treatments and atomoxetine[3], whereas the most recent review included all potential pharmacologic treatments for ADHD.[1] Comparative effectiveness data was generally not available. Overall efficacy and safety data show few differences between agents, with difference in formulations showing temporal benefits consistent with pharmacokinetic properties associated with the formulation. Efficacy and tolerability findings were evaluated separately in young children, children adolescents, and adults. The DERP review of the available evidence concludes the following regarding comparative effectiveness and harms:

Effectiveness and Efficacy:

- Effectiveness data was generally lacking, with available data having notable methodological limitations
- Efficacy data supports the superiority of stimulants (methylphenidate, amphetamines) and non-stimulant (atomoxetine, guanfacine, clonidine) over placebo.
- No consistent superiority has been demonstrated between immediate and extended release stimulant formulations.
- No consistent superiority has been demonstrated between immediate release stimulants and non-stimulants.
- Limited data suggests some extended release formulation stimulants may be superior to atomoxetine for selected patient populations.
- No comparative efficacy data exists for either extended release clonidine or extended release guanfacine.

Harms:

- Tolerability and side effect profiles are generally consistent with pharmacologic profile and delivery mechanism (immediate release, extended release, or transdermal).
- Long term safety data is of generally poor quality for both stimulants and non-stimulants.
- Atomoxetine may be associated with an increased risk of suicidal behaviors compared to placebo.
- Data evaluating cardiovascular risk was conflicting, with some data showing no significantly increased risk of cardiovascular events.
- Very limited data suggests that height and weight changes associated with stimulant therapy are also found in children treated with atomoxetine.

Recommendations:

- 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.

References

[1] McDonagh MS, Peterson K, Thakurta S, Low A. Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder. Final Update 4 Report. Prepared by the Oregon Evidence-based Practice Center for the Drug Effectiveness Review Project. Oregon Health and Science University. Portland, OR. 2011. Accessed 1/3/2012 from: http://derp.ohsu.edu/about/final-document-display.cfm

[2] Oregon Administrative Rules. Accessed 1/3/2012 from http://arcweb.sos.state.or.us/pages/rules/oars_400/oar_410/410_121.html.

[3] Origer B, Medak R, Klein T, O'Kane N, Clark R, Aebi C. Pharmacologic Treatments for ADHD. Health Resource Committee. June 2008. Accessed 1/3/2012 from http://www.oregon.gov/OHA/pharmacy/therapeutics/docs/hrc-2008-06-adhd.pdf?ga=t

Drug Class Review

Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder

Final Update 4 Report
Executive Summary

December 2011

The purpose of the Executive Summary is to summarize key information contained in the Drug Effectiveness Review Project report "Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder", dated December 2011. The full report can be accessed at the following web address: http://derp.ohsu.edu/about/final-document-display.cfm. Readers are advised to review the full report. 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. They are not intended to provide any legal or business advice. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Update 3: October 2009
Update 2: November 2007
Update 1: May 2006
Original Report: September 2005

The literature on this topic is scanned periodically.

Update 4 Authors:
Marian S. McDonagh, PharmD
Kim Peterson, MS
Sujata Thakurta, MPA:HA
Allison Low, BA

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Oregon Health & Science University

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) affects children and adults and is treated with both pharmacologic and nonpharmacologic interventions. Multiple drugs are used to treat ADHD. This review evaluates the evidence on how these drugs compare to each other in benefits and harms.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for ADHD. Included drugs are shown in Table 1.

Table 1. Attention deficit hyperactivity disorder drugs and indication

Active ingredient(s)	Referred to in this report as	Trade name	Forms
Amphetamine mixture (amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate)	Mixed amphetamine salts XR	Adderall XR®[a]	Extended-release oral capsule
Atomoxetine hydrochloride	Atomoxetine	Strattera®[b]	Oral capsule
Clonidine hydrochloride	Immediate-release clonidine	Catapres®[b]	Oral tablet
	Extended-release clonidine	Kapvay™[c]	Extended-release oral tablet
Dexmethylphenidate hydrochloride	Immediate-release dexmethylphenidate	Focalin®[b,c]	Oral tablet
	Extended-release dexmethylphenidate	Focalin XR®[c]	Extended-release oral capsule
Dextroamphetamine sulfate	Immediate-release dextroamphetamine	Dexedrine®[b]	Oral tablet[d]
	Sustained-release dextroamphetamine	Dexedrine Spansule®	Sustained-release oral capsule
Guanfacine hydrochloride	Immediate-release guanfacine	Tenex™[b, c]	Oral tablet
	Extended-release guanfacine	Intuniv®[c]	Extended-release oral tablet
Lisdexamfetamine dimesylate	Lisdexamfetamine	Vyvanse®	Oral capsule
Methamphetamine hydrochloride	Methamphetamine	Desoxyn®[b,c]	Oral tablet
Methylphenidate	Methylphenidate transdermal	Daytrana®[c]	Extended-release transdermal film
Methylphenidate hydrochloride	Methylphenidate osmotic-release oral system	Concerta®	Extended-release oral tablet

Active ingredient(s)	Referred to in this report as	Trade name	Forms
	Methylphenidate CD	Metadate CD®c, e	Extended-release oral capsule
	Methylphenidate ER	Metadate ER®c	Extended-release oral tablet
	Methylphenidate chewable Methylphenidate solution	Methylin®b,c	Oral chewable tablet and Oral solution
	Immediate-release methylphenidate	Ritalin®b	Oral tablet
	Methylphenidate long acting	Ritalin LA®c	Extended-release oral capsule
	Multilayer-release methylphenidate	Biphentin®d	Extended-release oral capsule
	Methylphenidate sustained-release	Ritalin SR®b	Extended-release oral tablet
Modafinil	Modafinil	Provigil®c	Oral tablet
		Alertec®d	Oral tablet

Abbreviations: ER, extended release; LA, long acting; SR, sustained release; XR, extended release.
[a] The active ingredient for Adderall XR in Canada is amphetamine aspartate monohydrate.
[b] Or generic equivalent.
[c] Not available in Canada.
[d] Not available in the United States.
[e] Metadate CD® is marketed as Equasym XL® in some countries outside the United States and Canada.

The participating organizations of the Drug Effectiveness Review Project approved the following key questions to guide the review for this report:

1. Evidence on Effectiveness and Efficacy
    a. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders improve *effectiveness* outcomes?
        i. Comparisons include individual drugs, as well as between stimulants and nonstimulants, and immediate-release compared with intermediate-release compared with long-acting formulations.
        ii. Noncomparative evidence will be considered for drugs with no comparative evidence.
    b. What is the *comparative* efficacy between any included pharmacologic treatment, between stimulants and nonstimulants, and between immediate-release compared with intermediate-release compared with long-acting formulations, for attention deficit disorders?

2. Tolerability, Serious Adverse Events, Misuse, and Diversion
    a. What is the evidence of *comparative* tolerability of different pharmacologic treatments, between stimulants and nonstimulants, and between immediate-release compared with intermediate-release compared with long-acting formulations, for attention deficit disorders?
    b. What is the evidence of serious adverse events or long-term adverse events associated with use of pharmacologic treatments for attention deficit disorders?
    c. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders impact the risk of misuse or illicit diversion in patients with no history of misuse or diversion?
        i. Comparisons include individual drugs, as well as between stimulants and nonstimulants, and immediate-release compared with intermediate-release compared with long-acting formulations.
        ii. Noncomparative evidence will be considered for drugs with no comparative evidence.

3. Evidence in Subgroups of Patients
    a. What is the evidence of benefits and harms of pharmacologic treatments, between stimulants and nonstimulants, and between immediate-release compared with intermediate-release compared with long-acting formulations, for attention deficit disorders in subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications or therapy, or comorbidities (e.g. tics, anxiety, substance use disorders, disruptive behavior disorders)?
    b. What is the comparative or noncomparative evidence of misuse or illicit diversion of pharmacologic treatments for attention deficit disorders in patients with current or past substance use disorder comorbidities?
        i. Comparisons include individual drugs, as well as between stimulants and nonstimulants, and immediate-release compared with intermediate-release compared with long-acting formulations.
        ii. Noncomparative evidence will be considered for drugs with no comparative evidence.

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (2nd Quarter 2011), Cochrane Database of Systematic Reviews (2005 to June 2011), MEDLINE (1996 to June 1 Week 4 20011), and PsycINFO (1806 to June Week 4 2011) using terms for included drugs, indications, and study designs. We also searched reference lists of included studies and reviews, and the US Food and Drug Administration Center for Drug Evaluation and

Research website. Finally, we requested published and unpublished information from the relevant pharmaceutical companies for this review.

Validity Assessment

We assessed the internal validity (quality) of all studies using predefined criteria based on study design (see www.ohsu.edu/drugeffectiveness). We also determined the quality of studies to be *good, fair, or poor* based on predefined criteria. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality.

RESULTS AND SUMMARY

We included 404 studies and of these, 60 were identified in the most recent update. Dossiers were submitted by 4 pharmaceutical manufacturers for Update 4: Shire US, Inc (guanfacine and lisdexamfetamine); UCB, Inc, (methylphenidate CD); Shionogi Inc (clonidine); and Ortho-McNeil Janssen Scientific Affairs, LLC (methylphenidate OROS).

There were no *trials* of comparative effectiveness of these drugs for treatment of ADHD. The evidence for comparative efficacy of drugs for treating ADHD was severely limited by small sample sizes, very short durations, and the lack of studies measuring functional or long-term outcomes. Methods of measuring or reporting symptom control varied significantly across studies.

Characterization of ADHD symptomatology across studies was limited due to use of varied or indeterminate diagnostic processes. Minorities and the most seriously ill patients were underrepresented and the small sample sizes of these trials did not allow for statistical analyses of potential effects of these factors. The evidence in preschool-age children is most applicable to white boys, ages 4 to 5, with moderately severe symptoms, and evidence in school-aged children applies best to white boys age 8 to 9 years, with the combined subtype of ADHD, often with comorbid oppositional defiant disorder, conduct disorder, or anxiety. The evidence in adolescents is more diverse; while many studies reflect populations that are mainly white boys (mean age 14) with moderate to severe symptoms, a few studies included populations with close to 50% girls and 50% boys, and higher percentages of non-white teens. Evidence in adults applies best to white men or women in their mid-thirties, but other characteristics were too poorly reported to assess.

The results of this review are summarized in Table 2 below.

Table 2. Summary of the evidence

Comparison: Overall strength of the evidence	Conclusion
Key Question 1. Benefits	
General: Effectiveness	
No trials found: Insufficient	No conclusions about comparative effectiveness of different pharmacotherapies for ADHD could be made.
Young children: Efficacy	
MPH IR: Low	The evidence on efficacy of MPH IR compared with placebo in the short term was inconsistent.
Atomoxetine: Insufficient	One placebo-controlled trial.

	Comparison: Overall strength of the evidence	Conclusion
Children: Efficacy		
Stimulants		
IR vs. SR formulations	MPH IR vs. MPH SR: Moderate	Studies of MPH IR vs. extended-release formulations in children generally were unable to identify significant differences in symptom improvement. Studies of MPH IR and MPH OROS were conflicting; a difference was not found in double-blind studies while open-label studies indicated greater improvement with MPH OROS on some measures.
SR vs. SR formulations	MPH SR vs. MPH SR formulations: Low	Limited evidence from 2 small crossover studies suggested that MPH LA was superior to MPH OROS on some, but not all efficacy outcomes. Limited evidence suggested that MPH CD was superior to MPH OROS on outcomes in the morning; they had similar effects in the afternoon; and MPH OROS was superior in the evening. d-MPH ER was superior to MPH OROS at 2 to 6 hours post-dose and MPH OROS was superior at 10 to 12 hours in 1 trial.
IR vs. IR	DEX IR vs. MPH IR: High	The body of evidence clearly indicated no difference in efficacy between DEX and MPH IR.
	MAS IR vs. MPH IR: Moderate	MAS IR was superior to MPH IR on a few efficacy outcome measures in 2 trials but clear evidence of superiority was lacking.
	DEX IR vs. DEX ER vs. MAS: Low	Evidence on the comparison of DEX IR vs. DEX SR vs. MAS may suggest that measures made in the morning show DEX IR superior to DEX SR, and afternoon measures show DEX SR superior to MAS.
	Modafinil vs. MPH IR: Moderate	Based on 1 trial, modafinil was similar to MPH IR in efficacy
	Dexmethylphenidate: Insufficient	Only placebo-controlled evidence was found.
Transdermal MPH	MTS vs. MPH OROS: Moderate MTS vs. MPH IR: Low	Based on 1 trial each, MTS had similar efficacy compared with MPH OROS or MPH IR.
Lisdexamfetamine	Moderate	Lisdexamfetamine was comparable to MAS XR on average SKAMP-DS scores and superior to placebo on same, as well as on ADHD rating scale IV mean changes.
Atomoxetine	Atomoxetine vs. MPH IR: Low	Limited evidence suggested a lack of a difference in efficacy compared with MPH IR.
	Atomoxetine vs. MAS XR: Low	Limited evidence suggested that MAS XR is superior to atomoxetine on most efficacy measures.
	Atomoxetine vs. MPH OROS: Moderate	MPH OROS was superior to atomoxetine in response rates.
Clonidine	Clonidine IR vs. MPH IR: Moderate	Clonidine IR was found to be similar to MPH IR on teacher assessment of ADHD symptoms, but other findings were inconsistent.
	Clonidine ER: Insufficient	No head-to-head evidence. Placebo-controlled trials indicated modest benefit as add-on or monotherapy.
Guanfacine	Guanfacine IR: Low	No head-to-head evidence. Indirect evidence was insufficient to make conclusions.
	Guanfacine XR: Insufficient	No head-to-head evidence. Placebo-controlled trials indicated modest benefit up to 8 hours post-dose.
Adolescents: Efficacy		
	MPH OROS vs. MAS IR: Moderate	Effectiveness outcomes: NR Short-term improvements in core ADHD symptoms: No

	Comparison: Overall strength of the evidence	Conclusion
		differences. Other: MPH OROS > MAS IR on overall simulator driving performance.
	MPH IR vs. MPH OROS: Moderate	Functional capacity: NR Short-term improvements of core ADHD symptoms: NR. Driving performance: MPH OROS > MPH IR in evening and at night.
	Placebo-controlled studies of MPH IR and Lisdexamfetamine: Insufficient	Functional capacity: NR Short-term improvements of core ADHD symptoms.
Adults: Efficacy		
	Switch to MPH OROS vs. continuing on MPH IR: Low	No significant difference in maintenance of response at 6 weeks.
	IR guanfacine vs. DEX IR: Low	No significant difference in mean total symptom score of the DSM-IV ADHD Behavior Checklist for Adults.
	Modafinil vs. DEX IR: Low	No significant difference in response rates.
	Placebo-controlled evidence of atomoxetine, DEX IR, d-MPH XR, lisdexamfetamine, MPH ER, MPH IR, MPH OROS, MAS IR, MAS XR: Insufficient	Compared with placebo, response rates were significantly greater for all. *Other efficacy outcomes:* Atomoxetine: Not consistently significantly superior to placebo in improving quality of life and driving performance outcomes. MPH IR: Consistently superior to placebo in improving driving performance outcomes; not significantly superior to placebo on 5 of 6 sleep outcomes in 1 trial. MAS XR: Superior to placebo in improving overall simulated driving performance outcomes in 1 trial. MPH OROS: Superior to placebo in improvements on some parenting skill measures in 1 trial.
	Methylphenidate transdermal system: Insufficient	No conclusions could be drawn based on the single included poor-quality, placebo-controlled trial.
Key Question 2. Safety		
2b. Short-term trial evidence		Very few studies reported methods for assessing adverse events a priori.
Young children		
	1 placebo-controlled trial of MPH: Insufficient	Indirect comparisons cannot be made; MPH associated with higher rates of adverse events than placebo.
Children		
	Moderate	Very few studies reported methods for assessing adverse events a priori.
	MPH IR vs. MPH SR	There is no evidence of a difference in adverse events between IR and SR formulations.
	MPH SR vs. MPH SR formulations	No differences in adverse events were found, except that MPH OROS had higher rates of insomnia and decreased appetite than MPH CD.
	MTS vs.MPH IR or OROS	No differences found in overall adverse events.
	DEX vs. MPH IR	Limited evidence from short-term trials suggested that weight loss is greater with DEX than MPH IR.
	MAS vs. MPH IR	Very limited evidence suggested that twice daily dosing of MAS led to higher rates of loss of appetite and sleep trouble.
	DEX IR vs. DEX ER vs. MAS	Transient weight loss was greater with MAS and DEX SR than with DEX IR.
	Lisdexamfetamine	No differences in adverse event rates between lisdexamfetamine vs. MAS XR.

	Comparison: Overall strength of the evidence	Conclusion
	Atomoxetine vs. MPH IR, MPH OROS, MAS XR	Vomiting: atomoxetine rates 12% to 13%, approximately 3 times greater than rates for MPH IR or MAS XR. Somnolence: atomoxetine rates 6% to 26%, which was 3 to 4 times greater than MPH OROS and MPH XR; 7 times greater than MPH IR. Nausea and anorexia: greater with atomoxetine than MPH IR in 1 trial. Insomnia: 13% MPH OROS, 28% MAS XR vs. 7% atomoxetine.
	Clonidine IR vs. MPH IR: Moderate	Sedation: 42% with clonidine, 14% MPH IR. 28% reported as moderate to severe, may improve over time.
	Clonidine ER: Insufficient	No head-to-head evidence. In placebo-controlled trials somnolence and fatigue were the most common adverse events with clonidine ER and peaked at 2 weeks. Dose-response in withdrawal due to adverse events, flexible dosing improved discontinuation rate.
	Guanfacine XR: Insufficient	No head-to-head evidence. Placebo-controlled trials indicated somnolence, fatigue, and headache most common adverse events with guanfacine XR, dose-response in withdrawals due to adverse events; flexible dosing did not resolve the difference compared with placebo.
Adults		
	Switch to MPH OROS vs. continuing on MPH IR: Insufficient	Difference in proportions of patients with no adverse events was unclear due to serious methodological limitations of the trial.
	IR guanfacine vs. DEX IR: Low	No significant difference in number of adverse events. Withdrawals due to adverse events were not reported.
	Modafinil vs. DEX IR: Low	No withdrawals due to adverse events. No significant differences in insomnia or appetite suppression.
	Placebo-controlled evidence on atomoxetine, DEX IR, d-MPH XR, lisdexamfetamine, MPH ER, MPH IR, MPH OROS, MAS IR, MAS XR: Insufficient	Indirect meta-analysis of harms was not undertaken due to concerns about sparse data and heterogeneity in outcome measurement methods and trial duration. Conclusions about comparisons to placebo were also limited by a scarcity of statistical analyses.
	Methylphenidate transdermal system: Insufficient	No conclusions could be drawn based on the single included poor-quality, placebo-controlled trial.
2b. Long-term safety: Observational studies		
Mixed populations, primarily children		
	Suicidal behavior/suicide: Low	Increased risk with atomoxetine compared with placebo (risk difference, 0.52; 95% CI, 0.12 to 0.91) based on meta-analysis. Time to onset of behavior 9 to 32 days. Overall rate of suicidal behavior and ideation was 0.44% in this study compared with 1.7% in another meta-analysis of longer-term duration.
	Sudden cardiac death: Low	Evidence was inconsistent. Stimulant medications, particularly MPH IR, may have increased risk compared with nonuse, but comparative evidence was insufficient to make conclusions.

	Comparison: Overall strength of the evidence	Conclusion
	Cardiac events: Low	Emergency room visits for cardiac causes were not found statistically significantly different between current users of methylphenidate products and amphetamine products. Former use of these products also resulted in a nonsignificant finding. In adults, risk of stroke or TIA not found different between atomoxetine and stimulants.
	Height: Moderate	Evidence on DEX IR compared with MPH IR was inconsistent. Evidence suggested that MPH IR and MPH OROS adversely impacts expected height gain at least during the first 12 months of treatment. Limited evidence suggested that height changes resulting from atomoxetine were similar to those reported with MPH IR and were also transient, with peak impact at 18 months, but the difference resolved by 2 years.
	Weight: Moderate	DEX IR was associated with significantly greater suppression of weight gain than MPH IR in the first 1-2 years, but the difference resolved by the second year. Higher relative doses of DEX IR may have influenced findings. Noncomparative evidence indicated a small reduction in expected weight gain, especially among those with greater weight at baseline for MPH IR, MPH OROS, and MAS XR for at least the first year of treatment. Limited evidence suggested that weight changes resulting from atomoxetine were similar to those reported with MPH IR, and were also transient, but longer lasting - resolving by 5 years of treatment.
	Tics, seizures, cardiovascular adverse events, injuries, and suicidal behavior	No comparative evidence.
2c. Abuse/misuse/diversion		
Abuse	Low	Stimulant use during childhood was not associated with alcohol abuse later. May be protective against or delay nicotine dependence, but comorbid conduct disorder may be a significant confounder. Stimulant use may protect against later substance abuse, but again comorbid conduct disorder may be a confounder. Evidence on misuse and diversion reported wide ranges of prevalence with no comparative data.
Misuse	Low	Children and adolescents: 5% to 8% College students: 5% to 35% (26% to 63% for enhancement of academic performance) Adults: 29% Misuse of methylphenidate associated with illicit use of cocaine or amphetamines

	Comparison: Overall strength of the evidence	Conclusion
Diversion	Low	Children and adolescents: 15% to 24% gave them away 7% to 19% sold them 4% to 6% had them stolen College students: 26% reported selling or giving medication away. Of these: 70.5% Amphetamine/dextroamphetamine 37% Methylphenidate 39.1% methylphenidate OROS Adults: 44% reported diversion 97% gave it away 17% sold it 14% both Diversion is associated with younger age both at the time of the survey and at the time methylphenidate was first prescribed.
Key Question 3. Subgroups		
Children	Low	
	ADHD subtypes or severity	Atomoxetine, MPH IR, and MPH OROS had superior efficacy relative to placebo in children with ADHD, regardless of diagnostic subtype. There was inconsistency in evidence that response may be better in those with combined or inattentive subtype.
	Race/ethnicity	Children: Most trials were conducted in primarily White populations. Ethnicity/race was only reported in one half of studies. No analyses based on race. Very limited evidence suggested MPH IR in African American boys results in response rates similar to other populations studied. Evidence from subgroup analysis of a placebo-controlled trial suggested that effects of lisdexamfetamine may be less robust in non-Caucasian children. Adults: Significantly greater reduction of ADHD Rating Scale scores with methylphenidate OROS vs. placebo subgroups of white and non-white patients
	Gender	Subgroup analyses based on gender were limited. Evidence from subgroup analysis of a placebo-controlled trial suggested that lisdexamfetamine may be less efficacious in girls. Exploratory analysis indicated atomoxetine may have better response on emotional regulation items in women than men.
Common comorbidities	Low	Head-to-head trials provided no evidence in subgroups of interest.

Comparison: Overall strength of the evidence	Conclusion
Anxiety	Children: The rate of anxiety being reported as an adverse event did not differ statistically significantly in head-to-head comparisons of: MPH IR compared with IR DEX, MAS, MPH SR, MPH OROS, or atomoxetine. Limited evidence suggested that MPH IR is somewhat less effective in reducing ADHD symptoms in children with baseline anxiety symptoms compared with those without these symptoms. Atomoxetine was superior to placebo in improving ADHD and anxiety symptoms in children with anxiety at baseline. Adults: In adults with ADHD and comorbid social anxiety disorder, there was significantly greater improvement in ADHD and anxiety symptoms for atomoxetine vs. placebo. MPH IR was generally significantly more effective than placebo in improving ADHD and anxiety symptoms in patients with ADHD but no diagnosis of anxiety disorder.
Tic disorders	No consistent evidence that atomoxetine, DEX IR, or MPH IR increased tic severity or frequency compared with placebo. MPH IR showed a benefit on ADHD symptoms compared with placebo. MPH IR and IR clonidine both improved ADHD symptom scores and were not found to significantly differ from each other in children with Tourette's disorder. Guanfacine resulted in improvement in tic severity relative to placebo in children with tic disorders (58.8% = Tourette's disorder).
Oppositional defiant disorder	Very limited evidence suggested that atomoxetine is beneficial on most ADHD outcomes compared with placebo. Guanfacine XR was superior to placebo in improving both ADHD and oppositional defiant symptoms compared with placebo.
Bipolar disorder	Very limited evidence suggested that MAS IR or MPH IR have benefit on most ADHD outcomes compared with placebo. MPH IR did not improve ADHD symptoms when added to aripiprazole in children with comorbid ADHD and bipolar disorder.
Substance abuse/substance use disorder	Adolescents: MPH SODAS was superior to placebo in reducing ADHD symptoms in teens with SUD. No significant treatment effect on drug use. Atomoxetine was not superior to placebo in improving ADHD symptoms in teens with SUD; number of days with abuse also was not affected. Adults: Substance use disorder: Atomoxetine and lisdexamfetamine both had limited evidence of significantly improving ADHD symptoms vs. placebo in adults, whereas no significant benefits were found with IR MPH and SR MPH vs. placebo.

Abbreviations: ADHD, attention deficit hyperactivity disorder; d-MPH, dexmethylphenidate; DEX, dextroamphetamine; ER, extended release; IR, immediate release; LA, long acting; MAS, mixed amphetamine salts; MPH, methylphenidate; NR, not reported; SR, sustained release; SUD, substance abuse disorder; TIA, transient ischemic attack.

CONCLUSION

Evidence on the comparative effectiveness of drugs to treat ADHD was insufficient. Evidence on the comparative efficacy in children and adolescents was moderate to low strength and indicated very few differences among the drugs in improving symptoms or in adverse event rates. Sustained-release formulations of stimulants showed benefit over comparators at specific times of day depending on the pharmacokinetics of the specific formulation, but overall differences were not found. Atomoxetine (a nonstimulant) was not found superior to some extended-release stimulant products. Atomoxetine resulted in higher rates of vomiting and somnolence, similar rates of nausea and anorexia, and lower rates of insomnia than stimulants. Extended-release formulations of other nonstimulant drugs (clonidine, guanfacine) have no comparative evidence to date. Immediate-release clonidine was similar to immediate-release methylphenidate.

Comparative evidence in adults provided low-strength evidence of no significant differences in efficacy between switching to methylphenidate OROS compared with continuing with immediate-release methylphenidate or between immediate-release guanfacine or modafinil compared with immediate-release dextroamphetamine. Low-strength evidence found no significant differences between immediate-release guanfacine or modafinil compared with immediate-release dextroamphetamine.

Evidence on the risk of serious harms was primarily indirect, and indicated atomoxetine has increased risk of suicidal behavior compared with placebo. Differences in risk for sudden death was unclear, cardiac adverse events were not different between stimulants, and cerebrovascular adverse events in adults did not differ between stimulants and atomoxetine. Dextroamphetamine immediate-release caused more inhibition of growth than other stimulants, but the difference was influenced by dose and resolved after 2 years of treatment. Atomoxetine caused similar inhibition of weight gain that lasted up to 5 years. Evidence on abuse, misuse, and diversion was limited, but indicated that stimulant use during childhood is not associated with increased risk of substance use later. Misuse and diversion rates varied by age and were highest among college students, and rates of diversion were highest with amphetamine-based products but similar among methylphenidate products. Evidence of effects in important subgroups of patients with ADHD (e.g. comorbid anxiety) was not comparative.

OSU
Oregon State UNIVERSITY College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | Fax 503-947-1119

Month/Year of Review: March 2012
PDL Class: Sedative Hypnotics

Date of Last Review: October 2008
Source Document: DERP

Current Preferred Agents:
Zolpidem tartrate
Trazodone
Mirtazapine
Diphenydramine
Tricyclic Antidepressants

Current Non-Preferred Agents:

Benzodiazepines	Non-Benzodiazepines
Flurazepam	Zolpidem tartrate (Ambien CR®)
Temazepam	Zolpidem tartrate (Zolpimist spray®)
Quazapam (Doral®)	Zolpidem sublingual (Edluar®)
Estazolam	Zaleplon
Triazolam	Eszopiclone (Lunesta®)
	Ramelteon (Rozerem®)

Previous Recommendations:
- There is good quality evidence that zaleplon and zolpidem are similarly effective for subjective sleep latency .
- There is no comparative evidence in children.
- There is fair quality evidence that there is no significant difference between zolpidem and eszopiclone on measured sleep outcomes.
- There is fair quality evidence that there is no difference in rates of withdrawals due to adverse events between the newer sedative hypnotics.
- There is no comparative evidence about long-term safety.
- There is fair to poor quality evidence that the efficacy of zolpidem and zaleplon was similar in older and younger adults, although somnolence was more common with zolpidem in older adults.
- The risk of hip fracture in older women was increased with the use of zolpidem compared to both non-use and use of benzodiazepines.
- No evidence that one newer insomnia drug is safer or more effective in any subgroup based on gender or race was found.

PA Criteria: Treatment of uncomplicated insomnia is not covered, but insomnia contributing to a covered comorbid condition is. A benzodiazepine quantity limit PA is required for a quantity exceeding 15 doses/30 days. A prior authorization is in place to prevent duplicate sedative use requiring PA when a client is receiving two oral sedative medications at the same time.

Methods
Two scans were completed by the Oregon Evidence-based Practice Center Drug Effectiveness Review project which included a literature search through September 2010. The 2009 scan identified 5 potentially relevant new trials (Appendix A). None of these were head-to-head trials. The 2010 DERP scan resulted in another 5 potentially relevant new trials (Appendix B). These included placebo-controlled trials of eszopiclone in elderly patients, patients with comorbid depression, and women with menopausal symptoms; and one placebo-controlled trial of zolpidem compared to placebo. A head-to-head trial of sublingual zolpidem compared to oral zolpidem was also identified. A MEDLINE OVID search was conducted using all treatments for insomnia and limited to randomized controlled trials and meta-analysis, English language, and conducted in humans from October 2010 (date from last DERP scan) to current. The Agency for

Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality 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.

New Trials:
A total of 25 citations resulted from initial literature search. After inclusion for further review, 18 were evaluated further and nine potentially relevant randomized trials were identified (Appendix C). These trials are briefly described in table 1.

Table 1: Potentially relevant new trials

Study	Comparison	Population	Primary Outcome	Results	
Krystal, 2011[1] RCT, DB, PG, PC	Doxepin 3mg, Doxepin 6mg, placebo	Primary Insomnia	Wake time after sleep onset (WASO)	<u>WASO at night 1</u> 3mg: 41 minutes 6mg: 36 minutes Pl: 67 minutes P<0.001 for both doses vs. placebo	<u>WASO at night 29</u> 3mg: 47 minutes 6mg: 41minutes Pl: 61 minutes P=0.0025 3mg P=0.0009 6mg
Pollack, 2011[2] RCT, DB, PC, CO	Eszoplicone 3mg vs. placebo	Post-traumatic stress disorder associated insomnia	Changes in scores on the Short PTSD Rating Interview and Pittsburgh Sleep Quality Index (PSQI)	<u>Reduction in PSQI score</u> E: -3.2 P: -0.87 P=0.011	
Fava, 2011[3] RCT, DB, PC, PG	Zolpidem ER 12.5mg vs. placebo + open label escitalopram 10mg	Insomnia associated with major depressive disorder	Change from baseline in subjective total sleep time at week 8	<u>Least Squares mean difference :</u> Z: 100 min P: 58 min P<0.001 The superiority of zolpidem ER (P<0.05) was maintained through week 16 but not at weeks 20 and 24.	
Fava, 2011[4] Post Hoc Analysis	Eszoplicone 3mg + SSRI vs. placebo + SSRI	Insomnia associated with anxious depression	Mean improvements from baseline Insomnia Severity Index (ISI) scores	<u>Mean improvement in ISI total score at week 8:</u> E + SSRI: -10.9 ± 6.8 P+ SSRI: -8.5 ± 7.4 P<0.001	
Roth, 2010[5] RCT, DB, PC, PG	Doxepin 6 mg versus placebo	Induced transient insomnia in healthy adults	Latency to persistent sleep	<u>Latency to persistent sleep:</u> D: 21 minutes P: 34 minutes P<0.001	
Huang, 2011[6] RCT, DB,	Zaleplon 10mg vs. zolpidem 10mg	Primary Insomnia	Change in sleep latency from baseline to week 2	No statistically significant difference was observed in sleep latency (p=0.084), sleep duration (p=0.868), or number of awakenings (p=0.637) at week 2.	
McElroy, 2011[7] RCT, PC, DB	Ramelteon 8mg vs. placebo	Bipolar 1 disorder with manic symptoms and sleep disturbance	Change in Pittsburgh Insomnia Rating Scale (PIRS)	patients receiving ramelteon had a similar rate of reduction in mean total PIRS scores compared to patients receiving placebo (p=0.59) *38% overall attrition rate	
Gooneratne, 2010[8] RCT, PG,	Ramelteon 8mg versus placebo	≥ 60 years old with obstructive sleep apnea	Change in sleep onset latency at 4 weeks.	<u>Sleep Onset Latency:</u> R: -10.7 min P: 17.8 min	

DB	N=27			P=0.008 Mean Difference 28.5 m 95% CI (8.5 to 48.6) * neither objective nor subjective sleep efficiency differed significantly between study arms.
Krystal, 2010[9] RCT, DB, PC, PG	Doxepin 1mg vs. doxepin 3mg vs. placebo N=240	Elderly patients with chronic primary insomnia	Wake time after sleep onset (WASO) on night 1	Mean WASO at night 1 1mg: 91.8 minutes 3mg: 74.5 minutes Pl: 108.9 minutes P=0.0053 for 1mg ; P<0.001 for 3mg vs. placebo

New drugs:
None

New Dosage forms/New Indications:
Doxepin hydrochloride (Silenor®) was FDA approved in March 2010 for the treatment of insomnia characterized by difficulties with sleep maintenance. Approved doses are 6 mg for adults and 3 mg for elderly patients. Doxepin was originally developed as a Tricyclic antidepressant but also exhibits sedative properties.

A sublingual form of zolpidem tartrate (Edluar®) was approved by the FDA in March 2009 for the treatment of insomnia characterized by difficulty with sleep initiation.

An oral spray form of zolpidem tartrate (Zolpimist®) was approved by the FDA in December 2008 for the treatment of insomnia characterized by difficulty with sleep initiation.

New FDA Indications:
None

New FDA safety alerts:
None

New Systematic Reviews:
None

Evidence-based Clinical Guidelines:
The American Academy of Sleep Medicine 2008 treatment guidelines for primary insomnia do not distinguish amongst the agents in this review.[10] There are considerations to be made for individual patients, but there is no clear agent for the population at large.

Recommendations:
1. No further research or review needed.
2. Make doxepin (Silenor) non-preferred due to lack of data showing doxepin to be superior to other agents in this class.
3. Maintain specialized formulations of zolpidem (Edluar and Zolpimist) non- preferred due to no significant clinical advantage over tablets.

Appendix A: potentially relevant trials from 2009 DERP Scan (n=5)

Blumer, J. L., R. L. Findling, et al. (2009). "Controlled clinical trial of zolpidem for the treatment of insomnia associated with attention-deficit/ hyperactivity disorder in children 6 to 17 years of age." Pediatrics 123(5): e770-6.
OBJECTIVE: The goal was to evaluate the hypnotic efficacy of zolpidem at 0.25 mg/kg per day (maximum of 10 mg/day), compared with placebo, in children 6 through 17 years of age who were experiencing insomnia associated with attention-deficit/hyperactivity disorder. METHODS: An 8-week, North American, multicenter, double-blind, placebo-controlled, parallel-group study was conducted. Patients underwent stratification according to age (6-11 years [N = 111] or 12-17 years [N = 90]) and were assigned randomly to receive treatment with the study drug or placebo (in a 2:1 ratio). The primary efficacy variable was latency to persistent sleep between weeks 3 and 6. Secondary efficacy variables also were assessed, and behavioral and cognitive components of attention-deficit/hyperactivity disorder were monitored. Safety was assessed on the basis of reports of adverse events, abnormal laboratory data, vital signs, and physical examination findings. The potential for next-day residual effects also was assessed. RESULTS: The baseline-adjusted mean change in latency to persistent sleep at week 4 did not differ significantly between the zolpidem and placebo groups (-20.28 vs -21.27 minutes). However, differences favoring zolpidem were observed for the older age group in Clinical Global Impression scores at weeks 4 and 8. No next-day residual effects of treatment were associated with zolpidem, and no rebound phenomena occurred after treatment discontinuation. Central nervous system and psychiatric disorders were the most-frequent treatment-emergent adverse events (>5%) that were observed more frequently with zolpidem than with placebo; these included dizziness, headache, and hallucinations. Ten (7.4%) patients discontinued zolpidem treatment because of adverse events. CONCLUSION: Zolpidem at a dose of 0.25 mg/kg per day to a maximum of 10 mg failed to reduce the latency to persistent sleep on polysomnographic recordings after 4 weeks of treatment in children and adolescents 6 through 17 years of age who had attention-deficit/hyperactivity disorder-associated insomnia.

Fava, M., G. M. Asnis, et al. (2009). "Zolpidem extended-release improves sleep and next-day symptoms in comorbid insomnia and generalized anxiety disorder." Journal of Clinical Psychopharmacology 29(3): 222-30.
A multicenter, double-blind, parallel-group study was designed to assess the efficacy and safety of zolpidem extended-release coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. Patients (N = 383) received open-label escitalopram 10 mg/d and were randomized to either adjunct zolpidem extended-release 12.5 mg or placebo. The primary efficacy measure was change from baseline to week 8 in subjective total sleep time. Secondary efficacy measures included subjective sleep onset latency, number of awakenings, wake time after sleep onset, sleep quality, the Hamilton Rating Scale for Anxiety, the Beck Anxiety Inventory, the Sleep Impact Scale, the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, and the Sheehan Disability Scale. The last-observation-carried-forward method was used to impute missing values for most efficacy measures. Safety was monitored at each visit. At week 8 and all time points, there was a significant improvement in the zolpidem extended-release/escitalopram group compared with placebo/escitalopram for total sleep time ($P < 0.0001$). Most of the secondary efficacy measures also significantly favored zolpidem at most visits ($P < 0.0001$). The most common treatment-emergent adverse events in both groups were nausea, dizziness, headache, fatigue, and dry mouth. Concurrent zolpidem extended-release/escitalopram, compared with placebo/escitalopram, significantly improved insomnia and sleep-related next-day symptoms, but not anxiety symptoms, in patients with comorbid insomnia and generalized anxiety disorder.

Mayer, G., S. Wang-Weigand, et al. (2009). "Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia." Sleep 32(3): 351-60.
STUDY OBJECTIVES: Long-duration (> or = 6 months) polysomnographic studies of insomnia medications are lacking. This study evaluated the long-term efficacy of ramelteon, a selective MT1/MT2 melatonin-receptor agonist used for insomnia treatment. DESIGN: Six-month, randomized, double-blind, placebo-controlled study. SETTING: Forty-six investigative sites in the United States, Europe, Russia, and Australia. PARTICIPANTS: Four hundred fifty-one adults (age > or = 18 years) with chronic primary insomnia. INTERVENTIONS: Ramelteon, 8 mg, or placebo 30 minutes before bedtime nightly for 6 months. MEASUREMENTS: Sleep was evaluated by polysomnography and morning questionnaires

on the first 2 nights of Week 1; the last 2 nights of Months 1, 3, 5, and 6; and Nights 1 and 2 of the placebo run-out. Next-morning residual effects as well as adverse effects and vital signs were recorded at each visit. Rebound insomnia and withdrawal effects were evaluated during placebo run-out. RESULTS: Over the 6 months of treatment, ramelteon consistently reduced latency to persistent sleep compared with baseline and with placebo; significant decreases were observed at Week 1 and Months 1, 3, 5, and 6 ($P < 0.05$). Ramelteon significantly reduced subjective sleep latency relative to placebo at Week 1, Month 1, and Month 5 ($P < 0.05$), with reductions nearing statistical significance at Months 3 and 6 ($P <$ or $= 0.08$). No significant next-morning residual effects were detected during ramelteon treatment. No withdrawal symptoms or rebound insomnia were detected after ramelteon discontinuation. Most adverse events were mild or moderate in severity. CONCLUSIONS: In adults with chronic insomnia, long-term ramelteon treatment consistently reduced sleep onset, with no next-morning residual effects or rebound insomnia or withdrawal symptoms upon discontinuation.

Morin, C. M., A. Vallieres, et al. (2009). "Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial." JAMA : the journal of the American Medical Association 301(19): 2005-15.

CONTEXT: Cognitive behavioral therapy (CBT) and hypnotic medications are efficacious for short-term treatment of insomnia, but few patients achieve complete remission with any single treatment. It is unclear whether combined or maintenance therapies would enhance outcome. OBJECTIVES: To evaluate the added value of medication over CBT alone for acute treatment of insomnia and the effects of maintenance therapies on long-term outcome. DESIGN, SETTING, AND PATIENTS: Prospective, randomized controlled trial involving 2-stage therapy for 160 adults with persistent insomnia treated at a university hospital sleep center in Canada between January 2002 and April 2005. INTERVENTIONS: Participants received CBT alone or CBT plus 10 mg/d (taken at bedtime) of zolpidem for an initial 6-week therapy, followed by extended 6-month therapy. Patients initially treated with CBT attended monthly maintenance CBT for 6 months or received no additional treatment and those initially treated with combined therapy (CBT plus 10 mg/d of zolpidem) continued with CBT plus intermittent use of zolpidem or CBT only. MAIN OUTCOME MEASURES: Sleep onset latency, time awake after sleep onset, total sleep time, and sleep efficiency derived from daily diaries (primary outcomes); treatment response and remission rates derived from the Insomnia Severity Index (secondary outcomes). RESULTS: Cognitive behavioral therapy used singly or in combination with zolpidem produced significant improvements in sleep latency, time awake after sleep onset, and sleep efficiency during initial therapy (all $P<.001$); a larger increase of sleep time was obtained with the combined approach ($P = .04$). Both CBT alone and CBT plus zolpidem produced similar rates of treatment responders (60% [45/75] vs 61% [45/74], respectively; $P = .84$) and treatment remissions (39% [29/75] vs 44% [33/74], respectively; $P = .52$) with the 6-week acute treatment, but combined therapy produced a higher remission rate compared with CBT alone during the 6-month extended therapy phase and the 6-month follow-up period (56% [43/74 and 32/59] vs 43% [34/75 and 28/68]; $P = .05$). The best long-term outcome was obtained with patients treated with combined therapy initially, followed by CBT alone, as evidenced by higher remission rates at the 6-month follow-up compared with patients who continued to take zolpidem during extended therapy (68% [20/30] vs 42% [12/29]; $P = .04$). CONCLUSION: In patients with persistent insomnia, the addition of medication to CBT produced added benefits during acute therapy, but long-term outcome was optimized when medication is discontinued during maintenance CBT. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00042146.

Omvik, S., B. Sivertsen, et al. (2008). "Daytime functioning in older patients suffering from chronic insomnia: treatment outcome in a randomized controlled trial comparing CBT with Zopiclone." Behaviour Research and Therapy 46(5): 623-41.

The paper presents data from a randomized controlled trial comparing treatment effects of cognitive behavioural therapy (CBT), hypnotic treatment (Zopiclone), and placebo in a sample of insomnia patients. Data from the same trial have already demonstrated that CBT was more efficient in improving sleep than Zopiclone. The novel outcomes that are reported here concern daytime functioning. Forty-six older patients (age >or= 55) qualifying for a diagnosis of primary insomnia were recruited to participate. Assessments were completed at baseline, post-treatment, and at a 6-months follow-up, and measures of worry, anxiety, depression, interpersonal relationships, subjective alertness, vigilance, and quality of life were used. The participants in both treatment conditions scored within the normal range on the outcome

measures at baseline with the exception of reporting less alertness, relative to a group of good sleepers. One interaction effect indicated that subjective alertness improved more in the Zopiclone group than the CBT group from baseline to post-treatment, and another that CBT was more effective than Zopiclone in reducing trait anxiety from baseline to follow-up. It was concluded that the treatments yielded only minor effects on the measures of daytime functioning, and that none of them was clearly superior to the other.

Appendix B: Potentially relevant new trials from 2010 DERP scan (n=5)

Ancoli-Israel, S., A. D. Krystal, et al. (2010). "A 12-week, randomized, double-blind, placebo-controlled study evaluating the effect of eszopiclone 2 mg on sleep/wake function in older adults with primary and comorbid insomnia." Sleep 33(2): 225-34.

BACKGROUND: Longer-term pharmacologic studies for insomnia in older individuals are sparse. OBJECTIVE: To evaluate the efficacy and safety of 12 weeks of nightly eszopiclone in elderly outpatients with insomnia. METHODS: Participants (65-85 years) met DSM-IV-TR criteria for insomnia with total sleep times (TST) < or = 6 h, and wake time after sleep onset (WASO) > or = 45 min. Participants were randomized to 12 weeks of eszopiclone 2 mg (n = 194) or placebo (n = 194), followed by a 2-week single-blind placebo run-out. Subject-reported measures of sleep (sTST, sleep latency [sSL], sWASO) and daytime function (alertness, concentration, wellbeing, ability to function) were assessed. AEs were monitored. RESULTS: Subjects treated with 2 mg eszopiclone slept longer at night on average and at every individual time point compared to baseline than placebo subjects, as measured by TST over the 12-week double-blind period (P < 0.0001). Mean sTST over the double-blind period for eszopiclone-treated subjects was 360.08 min compared to 297.86 min at baseline, a mean change of 63.24 min. Over the double-blind period, eszopiclone-treated subjects also experienced a significantly greater improvement in sSL compared to placebo, with a mean decrease of 24.62 min versus a mean decrease of 19.92 min, respectively (P = 0.0014). Eszopiclone subjects also experienced a significantly greater decrease in WASO (mean decrease of 36.4 min) compared to placebo subjects (decrease of 14.8 min) (P < 0.0001). Post-discontinuation, sleep parameters were statistically improved versus baseline for eszopiclone (P-values < or = 0.01), indicating no rebound. The most common AEs (> or = 5%) were headache (eszopiclone 13.9%, placebo 12.4%), unpleasant taste (12.4%, 1.5%), and nasopharyngitis (5.7%, 6.2%). CONCLUSION: In this Phase IV trial of older adults with insomnia, eszopiclone significantly improved patient-reported sleep and daytime function relative to placebo. Improvements occurred within the first week and were maintained for 3 months, with no evidence of rebound insomnia following discontinuation. The 12 weeks of treatment were well tolerated. Clinical Trial Information: A Long-Term Safety and Efficacy Study of Eszopiclone in Elderly Subjects With Primary Chronic Insomnia; Registration #NCT00386334; URL - http://www.clinicaltrials.gov/ct2/show/NCT00386334?term=eszopiclone&rank=24

Hajak, G., J. Hedner, et al. (2009). "A 2-week efficacy and safety study of gaboxadol and zolpidem using electronic diaries in primary insomnia outpatients." Sleep Medicine 10(7): 705-12.

OBJECTIVES: To evaluate the efficacy and safety profile of gaboxadol, a selective extrasynaptic GABA(A) agonist (SEGA) previously in development for the treatment of insomnia. METHODS: This was a randomised, double-blind, placebo-controlled, parallel-group, 2-week, Phase III study of gaboxadol 5, 10 and 15mg in outpatients meeting the DSM-IV criteria of primary insomnia (N=742). Zolpidem 10mg was used as active reference. RESULTS: At weeks 1 and 2, significant improvement in total sleep time (sTST) compared to placebo was seen for all doses of gaboxadol (all p<0.05). In addition, gaboxadol 10 and 15mg decreased the number of awakenings (sNAW) (p<0.05) while only gaboxadol 15mg improved wakefulness after sleep onset (sWASO) (p<0.05). At week 1, all doses of gaboxadol significantly improved time-to-sleep onset (sTSO) (p<0.05). At week 2, a sustained effect on sTSO was observed for gaboxadol 15mg. Zolpidem also showed effect on all of these variables. Gaboxadol and zolpidem improved sleep quality, freshness after sleep, daytime function and energy at both weeks. Transient rebound insomnia was observed following discontinuation of treatment with zolpidem, but not gaboxadol. CONCLUSIONS: Gaboxadol 15mg treatment for 2 weeks significantly improved sleep onset and maintenance variables as well as sleep quality and daytime function, as did zolpidem. Gaboxadol 5 and 10mg also showed benefits on most efficacy variables. Gaboxadol was generally safe and well tolerated, with no evidence of withdrawal symptoms or rebound insomnia after discontinuation of short-term treatment. For zolpidem, transient rebound insomnia was observed.

Joffe, H., L. Petrillo, et al. (2010). "Eszopiclone improves insomnia and depressive and anxious symptoms in perimenopausal and postmenopausal women with hot flashes: a randomized, double-blinded, placebo-controlled crossover trial." American Journal of Obstetrics & Gynecology 202(2): 171.e1-171.e11.
OBJECTIVE: Menopause-associated insomnia is commonly associated with other symptoms (hot flashes, depression, anxiety). Given frequent symptom cooccurrence, therapies targeting sleep may provide an important approach to treatment during midlife. STUDY DESIGN: Peri/postmenopausal women (40-65 years old) with sleep-onset and/or sleep-maintenance insomnia cooccurring with hot flashes and depressive and/or anxiety symptoms were randomized to eszopiclone 3 mg orally or placebo in a double-blinded, crossover 11 week trial. Changes in the Insomnia Severity Index (ISI) scale and secondary outcomes (diary-based sleep parameters, depression/anxiety, hot flashes, quality of life) were analyzed using repeated-measure linear models. RESULTS: Of 59 women, 46 (78%) completed the study. Eszopiclone reduced ISI scores by 8.7 + or - 1.4 more points than placebo ($P < .0001$). Eszopiclone improved ($P < .05$) all sleep parameters, depressive symptoms, anxiety symptoms, quality of life, and nighttime but not daytime hot flashes. CONCLUSION: Eszopiclone treats insomnia and cooccurring menopause-related symptoms. Our results provide evidence that hypnotic therapies may improve multiple domains of well-being during midlife.

McCall, W. V., J. N. Blocker, et al. (2010). "Treatment of insomnia in depressed insomniacs: effects on health-related quality of life, objective and self-reported sleep, and depression." Journal of Clinical Sleep Medicine 6(4): 322-9.
STUDY OBJECTIVES: Insomnia is associated with poor health related quality of life (HRQOL) in depressed patients. Prior clinical trials of hypnotic treatment of insomnia in depressed patients have shown improvement in HRQOL, but in these studies HRQOL was relegated to a secondary outcome, and objective measures of sleep were not undertaken. DESIGN: Double-blind, randomized, placebo-controlled clinical trial. SETTING: Outpatient clinic and sleep laboratory. PATIENTS: 60 depressed, insomniac outpatients. INTERVENTIONS: One week of open-label fluoxetine (FLX), followed by 8 more weeks of FLX combined with either eszopiclone (ESZ) 3 mg or placebo at bedtime. MEASUREMENTS: The primary HRQOL measure was the daily living and role functioning subscale (DLRF) of the Basis-32. Other measures included the Q-LES-Q, self-reported sleep, PSG, actigraphy, depression severity (HRSD). RESULTS: At the end of randomized treatment, patients receiving ESZ had lower (better) DLRF scores (0.81 +/- 0.64) than those receiving placebo (1.2 +/- 0.72), $p = 0.01$. The effect size for DLRF was 0.62, indicating a moderate effect. An advantage for ESZ was also seen in other measures of HRQOL, and most assessments of antidepressant efficacy and sleep. Women reported better end of treatment HRQOL scores than men. CONCLUSIONS: ESZ treatment of insomnia in depressed patients is associated with multiple favorable outcomes, including superior improvement in HRQOL, depression severity, and sleep.

Staner, C., F. Joly, et al. (2010). "Sublingual zolpidem in early onset of sleep compared to oral zolpidem: polysomnographic study in patients with primary insomnia." Current Medical Research & Opinion 26(6): 1423-31.
OBJECTIVE: To compare the hypnotic effects of a single dose of a sublingual formulation of zolpidem (Edluar*) 10 mg vs oral formulation (Ambien dagger) 10 mg by polysomnography (PSG) in DSM-IV primary insomnia patients. Primary objective was to compare the two formulations on sleep induction, measured by latency to persistent sleep (LPS), sleep onset latency (SOL) and latency to stage 1 (ST1L). RESEARCH AND METHODS: This was a randomized, double-blind, two-period, cross-over multi-centre study in which each period comprised two successive PSG recording nights. Treatment was administered when PSG recordings started. Subjective sleep and residual effects were assessed the next morning. RESULTS: Seventy female and male patients aged 19-64 were analysed. Sublingual zolpidem significantly shortened LPS by 34% or 10.3 minutes as compared to oral zolpidem (95% CI: -4.3 min to -16.2 min, $p = 0.001$). SOL and ST1L were also significantly shortened ($p < 0.01$). Furthermore the two formulations were comparable in terms of sleep maintenance properties based on total sleep time (TST). The improvement in subjective sleep and next-day residual effects did not differ between the two treatments. Both routes of administration were well tolerated. CONCLUSIONS: The results demonstrate that sublingual zolpidem is superior to an equivalent dose of oral zolpidem in terms of sleep inducing properties in a carefully selected sample of primary insomnia patient

Appendix C : Relevant new trials from current scan (n=9)

1. **Krystal AD, Lankford A, Durrence HH, Ludington E, Jochelson P, Rogowski R, Roth T. Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. Sleep. 2011 Oct 1;34(10):1433-42.**

STUDY OBJECTIVES: To evaluate the efficacy and safety of doxepin (DXP) 3 mg and 6 mg in adults diagnosed with primary insomnia. DESIGN AND METHODS: The study was a randomized, double-blind, parallel-group, placebo-controlled trial. Patients meeting DSM-IV-TR criteria for primary insomnia were randomized to 35 days of nightly treatment with DXP 3 mg (n=75), DXP 6 mg (n=73), or placebo (PBO; n=73), followed by 2 nights of single-blind PBO to evaluate discontinuation (DC) effects. Efficacy was assessed using polysomnography (PSG) and patient reports. Efficacy data were examined for Night (N) 1, N15, and N29. Safety assessments were conducted throughout the study. RESULTS: Compared with PBO, DXP 3 and 6 mg significantly improved wake time after sleep onset (WASO) on N1 (3 mg and 6 mg; P<0.0001), N15 (3 mg P=0.0025; 6 mg P=0.0009), and N29 (3 mg P=0.0248; 6 mg P=0.0009), latency to persistent sleep (LPS) on N1 (3 mg P=0.0047; 6 mg P=0.0007), and total sleep time (TST) on N1 (3 mg and 6 mg P<0.0001), N15 (6 mg P=0.0035), and N29 (3 mg P=0.0261; 6 mg P<0.0001). In terms of early morning awakenings, DXP 3 and 6 mg demonstrated significant improvements in SE in the final quarter of the night on N1, N15, and N29, with the exception of 3 mg on N29 (P=0.0691). Rates of discontinuation were low, and the safety profiles were comparable across the 3 treatment groups. There were no significant next-day residual effects, and there were no spontaneous reports of memory impairment, complex sleep behaviors, anticholinergic effects, weight gain, or increased appetite. Additionally, there was no evidence of rebound insomnia after DXP discontinuation. CONCLUSIONS: Five weeks of nightly administration of DXP 3 mg and 6 mg to adults with chronic primary insomnia resulted in significant and sustained improvements in sleep maintenance and early morning awakenings (with the exception of SE in the final quarter of the night on N29 for 3 mg [P=0.0691]). These sleep improvements were not accompanied by next-day residual effects or followed by rebound insomnia or withdrawal effects upon discontinuation. These findings confirm the unique profile of sleep maintenance efficacy and safety of DXP observed in prior studies

2. **Pollack MH, Hoge EA, Worthington JJ, Moshier SJ, Wechsler RS, Brandes M, Simon NM. Eszopiclone for the treatment of posttraumatic stress disorder and associated insomnia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011 Jul;72(7):892-7. Epub 2011 Feb 22.**

OBJECTIVE: The development of novel strategies for the treatment of posttraumatic stress disorder (PTSD) represents a critical public health need. We present the first prospective, randomized, double-blind, placebo-controlled trial of a non-benzodiazepine hypnotic agent for the treatment of PTSD and associated insomnia. METHOD: Twenty-four patients with PTSD by DSM-IV criteria and sleep disturbance were treated in a randomized, double-blind, placebo-controlled crossover study of 3 weeks of eszopiclone 3 mg at bedtime compared to placebo. The primary outcome measures were changes in scores on the Short PTSD Rating Interview (SPRINT) and the Pittsburgh Sleep Quality Index (PSQI). The data were collected from April 2006 to June 2008. RESULTS: Three weeks of eszopiclone pharmacotherapy was associated with significantly greater improvement than placebo on PTSD symptom measures including the SPRINT (P = .032) and the Clinician-Administered PTSD Scale (P = .003), as well as on measures of sleep including the PSQI (P = .011) and sleep latency (P = .044). Greater improvement with eszopiclone on PTSD measures was present even when specific sleep-related items were excluded. Adverse events were consistent with the known profile of the drug. CONCLUSIONS: This study provides initial evidence that pharmacotherapy with eszopiclone may be associated with short-term improvement in overall PTSD severity as well as associated sleep disturbance. Longer, more definitive study of eszopiclone in PTSD is warranted.

3. **Fava M, Asnis GM, Shrivastava RK, Lydiard B, Bastani B, Sheehan DV, Roth T. Improved insomnia symptoms and sleep-related next-day functioning in patients with comorbid major depressive disorder and insomnia following concomitant zolpidem extended-release 12.5 mg and escitalopram treatment: a randomized controlled trial. J Clin Psychiatry. 2011 Jul;72(7):914-28. Epub 2010 Dec 28.**

OBJECTIVE: This investigation was performed to assess the efficacy and safety of zolpidem extended-release in patients with insomnia associated with major depressive disorder (MDD). METHOD: Patients (N = 385) received open-label escitalopram 10 mg/d and were randomized to concomitant zolpidem extended-release 12.5 mg/night or placebo for 8 weeks (phase 1) in a randomized, parallel-group, multicenter trial. Responders (≥ 50% in 17-item Hamilton Depression Rating Scale [HDRS(17)] score) continued 16 weeks of double-blind treatment (phase 2); escitalopram only was given during a 2-week run-out period. The study was conducted between February 2006 and June 2007. The primary efficacy measure was change from baseline in subjective total sleep time. Secondary efficacy measures included subjective sleep-onset latency, number of awakenings, wake time after sleep onset, sleep quality, sleep-related next-day functioning, HDRS(17), Sleep Impact Scale score, Patient and Clinical Global Impressions of Insomnia Treatment, the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, and the Quality of Life Enjoyment and Satisfaction Questionnaire. Adverse events were recorded throughout the study; sleep measures were also evaluated during the run-out period. RESULTS: Throughout phase 1, zolpidem extended-release led to significantly greater improvements in total sleep time ($P < .0001$), wake time after sleep onset, sleep onset latency, number of awakenings, and sleep quality ($P \leq .0003$), and some measures of sleep-related next-day functioning but not in depressive symptoms or quality of life. During phase 2, improvements with the zolpidem extended-release/escitalopram group occurred for total sleep time (significant [$P < .05$] at weeks 12 and 16), as well as for a few other secondary efficacy measures but not in depressive symptoms or quality of life. The most common adverse events associated with combination treatment included nausea, somnolence, dry mouth, dizziness, fatigue, and amnesia. CONCLUSIONS: Zolpidem extended-release administered concomitantly with escitalopram for up to 24 weeks was well tolerated and improved insomnia and some sleep-related next-day symptoms and next-day functioning in patients with MDD but did not significantly augment the antidepressant response of escitalopram.

4. **Fava M, Schaefer K, Huang H, Wilson A, Iosifescu DV, Mischoulon D, Wessel TC. A post hoc analysis of the effect of nightly administration of eszopiclone and a selective serotonin reuptake inhibitor in patients with insomnia and anxious depression. J Clin Psychiatry. 2011 Apr;72(4):473-9. Epub 2010 Nov 2.**

OBJECTIVE: Patients with major depressive disorder (MDD) and significant anxiety are less responsive to antidepressants than those without anxiety. In this post hoc analysis of patients with insomnia and comorbid anxious depression, eszopiclone cotherapy with a selective serotonin reuptake inhibitor (SSRI) was compared with placebo cotherapy. METHOD: Data were pooled from 2 randomized, double-blind, 8-week trials. One trial (conducted from January 2004 to October 2004) included patients with DSM-IV insomnia and comorbid MDD treated with fluoxetine concurrently with eszopiclone 3 mg/d or placebo. The other trial (conducted from July 2005 to April 2006) included patients with DSM-IV-TR insomnia and comorbid generalized anxiety disorder treated with escitalopram concurrently with eszopiclone 3 mg/d or placebo. Anxious depression was defined as a baseline 17-item Hamilton Depression Rating Scale (HDRS-17) score ≥ 14 (excluding insomnia items) and an anxiety/somatization factor score ≥ 7. Treatment group differences were determined for mean changes in HDRS-17 scores (with and without insomnia items), HDRS anxiety/somatization scores, and response and remission rates. Severity of insomnia was assessed by the Insomnia Severity Index (ISI). RESULTS: In the combined dataset, 347 of 1,136 patients (30.5%) had insomnia and comorbid anxious depression. Significant improvements in insomnia were observed for eszopiclone cotherapy relative to placebo cotherapy (mean change from baseline on the ISI: -11.0 vs -7.8, respectively; $P < .001$). There were greater reductions in HDRS-17 scores at week 8 following cotherapy with eszopiclone compared with placebo when the insomnia items were included (mean change: -14.1 vs -11.2, respectively; $P < .01$) or excluded (-10.6 vs -8.9; $P < .01$), but not for anxiety/somatization (-4.3 vs -4.1; $P = .23$). Response rates were greater for eszopiclone cotherapy than for placebo cotherapy (55.6% vs 42.0%, respectively; $P = .01$; 50.0% vs 44.4% when insomnia items were removed; $P = .3$). Remission rates were not significantly different (32.6% vs 27.2%, respectively; $P = .28$). CONCLUSIONS: In this post hoc analysis of

patients with insomnia and comorbid anxious depression derived from 2 trials, 8 weeks of eszopiclone therapy coadministered with an SSRI resulted in significantly greater improvements in insomnia, significantly greater reductions in HDRS-17 total score, and significantly greater HDRS-17 response rates compared with placebo coadministration. There were no significant differences in response rates (when insomnia items were excluded) and remission rates, as well as in anxiety/somatization scores. Further research is warranted to determine whether these modest antidepressant effects can be replicated, and anxiolytic effects demonstrated, when evaluated in a prospective manner.

5. **Roth T, Heith Durrence H, Jochelson P, Peterson G, Ludington E, Rogowski R, Scharf M, Lankford A. Efficacy and safety of doxepin 6 mg in a model of transient insomnia. Sleep Med. 2010 Oct;11(9):843-7.**

INTRODUCTION: The efficacy and safety of doxepin (DXP) 6mg tablets were evaluated in healthy adults in a model of transient insomnia. METHODS: This was a randomized, double-blind, parallel-group, placebo-controlled study in healthy adults using a model of transient insomnia. A first-night effect combined with a 3-h phase advance was implemented to induce transient insomnia in healthy adults. Subjects received a single night time dose of placebo (PBO; N=282) or DXP 6mg (N=283) in a sleep laboratory. Efficacy was evaluated objectively (polysomnography; PSG) and subjectively (morning questionnaire). Consistent with the model utilized, the primary endpoint was latency to persistent sleep (LPS); secondary PSG endpoints included wake after sleep onset (WASO; key secondary endpoint), total sleep time (TST), wake time after sleep (WTAS) and sleep efficiency (SE; overall, by quarter of the night and hourly); secondary subjective endpoints included latency to sleep onset (LSO), subjective WASO (sWASO), subjective TST (sTST) and sleep quality. RESULTS: DXP 6mg demonstrated statistically significant improvements in LPS (13min decrease versus PBO; p<0.0001), WASO (39min less than PBO; p<0.0001), TST (51min more than PBO; p<0.0001), WTAS (p<0.0001), overall SE (p<0.0001), SE in each quarter of the night (p<0.0001) and SE in each of the 8h (p□0.0003), all versus PBO. Additionally, DXP 6mg significantly improved subjective variables including LSO (p<0.0001), sWASO (p=0.0063), sTST (p<0.0001), and sleep quality (p=0.0004), versus PBO. There was no consistent evidence of next-day residual sedation and also minor sleep stages alterations. The incidence of adverse events was comparable to placebo. CONCLUSIONS: In this model of transient insomnia, DXP 6mg demonstrated significant improvements in sleep onset, sleep maintenance, sleep duration and sleep quality, and also appeared to reduce early morning awakenings. These data suggest that DXP 6mg may be effective and well tolerated in adults experiencing transient insomnia.

6. **Huang YS, Hsu SC, Liu SI, Chen CK. A double-blind, randomized, comparative study to evaluate the efficacy and safety of zaleplon versus zolpidem in shortening sleep latency in primary insomnia. Chang Gung Med J. 2011 Jan-Feb;34(1):50-6.**

BACKGROUND: Benzodiazepines cause a high proportion of adverse effects while non-benzodiazepine compounds have demonstrated high efficacy and less adverse effects in patients with insomnia. The objective of this study was to compare the effectiveness and safety of non-BZ zaleplon and zolpidem in primary insomnia. METHODS: This was a randomized, double-blind, active-controlled, double-dummy, comparative study. A total of 48 patients were enrolled, of which 45 patients completed the study. Patients who entered the study were required to take the study drug orally once daily at bedtime for two weeks. Each patient kept a sleep diary and answered a questionnaire. We used these documents to measure and evaluate changes from baseline to Week 2 in sleep latency, duration and quality of sleep, the number of awakenings and incidence of rebound insomnia. RESULTS: The data revealed a significant decrease in sleep latency from baseline to Week 2 for patients receiving zaleplon 10 mg and zolpidem 10 mg. Patients receiving zaleplon exhibited a marginally greater, but not statistically significant, reduction in sleep latency than those who received zolpidem. There was no significant difference in the frequency of adverse effects between the zaleplon and zolpidem groups; however, during this clinical trial there was one lethal event caused by a traffic accident in the zaleplon group. CONCLUSION: There was no significant difference between zaleplon and zolpidem in the efficacy of reducing sleep latency or adverse effects. A large pharmacovigilance study is needed before concluding that either zolpidem or zaleplon is free from next-day residual effects.

7. **McElroy SL, Winstanley EL, Martens B, Patel NC, Mori N, Moeller D, McCoy J, Keck PE Jr. A randomized, placebo-controlled study of adjunctive ramelteon in ambulatory bipolar I disorder with manic symptoms and sleep disturbance. Int Clin Psychopharmacol. 2011 Jan;26(1):48-53.**

This study evaluated the efficacy and tolerability of ramelteon in ambulatory bipolar I disorder with manic symptoms and insomnia. Twenty-one outpatients with bipolar I disorder by Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria with mild-to-moderate manic symptoms and sleep disturbance were randomized to receive either ramelteon (N=10) or placebo (N=11) in an 8-week, double-blind, fixed-dose (8 mg/day) study. Ramelteon and placebo had similar rates of reduction in ratings of symptoms of insomnia, mania, and global severity of illness. However, ramelteon was associated with improvement in a global rating of depressive symptoms. It was also well tolerated and associated with no serious adverse events. The small sample size may have limited the ability of the study to detect potentially clinically important drug-placebo differences. Further studies of ramelteon in subgroups of bipolar patients with sleep disturbance, including those with depression or euthymia, seem indicated.

8. **Gooneratne NS, Gehrman P, Gurubhagavatula I, Al-Shehabi E, Marie E, Schwab R. Effectiveness of ramelteon for insomnia symptoms in older adults with obstructive sleep apnea: a randomized placebo-controlled pilot study. J Clin Sleep Med. 2010 Dec 15;6(6):572-80.**

STUDY OBJECTIVES: To evaluate the effectiveness of ramelteon, a melatonin receptor agonist, for the treatment of insomnia in older adults starting auto-titrating positive airway pressure (APAP) therapy for sleep apnea. METHODS: A parallel group, randomized, double-blind, placebo-controlled pilot effectiveness clinical trial. The study enrolled 21 research study participants who were ≥ 60 years old and had obstructive sleep apnea, defined by an apnea-hypopnea index (AHI) ≥ 5 events/h, with complaints of insomnia. The primary outcome measure was change in sleep onset latency determined from polysomnography at 4 weeks. Research study participants, all of whom were starting on APAP, were randomized to ramelteon 8 mg (n = 8) or placebo (n = 13). RESULTS: Ramelteon treatment was associated with a statistically significant difference in sleep onset latency (SOL) as measured by polysomnography of 28.5 min (± 16.2 min) compared to placebo (95% C.I. 8.5 min to 48.6 min, effect size 1.35, p = 0.008). This was due to a 10.7 (± 17.0) min SOL reduction in the ramelteon arm and a 17.8 (± 23.5) min SOL increase in the placebo arm. No change was noted in subjective sleep onset latency (-1.3 min, ± 19.3 min, 95% C.I.: -21.4 min to 18.7 min). No statistically significant changes were noted in the AHI, sleep efficiency (polysomnography and self-report), APAP adherence, Pittsburgh Sleep Quality Index global score, or Epworth Sleepiness Scale score when comparing ramelteon vs. placebo. Four adverse events occurred in the ramelteon arm and 2 in the placebo arm; none were considered to be related to treatment. CONCLUSIONS: Ramelteon was effective in improving objective, but not subjective, sleep onset latency even in older adults who were starting APAP therapy for sleep apnea. Further research is warranted in examining the role of ramelteon in the care of older adults with insomnia symptoms and sleep apnea.

9. **Krystal AD, Durrence HH, Scharf M, Jochelson P, Rogowski R, Ludington E, Roth T. Efficacy and Safety of Doxepin 1 mg and 3 mg in a 12-week Sleep Laboratory and Outpatient Trial of Elderly Subjects with Chronic Primary Insomnia. Sleep. 2010 Nov;33(11):1553-61.**

STUDY OBJECTIVES: to evaluate the efficacy and safety of doxepin 1 mg and 3 mg in elderly subjects with chronic primary insomnia. DESIGN AND METHODS: the study was a randomized, double-blind, parallel-group, placebo-controlled trial. Subjects meeting DSM-IV-TR criteria for primary insomnia were randomized to 12 weeks of nightly treatment with doxepin (DXP) 1 mg (n = 77) or 3 mg (n = 82), or placebo (PBO; n = 81). Efficacy was assessed using polysomnography (PSG), patient reports, and clinician ratings. Objective efficacy data are reported for Nights (N) 1, 29, and 85; subjective efficacy data during Weeks 1, 4, and 12; and Clinical Global Impression (CGI) scale and Patient Global Impression (PGI) scale data after Weeks 2, 4, and 12 of treatment. Safety assessments were conducted throughout the study. RESULTS: DXP 3 mg led to significant improvement versus PBO on N1 in wake time after sleep onset (WASO; P < 0.0001; primary endpoint), total sleep time (TST; P < 0.0001), overall sleep efficiency (SE; P < 0.0001), SE in the last quarter of the night (P < 0.0001), and SE in Hour 8 (P < 0.0001). These improvements were sustained at N85 for all variables, with significance

maintained for WASO, TST, overall SE, and SE in the last quarter of the night. DXP 3 mg significantly improved patient-reported latency to sleep onset (Weeks 1, 4, and 12), subjective TST (Weeks 1, 4, and 12), and sleep quality (Weeks 1, 4, and 12). Several global outcome-related variables were significantly improved, including the severity and improvement items of the CGI (Weeks 2, 4, and 12), and all 5 items of the PGI (Week 12; 4 items after Weeks 2 and 4). Significant improvements were observed for DXP 1 mg for several measures including WASO, TST, overall SE, and SE in the last quarter of the night at several time points. Rates of discontinuation were low, and the safety profiles were comparable across the 3 treatment groups. There were no significant next-day residual effects; additionally, there were no reports of memory impairment, complex sleep behaviors, anticholinergic effects, weight gain, or increased appetite. CONCLUSIONS: DXP 1 mg and 3 mg administered nightly to elderly chronic insomnia patients for 12 weeks resulted in significant and sustained improvements in most endpoints. These improvements were not accompanied by evidence of next-day residual sedation or other significant adverse effects. DXP also demonstrated improvements in both patient- and physician-based ratings of global insomnia outcome. The efficacy of DXP at the doses used in this study is noteworthy with respect to sleep maintenance and early morning awakenings given that these are the primary sleep complaints of the elderly. This study, the longest placebo-controlled, double-blind, polysomnographic trial of nightly pharmacotherapy for insomnia in the elderly, provides the best evidence to date of the sustained efficacy and safety of an insomnia medication in older adults.

Additional References:

10. Schutte-Rodin S; Broch L; Buysse D; Dorsey C; Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008;4(5):487–504.

Oregon State University College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | Fax 503-947-1119

Month/Year of Review: March 2012
PDL Class: Skeletal Muscle Relaxants

Date of Last Review: May 2005
Source Document: DERP

Current Preferred Agents:
Cyclobenzaprine
Carisoprodol
Baclofen
Methocarbamol
Orphenadrine ER
Carisoprodol/aspirin
Tizanidine

Current Non-Preferred Agents:
Chlorzoxazone
Metaxalone (Skelaxin®)
Dantrolene (Dantrium®)
Cyclobenzaprine ER 24 hr (Amrix®)

Previous Recommendations:

- The evidence does not support any conclusions about the comparative effectiveness between baclofen, tizanidine, or dantrolene for spasticity. All are effective and equivalent to diazepam. Dantrolene is associated with rare serious dose-related hepatotoxicity.
- The evidence does not support any conclusions for the comparative efficacy or safety between skeletal muscle relaxants for musculoskeletal conditions.
- Cyclobenzaprine had the largest body of evidence to support its efficacy compared to placebo.
- Chlorzoxazone is associated with rare serious dose-related hepatotoxicity.
- The evidence does not support any conclusions about the comparative efficacy or adverse effects for different subpopulations of patients such as race, gender, or age.

PA Criteria: A Prior Authorization is in place to support preferred PDL skeletal muscle relaxants and to cover for OHP above the line diagnoses only. A quantity limit restricts carisoprodol products to less than 56 tablets within 90 days unless patient has a terminal illness.

Methods

Three scans were completed by the Oregon Evidence-based Practice Center Drug Effectiveness Review project w a literature search through May 2009. Of those, there were no new, potentially relevant studies. A MEDLINE OVID search was conducted using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials, controlled clinical trials, or meta-analysis from May 2009 (date from last DERP scan) to current. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality 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.

New Trials:

A total of 49 citations resulted from initial literature search. After inclusion for further review, 4 potentially relevant randomized trials were identified (Appendix A) and include two trials evaluating cyclobenzaprine ER (Amrix®), one study

comparing tizanidine sublingual and tizanidine oral, and a randomized trial evaluating carisoprodol 250mg in patients with low back pain. These trials are briefly described in table 1.

Table 1: Potentially relevant new trials

Study	Comparison	Population	Primary Outcome	Results	
Weill, 2010[1] Pooled analysis of 2 RCT, DB, PC, PG studies	Cyclobenzaprine ER (CER) 15mg, CER 30mg, Cyclobenzaprine IR (CIR) 10mg TID, or placebo N=330 14 days	Adults with local muscle spasm associated with neck/low back pain	Patient's rating of medication helpfulness and physicians' clinical global assessment of response at day 4	<u>Patient's rating of medication helpfulness good to excellent (day 4):</u> CER 15: 65 (51.2%) CER30: 68 (54%) CIR10: 71 (57.7%) PI: 46 (35.9%) P<0.025 for both doses of CER vs. placebo NS for both doses of CER vs. CIR 10mg TID	<u>Relief from local pain</u> CER 15: 74 (58.3%) CER30: 84 (66.7%) CIR10: 79 (64.2%) PI: 60 (46.9%) <u>physicians' clinical global assessment</u> NS for all treatment groups Overall 34.5% attrition
Vakhapova, 2010[2] RCT, DB, DD, PC	Tizanidine 8mg SL vs. tizanidine 8mg PO vs. placebo N=16	Adults with Multiple Sclerosis and spasticity requiring treatment	Spasticity as measured by the Ashworth Scale	<u>Spasticity (mean Ashworth scale)</u> TZ SL: 8.31 TZ PO: 9.5 Pla: 11.31 P=0.002; SL vs. placebo P=0.002; PO vs. placebo P=0.34 SL vs. PO tizanidine NS for all treatment groups in mobility time	
Malanga, 2009[3] 2 RCT, DB, PC	Cyclobenzaprine ER (CER) 15mg, CER 30mg, Cyclobenzaprine IR (CIR) 10mg TID, or placebo N=504 14 days	Adults with muscle spasm of cervical or lumbar origin associated with local pain	Patient's rating of medication helpfulness and physicians' clinical global assessment of response at day 4	*<u>Study 1105</u>* <u>Patient's rating of medication helpfulness good to excellent (day 4):</u> CER30: 38 (58.4%) CER15: 30 (16.9%) CIR10: 31 (49.9%) PI: 21 (32.8%) P=0.007; CER30 vs. Placebo P=0.29; CER14 vs. placebo P=0.061 CIR vs. placebo <u>physicians' clinical global assessment</u> NS for all treatment groups	*<u>Study 1106</u>* <u>Patient's rating of medication helpfulness good to excellent (day 4):</u> CER30: 30 (48.3%) CER 15: 35 (55.5%) CIR10: 40 (65.5%) PI: 25 (39.1%) P=0.018; CER15 vs. placebo P=0.092; CER30 vs. placebo P=0.007; CIR vs. placebo <u>physicians' clinical global assessment</u> NS for all treatment groups
Serfer, 2012[4] DB, RCT, PC	Carisoprodol 250mg QID vs. Carisoprodol 350mg QID vs. placebo (n=806) 1 week	Painful musculoskeletal spasm of the lower back	Patient-rated relief from starting backache and patient rated global impression of change	*<u>Patient-rated relief</u>* 250mg: 64.3% 350mg: 66.2% Pla: 52.2% P=0.0001 for 250mg v. pla P<0.001 for 350mg vs. pla P=NS for 250mg vs. 350mg	*<u>Global impression of change (mean improvement)</u>* P=0.0046 for 250mg vs. pla P=0.0011 for 350mg vs. pla P=NS for 250mg vs. 350mg *<u>Discontinuations due to adverse events</u>* 250mg: 3 (1.1%) 350mg: 15 (5.0%) Pla: 10 (3.3%)

New drugs:
None

New formulations/dosage forms:
Cyclobenzaprine Extended Release Oral Capsule (Amrix®) 15mg, 30mg strengths: Approved 2/1/07

New FDA Indications:
None

New FDA safety alerts:

SMR	Date	Alert type	Focus
Carisoprodol	9/07	Label Change: Warnings, Precautions and Adverse Reactions	Risk of sedative properties, drug dependence, withdrawal and abuse
Tizanidine	4/07	Label Change: Contraindications and warnings	When administered with fluvoxamine or ciprofloxacin (CYP1A2 inhibitors), the serum concentration of tizanidine was significantly increased and potentiated its hypotensive and sedative effects
Metaxalone	10/2008	Precaution	The sedative effects of Skelaxin and other CNS depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants) may be additive. Therefore, caution should be exercised with patients who take more than one of these CNS depressants simultaneously

New Systematic Reviews:
One review from the Cochrane Collaboration (Appendix B) assessed the effectiveness and safety of drugs for the long-term treatment of spasticity in Spinal Cord Injury (SCI) patients.[5] Nine studies were identified, two of these evaluating intrathecal baclofen. One study showed a significant improvement in spasticity as measured by the Ashworth scale in tizanidine compared to placebo (-3.70, SE 0.67; $p<0.001$) but no differences in activities of daily living. Results from studies for gabapentin, clonidine, diazepam, and baclofen did not provide evidence for clinically significant effectiveness. Overall, there was insufficient evidence to make conclusions for antispastic treatment in SCI patients.[5]

A second review from the Cochrane Collaboration evaluated anti-spasticity agents in patients with Multiple Sclerosis (MS) and again found insufficient evidence for comparative effectiveness conclusions between the medications.[6] Twenty six placebo controlled and thirteen comparative studies were included in this review and only three of the placebo-controlled trials and none of the comparative studies showed a statistically significant difference in the Ashworth scale for spasticity between the drugs. The remaining studies were assessed using unvalidated scores and results of functional assessments were inconclusive.[6]

Recommendations:
1. No further research or review needed.
2. Evaluate comparative costs for any further decisions or changes.

Appendix A: New Trial Abstracts

1. **Weil AJ, Ruoff GE, Nalamachu S, Altman CA, Xie F, Taylor DR. Efficacy and tolerability of cyclobenzaprine extended release for acute muscle spasm: a pooled analysis. Postgrad Med. 2010 Jul;122(4):158-69.**

OBJECTIVE: To assess the efficacy and tolerability of once-daily cyclobenzaprine extended release (CER) 15 and 30 mg in relieving acute muscle spasm. METHODS: This is a pooled analysis of 2 randomized, double-blind, placebo-controlled, parallel-group studies of identical design. Adults with local muscle spasm associated with neck/low back pain were randomized to treatment with once-daily CER 15 (n = 127) or 30 mg (n = 126), cyclobenzaprine immediate release (CIR) 10 mg 3 times daily (n = 123), or placebo (n = 128) for 14 days. Primary outcome measures were the patient's rating of medication helpfulness and physician's clinical global assessment of response to therapy at day 4. RESULTS: Of 504 patients, 330 (65.5%) completed the studies. Significantly greater improvements in patient's rating of medication helpfulness were reported with CER 15 and 30 mg versus placebo at day 4 ($P < 0.025$). No differences were reported between groups in physician's clinical global assessment. Significantly greater improvements ($P < 0.025$) were noted in patient-rated secondary measures versus placebo: relief from local pain at days 4 (CER 30 mg) and 8 (CER 15 and 30 mg), global impression of change at days 4 and 8 (CER 30 mg), and restriction of movement at day 4 (CER 30 mg). Improvements with CER 15 and 30 mg on most efficacy measures were similar to CIR. There was less reported daytime drowsiness with CER 15 and 30 mg than with CIR ($P < 0.05$). Most adverse events (AEs) were mild in intensity. The most common AEs for all groups were dry mouth, constipation, dizziness, headache, and somnolence. The rate of somnolence reported as an AE was lower ($P < 0.05$) with CER 15 (0.8%) and 30 mg (1.6%) than with CIR (7.3%). CONCLUSION: Once-daily CER was effective in relieving acute muscle spasm based on patient's rating of medication helpfulness at day 4 and was generally well tolerated with a low rate of reported somnolence.

2. **Vakhapova V, Auriel E, Karni A. Nightly sublingual tizanidine HCl in multiple sclerosis: clinical efficacy and safety. Clin Neuropharmacol. 2010 May;33(3):151-4.**

BACKGROUND: Approximately 90% of patients with multiple sclerosis (MS) experience spasticity during their lifetime. Tizanidine HCl is an alpha2 adrenergic agonist indicated for treating spasticity due to MS or spinal cord injury. OBJECTIVES: To compare the clinical efficacy and safety of once-nightly sublingual versus oral tizanidine HCl (8 mg) or placebo in MS patients with spasticity requiring treatment. METHODS: A double-blind, double-dummy, randomized, 3-treatment, 2-way crossover, comparative, placebo-controlled study was conducted in a neuroimmunology clinic of a university-affiliated medical center (December 2005 to March 2006). Enrolled patients received placebo once nightly and were then randomized to receive oral tizanidine HCl following sublingual tizanidine HCl or sublingual tizanidine HCl following oral tizanidine HCl, each arm for 7 days. The patients were evaluated for spasticity (Ashworth scale), mobility, Global Assessments of Disease Severity and Change, and safety parameters, including next-day somnolence (Epworth Sleepiness Scale), fatigue, hypotension, and hepatotoxicity. RESULTS: Sixteen MS patients aged 20 to 65 years with spasticity requiring treatment and Expanded Disability Status Scale score of 6.5 or less were enrolled. There were significant reductions in next-day (12-14 hours after dosing) spasticity following sublingual tizanidine compared with placebo and oral tizanidine, oral versus placebo treatment, and sublingual tizanidine versus placebo treatment. Fatigue, hypotension, or hepatotoxicity levels did not increase. CONCLUSIONS: Overnight sublingual tizanidine provides improvement in next-day spasticity compared with placebo, without increasing next-day somnolence. The Epworth somnolence score improved significantly with sublingual tizanidine treatment. This is contrary to the reported day-dose tizanidine use, in which increased somnolence is the most cited cause for patient dissatisfaction and noncompliance.

3. **Malanga GA, Ruoff GE, Weil AJ, Altman CA, Xie F, Borenstein DG. Cyclobenzaprine ER for muscle spasm associated with low back and neck pain: two randomized, double-blind, placebo-controlled studies of identical design. Curr Med Res Opin. 2009 May;25(5):1179-96.**

OBJECTIVE: To evaluate efficacy and tolerability of once-daily cyclobenzaprine extended release (CER) 15- and 30-mg capsules in patients with muscle spasm associated with acute, painful musculoskeletal conditions. METHODS: Two identically designed, randomized, double-blind, placebo- and active-controlled, parallel-group studies in patients aged 18-75 years with muscle spasm associated with neck or back pain. Patients received CER 15 or 30 mg once daily, cyclobenzaprine immediate release (CIR) 10 mg three times daily, or placebo for 14 days. Primary efficacy measures were patient's rating of medication helpfulness and physician's clinical global assessment of response to therapy at day 4. Secondary measures were patient's rating of medication helpfulness and physician's clinical global assessment of response (days 8 and 14), relief from local pain, global impression of change, restriction in activities of daily living, restriction of movement, daytime drowsiness, quality of nighttime sleep (days 4, 8, and 14), and quality of life (days 8 and 14). RESULTS: A total of 156/254 randomized patients in study 1 and 174/250 in study 2 completed 14 days of treatment. Significant improvements in patient's rating of medication helpfulness were reported with CER versus placebo (CER 30 mg, study 1, $p = 0.007$; CER 15 mg, study 2, $p = 0.018$) at day 4. Significant improvements with CER 30 mg versus placebo were also seen at day 4 in study 1 for patient-rated global impression of change ($p = 0.008$), relief of local pain ($p = 0.004$), and restriction of movement ($p = 0.002$). Neither study reported differences between study groups on the physician's clinical global assessment. Improvements with CER were comparable to that of CIR. In both studies, daytime drowsiness was reported more frequently in active treatment groups than in the placebo group; however, reports of drowsiness decreased over time in all groups. In general, daytime drowsiness was reported more frequently in CIR groups than in CER groups. More adverse events were reported in the active treatment groups versus placebo and were similar in the CER and CIR groups, except somnolence, which occurred more frequently with CIR. CONCLUSIONS: Once-daily CER 15 mg (study 2) and CER 30 mg (study 1) were effective in treating muscle spasm associated with painful musculoskeletal conditions after 4 days of treatment. Differences between CER and placebo groups did not reach statistical significance on all efficacy measures, and the protocols were not powered to detect differences between active treatment arms. CER was generally safe and well tolerated, with low rates of somnolence.

4. **Serfer GT, Wheeler WJ, Sacks HJ. Randomized, double-blind trial of carisoprodol 250 mg compared with placebo and carisoprodol 350 mg for the treatment of low back spasm. Curr Med Res Opin. 2010 Jan;26(1):91-9.**

BACKGROUND: Carisoprodol, a centrally active skeletal muscle relaxant, is widely used for the treatment of acute, painful musculoskeletal disorders. When administered at a dose of 350 mg four times daily, carisoprodol demonstrated significant clinical benefit in its early clinical development trials; however, some unfavorable side effects, such as drowsiness and dizziness, were reported. Recently, research was conducted to determine if a lower dose of carisoprodol would retain efficacy but improve tolerability compared to the higher 350-mg dose. OBJECTIVE: The purpose of this multicenter study was to compare the efficacy and safety of carisoprodol 250-mg tablets four times daily to 350-mg tablets four times daily and to placebo in patients with acute, painful musculoskeletal spasm of the lower back.RESEARCH DESIGN AND METHODS: In this 1-week double-blind, placebo-controlled, parallel-group multicenter trial, patients 18 to 65 years of age with moderate to severe back spasm were randomly assigned to treatment with carisoprodol 250-mg tablets ($n = 264$), 350-mg tablets ($n = 273$), or matching placebo tablets ($n = 269$) three times daily and at bedtime. MAIN OUTCOME MEASURES: The coprimary efficacy variables were patient-rated relief from starting backache and patient-rated global impression of change assessed on treatment day 3. RESULTS: The carisoprodol 250-mg regimen was significantly more effective than placebo as assessed by both patient-rated relief from starting backache ($p = 0.0001$) and patient-rated global impression of change ($p = 0.0046$). There were no significant differences between the 250-mg and 350-mg dosages for the coprimary efficacy endpoints, and patients improved with or without sedation. Fewer than 1% of patients in the carisoprodol 250-mg group discontinued prematurely because of treatment-emergent adverse events, and no patient discontinued because of drowsiness. CONCLUSIONS: When administered three times daily and at bedtime, carisoprodol 250 mg was as effective as 350 mg three times daily and at bedtime with a lower incidence of adverse events and fewer discontinuations of therapy due to adverse events. Patients improved whether or not they reported sedation as an adverse event.

5. **Taricco M, Adone R, Pagliacci C, Telaro E. Pharmacological interventions for spasticity following spinal cord injury. Cochrane Database of Systematic Reviews 2000, Issue 2. Art. No.: CD001131. DOI: 10.1002/14651858.CD001131.**

Objectives: To assess the effectiveness and safety of baclofen, dantrolene, tizanidine and any other drugs for the treatment of long-term spasticity in SCI patients, as well as the effectiveness and safety of different routes of administration of baclofen. Methods: We searched the Cochrane Injuries Group Specialised Register, CENTRAL, MEDLINE/PubMed, EMBASE, Zetoc, Web of Knowledge, CINAHL and Current Controlled Trials. We also checked the reference lists of relevant papers to identify any further studies. The searches were last conducted in July 2008. All parallel and cross-over randomised controlled trials (RCTs) including spinal cord injury patients complaining of 'severe spasticity'. Studies where less than 50% of patients had a spinal cord injury were excluded. Methodological quality of studies (allocation concealment, blinding, patient's characteristics, inclusion and exclusion criteria, interventions, outcomes, losses to follow up) was independently assessed by two investigators. The heterogeneity among studies did not allow quantitative combination of results. Results: Nine studies met the inclusion criteria. Study designs were: 8 cross-over and 1 parallel-group trial. Two studies (14 SCI patients), showed a significant effect of intrathecal baclofen in reducing spasticity (Ashworth Score and ADL performances), compared to placebo, without any adverse effects. The study comparing tizanidine to placebo (118 SCI patients) showed a significant effect of tizanidine in improving Ashworth Score but not in ADL performances. The tizanidine group reported significant rates of adverse effects (drowsiness, xerostomia). For the other drugs (gabapentin, clonidine, diazepam, amytal and oral baclofen) the results did not provide evidence for clinically significant effectiveness. Conclusion: There is insufficient evidence to assist clinicians in a rational approach to antispastic treatment for SCI. Further research is urgently needed to improve the scientific basis of patient care.

6. **Shakespeare D, Boggild M, Young CA. Anti-spasticity agents for multiple sclerosis. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD001332. DOI: 10.1002/14651858.CD001332.**

Objectives: To assess the absolute and comparative efficacy and tolerability of anti-spasticity agents in MS patients.

Methods: We searched the Cochrane MS Group trials register (June 2003), the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2003), MEDLINE (January 1966 to June 2003), EMBASE (January 1988 to June 2003), bibliographies of relevant articles, personal communication, manual searches of relevant journals and information from drug companies. Double-blind, randomised controlled trials (either placebo-controlled or comparative studies) of at least seven days duration. Two independent reviewers extracted data and the findings of the trials were summarised. Missing data were collected by correspondence with principal investigators. A meta-analysis was not performed due to the inadequacy of outcome measures and methodological problems with the studies reviewed. Results: Twenty-six placebo-controlled studies (using baclofen, dantrolene, tizanidine, botulinum toxin, vigabatrin, prazepam, threonine and cannabinoids) and thirteen comparative studies met the selection criteria and were included in this review. Only fifteen of these studies used the Ashworth scale, of which only three of the eight placebo-controlled trials and none of the seven comparative studies showed a statistically significant difference between test drugs. Spasms, other symptoms and overall impressions were only assessed using unvalidated scores and results of functional assessments were inconclusive. Conclusions: The absolute and comparative efficacy and tolerability of anti-spasticity agents in multiple sclerosis is poorly documented and no recommendations can be made to guide prescribing. The rationale for treating features of the upper motor neurone syndrome must be better understood and sensitive, validated spasticity measures need to be developed.

Oregon State University
College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | Fax 503-947-1119

Month/Year of Review: March 2012
PDL Class: Triptans

Date of Last Review: March 2010 (literature through 2008)
Source Document: DERP Report (June 2009)

Current Preferred Agents:		Current Non-Preferred Agents:	
Sumatriptan (Imitrex ®) Injection	Sumatriptan Succinate Oral	Eletriptan (Relpax®)	Zolmitriptan (Zomig®)
Sumatriptan (Imitrex®) Nasal	Zolmitriptan (Zomig®) Nasal	Frovatriptan (Frova®) oral	Sumatriptan/naproxen (Treximet®)
Naratriptan Oral		Naratriptan	
		Rizatriptan (Maxalt®) oral	Almotriptan (Axert®) oral

Previous Recommendations:

1. In comparing the effectiveness and duration of response of different triptans in reducing the severity and duration of symptoms in adult patients with moderate to severe migraine the oral triptans were similarly efficacious.
2. Good strength evidence for reformulated sumatriptan/naproxen versus reformulated sumatriptan 85 mg found the combination superior in pain-free at 2 hours and 24 hours and in normal renal function, overall productivity, and patient satisfaction. There is no evidence comparing the combination product to an available dose of sumatriptan. There is no evidence comparing the combination product to individual component therapy.
3. There are no fully published head-to-head trials of frovatriptan.
4. Injectable sumatriptan is effective, but there are no acceptable head-to-head studies comparing injectable to the oral form.
5. Nasal sumatriptan and zolmitriptan are effective, but there is insufficient data to determine a clinically significant difference for the comparison of zolmitriptan nasal spray vs. the oral form of the drug. There were no head to head trials comparing sumatriptan nasal spray to the oral form of the drug.
6. Most of the studies were rated fair quality or below because of variability in endpoints and lack of standard measures for pain relief or time to pain relief.
7. Based on poor strength evidence there is no evidence that any one triptan has a particular advantage or disadvantage over others in any subgroups based on age, gender, race, use of prophylactic treatment, or association with menstruation.

PA Criteria/QL: A Prior Authorization is in place to promote preferred PDL options, quantity limits to decrease potential for medication overuse, and therapeutic duplication denials.

Methods:
A MEDLINE OVID search was conducted using all included drugs in adults with any level of migraine and limits for humans, English language, and controlled clinical trials or meta-analysis from 2009 to current. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, the Department of Veteran Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality 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.

New Trials:
A total of 51 citations resulted and after review for inclusions, nine potentially relevant clinical trials were identified, including 2 head to head trials that were not post-hoc sub analysis. The abstracts of these are included in appendix 1.

Study	Comparison	Population	Primary Outcome	Results	
Steeburger, et al.[1] RCT, PC, DB	Rizatriptan 10-mg ODT vs. placebo	Non-responders to sumatriptan	Two hour pain relief	<u>Response rate – two hour pain relief:</u> Riza 51% Placebo 20% RR 2.55; P<0.001	
Bartolini et al.[2] RCT, DB	Frovatriptan 2.5mg vs. almotriptan 12.5mg	History of migraine with or without aura, with at least one attack in the preceding 6 mo	Patient satisfaction	<u>Preference Score:</u> F: 3.1 ± 1.3 A: 3.4 ± 1.3 P = NS	<u>Response rate – two hour pain relief:</u> F: 143 (54%) A: 144 (56%) RR 0.96; p=NS
Allias, et al.[3] RCT, DB, PC	Almotriptan vs. placebo	Women with menstrually related migraine	Two hour pain relief	<u>Pain free at two hours:</u> A: 59 (48.4%) Pl: 32 (26.2%) RR 1.81 95% CI (1.28 -2.57); P=0.008	
Tullo, et al.[4] RCT, DB	Frovatriptan 2.5mg vs. zolmitriptan 2.5mg	Male or female subjects, 18–65 y/o, current history of migraine with or without aura	Patient satisfaction	<u>Preference Score:</u> F: 2.9 ± 1.3 Z: 3.0 ± 1.3 P = NS	<u>Response rate – two hour pain relief:</u> F: 141 (57%) A: 142 (58%) RR 0.98; p=NS
Allias, et al.[5] Post-hoc subanalysis	Forvatriptan 2.5mg vs. zolmitriptan 2.5mg	Analysis of women with menstrually related migraine selected from Tullo RCT	Number of pain-relief episodes at 2 and 24 hr.	<u>Risk of Recurrence</u> F: 11 (15%) Z: 14 (22%) P<0.05	<u>Response rate – two hour pain relief:</u> F: 31 (52%) Z: 26 (53%) RR 0.98 95% CI (0.6 to 1.5) P = NS
Spierings, et al[6] Long term, open label	Frovatriptan 2.5mg vs. placebo	Male or female, 18–65 y/o, migraine with or without aura	Tolerability and safety of frovatriptan	173 (36%) of the 486 subjects in the study did not take a second dose at 2 hours for nonresponse.	
Matthew, et al.[7] Analysis of 2 RCT, DB, PC studies	Sumatriptan/naproxen vs. placebo	Those who had discontinued a short-acting triptan in the past year because of poor response or intolerance	Number of patients with 2-through 24-hour sustained pain-free response	<u>2-hour pain free response</u> *Study 1* S/N: 54 (40%) P: 23 (17%) RR 2.35 95% CI (1.5 - 3.7) P<0.001	 *Study 2* S/N: 58 (44%) P: 19 (14%) RR 3.14 95% CI (1.9 -5) P<0.001
Cady, et al.[8] RCT, PC, DB	Rizatriptan 10mg ODT vs. placebo	≥ 18 y/o, at least a 1-year history of migraine with or without aura	Pain freedom at 2 hours	<u>Response rate – two hour pain relief:</u> R: 66% P: 28% RR 2.4 95%CI (1.68 to 3.49); P<0.001	
Ng-Mak, et al.[9] Post-hoc subanalysis, open-label	Rizatriptan 10mg vs. almotriptan 12.5mg	≥ 18 y/o, recent history of ≥1 migraines/month, rizatriptan naïve.	the times to onset of Pain relief (PR) and pain freedom (PF)	<u>Onset of PR in 2 hr</u> R: 88.6% A: 73.4% RR 1.2; P=0.007	<u>Onset of PF in 2 hr</u> R: 55.7% A: 45.6% P=NS

RCT = randomized controlled trial, PC = placebo controlled, DB = double blind

New drugs:
There were no new molecular entities FDA approved. A new formulation of sumatriptan was FDA-approved in July, 2009 for the acute treatment of migraine attacks with or without an aura.[10] Sumavel DosePro (sumatriptan) is a needle-free subcutaneous delivery system that delivers 6 mg of sumatriptan subcutaneously with a high-pressure burst of nitrogen gas instead of a needle. The needle-free system works as fast and as well as the needle injections but it can actually cause more redness, swelling, bleeding, and bruising than a needle injection. Approval was based on the demonstration of bioequivalence with traditional injected subcutaneous sumatriptan. An open-label study found the rates of attacks associated with pain relief were 30.7%, 66.4%, 80.1%, 81.6%, and 77.6% at 0.25, 0.5, 1, 2, and 24 hours after dosing, respectively.[11] Also patient satisfaction improved from baseline to the end of treatment for efficacy and functionality, but declined for ease of use (79.6±16.0 versus 69.7±25.6, p=0.0007).[11]

New FDA Indications:
Almotriptan: Acute treatment of migraine in adolescents, aged 12 to 17 years - 5/2009

New FDA safety alerts:
The only new safety information identified included changes to the Warnings and Precautions section of the product labels for almotriptan and frovatriptan. In March of 2009, information concerning the risk of serotonin syndrome with concomitant use of SSRIs/SNRIs was added for both almotriptan and frovatriptan. Additionally for almotriptan, in April of 2009, advice was added that, due to its chemical structure containing a sulfonyl group, caution should be used in prescribing almotriptan to patients with known hypersensitivity to sulfonamides.

New Systematic Reviews:
Four recent systematic reviews from the Cochrane Collaboration were published evaluating the efficacy of sumatriptan as oral, subcutaneous, intransal, and rectal routes of administration in acute migraine attacks in adults (Appendix 2).[12-15] These reviews concluded that oral, subcutaneous, and intransal sumatriptan is effective as an abortive treatment for migraine attacks, relieving pain, nausea, photophobia, phonophobia, and functional disability, but are associated with increased adverse events. There was limited data for sumatriptan administered rectally (3 studies; 866 participants) that demonstrated 25 mg administered rectally an effective treatment for acute migraine attacks in reducing pain and functional disability.[12] But there was insufficient data to make conclusions on the relief of headache-associated symptoms or incidence of adverse events for rectal administration of sumatriptan.

Twelve studies (4755 participants) compared intranasal sumatriptan with placebo or an active comparator.[13] Most of the data were for the 10 mg and 20 mg doses. Sumatriptan surpassed placebo for all efficacy outcomes. Pain was reduced from moderate or severe to no pain by two hours in approximately 2 in 10 people (24%) taking sumatriptan 10 mg, compared with about 1 in 10 (10%) taking placebo.[13] Pain was reduced from moderate or severe to no worse than mild pain by two hours in 5 in 10 people (50%) taking sumatriptan 10 mg, compared with approximately 3 in 10 (32%) taking placebo. Direct comparison of sumatriptan with active treatments was limited to two studies, one comparing sumatriptan 20 mg and dihydroergotamine (DHE) 1 mg, and one comparing sumatriptan 20 mg with rizatriptan 10 mg. The proportion of participants who were pain-free at two hours was 37% (76/208) with sumatriptan 20 mg and 40% (79/200) with rizatriptan. In the one active comparator study with rizatriptan, the overall incidence of serious adverse events was 0.48% (1/208) for sumatriptan 20mg, compared with 0% for rizatriptan 10mg. The overall incidence of adverse event withdrawal compared to placebo was 0.19% for all doses of sumatriptan and there were no withdrawals due to adverse events when compared to rizatriptan.[13]

Thirty-five studies (9365 participants) compared subcutaneous sumatriptan with placebo or an active comparator.[14] The majority of included studies were of good methodological quality, Most of the data were for the 6 mg dose. Sumatriptan surpassed placebo for all efficacy outcomes (NNTs were 2.9, 2.3, 2.2, and 2.1 for pain-free at one and two hours, and headache relief at one and two hours, respectively). Results for the 4 mg and 8 mg doses were similar to the 6 mg dose. There was no evidence of increased migraine relief if a second dose of sumatriptan 6 mg was given after an inadequate

response to the first. Sumatriptan was compared directly with a number of active treatments, including other triptans, but there were insufficient data for any pooled analyses or to make firm conclusions for any outcomes of interest. Withdrawals due to adverse events were uncommon. In placebo-controlled studies the rate of adverse event withdrawal after treating with sumatriptan (1.2%) was marginally higher than that after placebo (0.40%).[14]

Sixty-one studies (37,250 participants) compared oral sumatriptan with placebo or an active comparator.[15] Most of the data were for the 50 mg and 100 mg doses. Sumatriptan surpassed placebo for all efficacy outcomes (NNTS were 6.1, 7.5, and 4.0 for pain-free at two hours and headache relief at one and two hours, respectively for 50mg versus placebo and 4.7, 6.8, 3.5 for sumatriptan 100mg). Results for the 25 mg dose were similar to the 50 mg dose, while sumatriptan 100 mg was significantly better than 50 mg for pain-free and headache relief at two hours, and for sustained pain-free during 24 hours. Sumatriptan was compared directly with a number of active treatments, including other triptans. For the outcome of pain-free at two hours, there was no significant difference between sumatriptan 50mg and rizatriptan 5mg or 10mg, sumatriptan 100mg and almotriptan 12.5mg. Rizatriptan 5mg and 10mg were superior to sumatriptan 25mg (NNT 18, 8.5 respectively), and eletriptan 40mg and 80mg were superior to sumatriptan 50mg (NNT 16, 8 respectively). For zolmitriptan 2.5 mg and 5 mg compared with sumatriptan 50 mg, there was no significant difference for headache relief at either one or two hours, There was insufficient comparative evidence to calculate relative risk or NNH for serious adverse events or withdrawals due to adverse events, but for the majority of adverse events, there was no significant difference between sumatriptan and any active comparator.[15]

Guidelines:
Guidelines from the European Federation of Neurological Societies published in 2009 recommend either triptans or NSAIDs for the treatment of acute migraine.[5] The use of subcutaneous sumatriptan is recommended for very severe attacks. These guidelines indicated the minor differences between the triptans including onset of efficacy of pain relief and recurrence rate. There is no evidence that different oral formulations such as rapidly dissolving tablets, wafer forms, or rapid release forms act earlier than others.

In 2011, the guidelines for the diagnosis and treatment of headache were updated by the Institute for Clinical Systems Improvement (ICSI) and recommend triptans as effective for mild to severe migraine headaches. Given a longer half-life of naratriptan, headache response is delayed when compared with other triptans. However, headache recurrence may be less frequent. Also, second doses of triptans have not been shown to relieve headache more if the first dose has been ineffective. Studies show that sumatriptan and naproxen sodium in combination may be more effective than either drug alone. However there are no studies that demonstrate that sumatriptan 85mg/naproxen sodium 500mg is more effective than sumatriptan and naproxen sodium taken together. These guidelines also state that use of drugs for acute treatment of headache for more than nine days per month is associated with an increased risk of chronic daily headache and second doses of triptans have not been shown to relieve headache more if the first dose has been ineffective. Studies show that sumatriptan and naproxen sodium in combination may be more effective than either drug alone.

Recommendations:

- Accept scan as is; no further research or review needed at this time.
- Further review comparative costs due to limited evidence of a difference in effectiveness or safety between agents.

Appendix 1: New Trials

1. **Seeburger JL, Taylor FR, Friedman D, Newman L, Ge Y, Zhang Y, Hustad CM, Lasorda J, Fan X, Hewitt D, Ho T, Connor KM. Efficacy and tolerability of rizatriptan for the treatment of acute migraine in sumatriptan non-responders. Cephalalgia. 2011 May;31(7):786-96. Epub 2010 Nov 15.**

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 100 mg 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 100 mg. 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 100 mg. Rizatriptan was generally well tolerated in this population.

2. **Bartolini M, Giamberardino MA, Lisotto C, Martelletti P, Moscato D, Panascia B, Savi L, Pini LA, Sances G, Santoro P, Zanchin G, Omboni S, Ferrari MD, Brighina F, Fierro B. A double-blind, randomized, multicenter, Italian study of frovatriptan versus almotriptan for the acute treatment of migraine. J Headache Pain. 2011 Jun;12(3):361-8. Epub 2011 Mar 25.**

Objective: The objective of this study was to evaluate patients' satisfaction with acute treatment of migraine with frovatriptan or almotriptan by preference questionnaire.
Methods: 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 6 months, were enrolled and randomized to frovatriptan 2.5 mg or almotriptan 12.5 mg, treating 1-3 attacks. The study had a multicenter, randomized, double blind, cross-over design, with treatment periods lasting <3 months. 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 4 h, and recurrent and sustained pain free episodes within 48 h.
Results: 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 2 h did not significantly differ between treatments. This was the case also at 4 h (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 30 min. No significant differences were observed in sustained pain free episodes (21% vs. 18%). The tolerability profile was similar between the two drugs.
Conclusions: 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.

3. **Allais G, Bussone G, D'Andrea G, Moschiano F, d'Onofrio F, Valguarnera F, Manzoni GC, Grazzi L, Allais R, Benedetto C, Acuto G. Almotriptan 12.5 mg in menstrually related migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia. 2011 Jan;31(2):144-51. Epub 2010 Jul 26.**

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.

Conclusions: Almotriptan was significantly more effective than placebo in women with MRM attacks, with consistent efficacy in longer-term follow-up.

4. **Allais G, Tullo V, Benedetto C, Zava D, Omboni S, Bussone G. Efficacy of frovatriptan in the acute treatment of menstrually related migraine: analysis of a double-blind, randomized, multicenter, Italian, comparative study versus zolmitriptan. Neurol Sci. 2011 May;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 2.5 mg or zolmitriptan 2.5 mg: after treating three episodes of migraine in no more than 3 months 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 2 h was 52% for frovatriptan and 53% for zolmitriptan (p = NS), while rate of pain free at 2 h was 22 and 26% (p = NS), respectively. At 24 h, 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 24 h 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.

5. **Tullo V, Allais G, Ferrari MD, Curone M, Mea E, Omboni S, Benedetto C, Zava D, Bussone G. Frovatriptan versus zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study. Neurol Sci. 2010 Jun;31 Suppl 1:S51-4.**

Objective: 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.

Methods: 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.
Results: 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).
Conclusions: In conclusion, our study suggests that F has a similar efficacy of Z, with some advantage as regards tolerability and recurrence.

6. **Spierings, E. L. H. and C. Keywood (2009). "Rapid responders to frovatriptan in acute migraine treatment: results from a long-term, open-label study." Pain Medicine 10(4): 633-8.**

Objectives: First, assessment of the tolerability and safety of frovatriptan, 2.5-7.5 mg taken orally over 24 hours, for the acute treatment of migraine, repeatedly over a 12-month period. Second, assessment of the efficacy and tolerability of a second, double-blind dose of 2.5-mg frovatriptan, compared with placebo, for nonresponse at 2 hours after treatment of moderate or severe headache with 2.5-mg frovatriptan.
Results: With regard to the first attack treated, 173 (36%) of the 486 subjects in the study did not take a second dose at 2 hours for nonresponse. At 2 hours and 4 hours, these "rapid responders" experienced a decrease in headache intensity from moderate or severe to mild or no pain in 84% and 98%, respectively ("headache response"). Six percent of them experienced recurrence of moderate or severe headache within 24 hours following a response at 4 hours and 12% took rescue medication. The response, measured in terms of median time to "complete migraine relief," was maintained over 30 subsequent migraine attacks, treated from attack 2 onwards over the course of 12 months.
Conclusion: Frovatriptan provides a remarkably fast and high headache response in a subgroup of more than one-third of migraineurs, with a very low 24-hour headache recurrence and low rescue medication intake.

7. **Mathew, N. T., S. Landy, et al. (2009). "Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life." Headache 49(7): 971-82.**

Objective: To evaluate efficacy and tolerability of a single, fixed-dose tablet of sumatriptan 85 mg/naproxen sodium 500 mg (sumatriptan/naproxen sodium) vs. placebo in migraineurs who had discontinued treatment with a short-acting triptan because of poor response or intolerance.
Background: Triptan monotherapy is ineffective or poorly tolerated in 1 of 3 migraineurs and in 2 of 5 migraine attacks. In April, 2008, the Food and Drug Administration approved the combination therapy sumatriptan/naproxen sodium, developed specifically to target multiple migraine mechanisms. This combination product offers an alternative migraine therapy for patients who have reported poor response or intolerance to short-acting triptans.
Methods: Two replicate, randomized, multicenter, double-blind, placebo-controlled, 2-attack crossover trials evaluated migraineurs who had discontinued a short-acting triptan in the past year because of poor response or intolerance. Patients were instructed to treat within 1 hour and while pain was mild. RESULTS: Patients (n = 144 study 1; n = 139 study 2) had discontinued an average of 3.3 triptans before study entry. Sumatriptan/naproxen sodium was superior ($P < .001$) to placebo for 2- through 24-hour sustained pain-free response (primary end point) (study 1, 26% vs 8%; study 2, 31% vs 8%) and pain-free response 2 hours post dose (key secondary end point) (study 1, 40% vs 17%; study 2, 44% vs 14%). A similar pattern of results was observed for other end points that evaluated acute (2- or 4-hour), intermediate (8-hour), or 2- through 24-hour sustained response for migraine (i.e., pain and associated symptoms), photophobia, phonophobia, or nausea (with the exception of nausea 2 and 4 hours post dose). The percentage of patients with at least 1 adverse event (regardless of causality) was 11% with sumatriptan/naproxen sodium compared with 4% with placebo in study 1 and 9% with sumatriptan/naproxen sodium compared with 5% with placebo in study 2. Only 1

adverse event in 1 study was reported in > or =2% of patients after treatment with sumatriptan/naproxen sodium and reported more frequently with sumatriptan/naproxen than placebo: chest discomfort was reported in 2% of subjects in study 1, and no events met this threshold in study 2. No serious adverse events attributed to study medication were reported in either study.
Conclusion: In migraineurs who reported poor response to a short-acting triptan, sumatriptan/naproxen sodium was generally well tolerated and significantly more effective than placebo in conferring initial, intermediate, and sustained efficacy for pain and migraine-associated symptoms of photophobia and phonophobia.

8. **Cady, R. K., V. T. Martin, et al. (2009). "Rizatriptan 10-mg ODT for early treatment of migraine and impact of migraine education on treatment response." Headache 49(5): 687-96.**

Objective: To examine the efficacy of rizatriptan 10-mg orally disintegrating tablet (ODT) for treating migraines of mild intensity soon after onset, with or without patient-specific migraine education.
Background: Studies have shown rizatriptan tablet efficacy in early migraine treatment.
Methods: In this randomized, placebo-controlled, double-blind, factorial design study, adults with a history of migraine were assigned to rizatriptan 10-mg ODT patient education (personalized summary of early migraine signs and symptoms) or placebo patient education in a 1 : 1 : 1 : 1 ratio. Patients were instructed to treat 1 attack at the earliest time they knew that their headache was a migraine, while pain was mild. During the next 24 hours, patients assessed pain severity, associated symptoms, functional disability, use of rescue medication, and treatment satisfaction. The primary endpoint was pain freedom at 2 hours; a key secondary endpoint was 24-hour sustained pain freedom. Results: Of 207 patients randomized to treatment, 188 (91%) treated a study migraine. Significantly more patients taking rizatriptan reported pain freedom at 2 hours compared with placebo (66.3% vs 28.1%, P < .001). Similarly, significantly more patients taking rizatriptan reported 24-hour sustained pain freedom (52.2% vs 17.7%, P < .001). A greater proportion of patients in the rizatriptan + education group reported pain freedom at 2 hours compared with those in the rizatriptan + no education group (71.7% vs 60.9%, P = .430). Few adverse events were reported. Conclusion: Rizatriptan 10-mg ODT, when taken early, while headache pain is mild, was superior to placebo at providing pain freedom at 2 hours and 24-hour sustained pain freedom.

9. **Ng-Mak, D. S., X. H. Hu, et al. (2009). "Migraine treatment with rizatriptan and almotriptan: a crossover study." Headache 49(5): 655-62.**

Background: Rizatriptan and almotriptan are effective and well-tolerated triptans that have not been compared directly.
Objective: To evaluate the effectiveness of rizatriptan 10 mg and almotriptan for the acute treatment of migraine, in a real-world setting.
Methods: Of a large, multicenter, open-label, crossover study, we conducted a substudy to contrast the effectiveness of rizatriptan 10 mg and almotriptan 12.5 mg for the acute treatment of 2 migraine attacks in a sequential, crossover manner. Time to outcome was assessed using stopwatches. Mean and median times to onset of pain relief (PR) and pain freedom (PF) for rizatriptan and almotriptan were compared. The
effect of rizatriptan on times to onset of PR and PF, adjusting for potential confounding factors (treatment sequence, treatment order, and use of rescue medication), was computed via a Cox proportional hazard model.
Results: Out of the 146 patients taking almotriptan as their usual care medication, 79 used stopwatch for both attacks. Significantly more patients taking rizatriptan achieved onset of PR within 2 hours after dosing than those taking almotriptan (88.6% vs 73.4%, P = .007). A higher proportion of patients taking rizatriptan achieved PF within 2 hours after dosing than those taking almotriptan (55.7% vs 45.6%, P = .10). Times to onset of PR and PF were significantly shorter with those patients taking rizatriptan than with those taking almotriptan (median time to PR: 45 vs 60 minutes, P = .002; median time to PF: 100 vs 135 minutes, P = .004). The adjusted proportional hazard ratios (rizatriptan vs almotriptan) for times to onset of PR and PF were 1.51 (95% confidence interval 1.20 to 1.88) and 1.42 (95% confidence interval 1.15 to 1.76), respectively. More patients were very satisfied when treating their attacks with rizatriptan than with almotriptan. Rizatriptan was preferred by most patients. Conclusions: Times to achieve PR and PF were significantly shorter for patients using rizatriptan, as compared with those using almotriptan

12. **Christopher J Derry, Sheena Derry, R Andrew Moore Sumatriptan (rectal route of administration) for acute migraine attacks in adults: Cochrane Pain, Palliative and Supportive Care Group Published Online: 15 FEB 2012 DOI: 10.1002/14651858.CD009664**

Background: Migraine is a highly disabling condition for the individual and also has wide-reaching implications for society, healthcare services, and the economy. Sumatriptan is an abortive medication for migraine attacks, belonging to the triptan family. Rectal administration may be preferable to oral for individuals experiencing nausea and/or vomiting. To determine the efficacy and tolerability of rectal sumatriptan compared to placebo and other active interventions in the treatment of acute migraine attacks in adults.

Methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, online databases, and reference lists for studies through 13 October 2011. We included randomised, double-blind, placebo- and/or active-controlled studies using rectally administered sumatriptan to treat a migraine headache episode, with at least 10 participants per treatment arm. Two review authors independently assessed trial quality and extracted data. We used numbers of participants achieving each outcome to calculate relative risk (or 'risk ratio') and numbers needed to treat to benefit (NNT) or harm (NNH) compared to placebo or a different active treatment.

Results: Three studies (866 participants) compared rectally administered sumatriptan with placebo or an active comparator. Most of the data were for the 12.5 mg and 25 mg doses. For the majority of efficacy outcomes, sumatriptan surpassed placebo. For sumatriptan 12.5 mg versus placebo the NNTs were 5.2 and 3.2 for headache relief at one and two hours, respectively. Results for the 25 mg dose were similar to the 12.5 mg dose, and there were no significant differences between the two doses for any of the outcomes analysed. The NNTs for sumatriptan 25 mg versus placebo were 4.2, 3.2, and 2.4 for pain-free at two hours, headache relief at one hour, and headache relief at two hours, respectively. Relief of functional disability was greater with sumatriptan than with placebo, with NNTs of 8.0 and 4.0 for the 12.5 mg and 25 mg doses, respectively. For the most part, adverse events were transient and mild and were more common with sumatriptan than with placebo, but there were insufficient data to perform any analyses. Direct comparison of sumatriptan with active treatments was limited to one study comparing sumatriptan 25 mg with ergotamine tartrate 2 mg + caffeine 100 mg.

Conclusions: Based on limited amounts of data, sumatriptan 25 mg, administered rectally, is an effective treatment for acute migraine attacks, with participants in these studies experiencing a significant reduction in headache pain and functional disability within two hours of treatment. The lack of data on relief of headache-associated symptoms or incidence of adverse events limits any conclusions that can be drawn.

13. **Christopher J Derry, Sheena Derry, R Andrew Moore Sumatriptan (intranasal route of administration) for acute migraine attacks in adults: Cochrane Pain, Palliative and Supportive Care Group Published Online: 15 FEB 2012 DOI: 10.1002/14651858.CD009663**

Background: Migraine is a highly disabling condition for the individual and also has wide-reaching implications for society, healthcare services, and the economy. Sumatriptan is an abortive medication for migraine attacks, belonging to the triptan family. Intranasal administration may be preferable to oral for individuals experiencing nausea and/or vomiting, although it is primarily absorbed in the gut, not the nasal mucosa. To determine the efficacy and tolerability of intranasal sumatriptan compared to placebo and other active interventions in the treatment of acute migraine attacks in adults.

Methods: We searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, online databases, and reference lists for studies through 13 October 2011. We included randomised, double-blind, placebo- and/or active-controlled studies using intranasal sumatriptan to treat a migraine headache episode, with at least 10 participants per

treatment arm. Two review authors independently assessed trial quality and extracted data. We used numbers of participants achieving each outcome to calculate relative risk (or 'risk ratio') and numbers needed to treat to benefit (NNT) or harm (NNH) compared to placebo or a different active treatment.

Results: Twelve studies (4755 participants) compared intranasal sumatriptan with placebo or an active comparator. Most of the data were for the 10 mg and 20 mg doses. Sumatriptan surpassed placebo for all efficacy outcomes. For sumatriptan 10 mg versus placebo the NNTs were 7.3, 7.4, and 5.5 for pain-free at two hours, and headache relief at one and two hours, respectively. For sumatriptan 20 mg versus placebo the NNTs were 4.7, 4.9, and 3.5, respectively, for the same outcomes. The 20 mg dose was significantly better than the 10 mg dose for each of these three primary efficacy outcomes. Relief of headache-associated symptoms, including nausea, photophobia, and phonophobia, was greater with sumatriptan than with placebo, and use of rescue medication was lower with sumatriptan than placebo. For the most part, adverse events were transient and mild and were more common with sumatriptan than placebo. Direct comparison of sumatriptan with active treatments was limited to two studies, one comparing sumatriptan 20 mg and dihydroergotamine (DHE) 1 mg, and one comparing sumatriptan 20 mg with rizatriptan 10 mg.

Conclusions: Intranasal sumatriptan is effective as an abortive treatment for acute migraine attacks, relieving pain, nausea, photophobia, phonophobia, and functional disability, but is associated with increased adverse events compared with placebo.

14. Christopher J Derry, Sheena Derry, R Andrew Moore Sumatriptan (subcutaneous route of administration) for acute migraine attacks in adults: Cochrane Pain, Palliative and Supportive Care Group Published Online: 15 FEB 2012 DOI: 10.1002/14651858.CD009665

Background: Migraine is a highly disabling condition for the individual and also has wide-reaching implications for society, healthcare services, and the economy. Sumatriptan is an abortive medication for migraine attacks, belonging to the triptan family. Subcutaneous administration may be preferable to oral for individuals experiencing nausea and/or vomiting. To determine the efficacy and tolerability of subcutaneous sumatriptan compared to placebo and other active interventions in the treatment of acute migraine attacks in adults.

Methods: We searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, online databases, and reference lists for studies through 13 October 2011. We included randomised, double-blind, placebo- and/or active-controlled studies using subcutaneous sumatriptan to treat a migraine headache episode, with at least 10 participants per treatment arm. Two review authors independently assessed trial quality and extracted data. We used numbers of participants achieving each outcome to calculate relative risk (or 'risk ratio') and numbers needed to treat to benefit (NNT) or harm (NNH) compared to placebo or a different active treatment.

Results: Thirty-five studies (9365 participants) compared subcutaneous sumatriptan with placebo or an active comparator. Most of the data were for the 6 mg dose. Sumatriptan surpassed placebo for all efficacy outcomes. For sumatriptan 6 mg versus placebo the NNTs were 2.9, 2.3, 2.2, and 2.1 for pain-free at one and two hours, and headache relief at one and two hours, respectively, and 6.1 for sustained pain-free at 24 hours. Results for the 4 mg and 8 mg doses were similar to the 6 mg dose, with 6 mg significantly better than 4 mg only for pain-free at one hour, and 8 mg significantly better than 6 mg only for headache relief at one hour. There was no evidence of increased migraine relief if a second dose of sumatriptan 6 mg was given after an inadequate response to the first. Relief of headache-associated symptoms, including nausea, photophobia, and phonophobia, was greater with sumatriptan than with placebo, and use of rescue medication was lower with sumatriptan than placebo. For the most part, adverse events were transient and mild and were more common with sumatriptan than placebo. Sumatriptan was compared directly with a number of active treatments, including other triptans, acetylsalicylic acid plus metoclopramide, and dihydroergotamine, but there were insufficient data for any pooled analyses.

Conclusion: Subcutaneous sumatriptan is effective as an abortive treatment for acute migraine attacks, quickly relieving pain, nausea, photophobia, phonophobia, and functional disability, but is associated with increased adverse events.

15. Christopher J Derry, Sheena Derry, R Andrew Moore Sumatriptan (oral route of administration) for acute migraine attacks in adults: Cochrane Pain, Palliative and Supportive Care Group Published Online: 15 FEB 2012 DOI: 10.1002/14651858.CD008615.pub2

Background: Migraine is a highly disabling condition for the individual and also has wide-reaching implications for society, healthcare services, and the economy. Sumatriptan is an abortive medication for migraine attacks, belonging to the triptan family. To determine the efficacy and tolerability of oral sumatriptan compared to placebo and other active interventions in the treatment of acute migraine attacks in adults.

Methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, online databases, and reference lists for studies through 13 October 2011. We included randomised, double-blind, placebo- and/or active-controlled studies using oral sumatriptan to treat a migraine headache episode, with at least 10 participants per treatment arm. Two review authors independently assessed trial quality and extracted data. We used numbers of participants achieving each outcome to calculate relative risk (or 'risk ratio') and numbers needed to treat to benefit (NNT) or harm (NNH) compared to placebo or a different active treatment.

Results: Sixty-one studies (37,250 participants) compared oral sumatriptan with placebo or an active comparator. Most of the data were for the 50 mg and 100 mg doses. Sumatriptan surpassed placebo for all efficacy outcomes. For sumatriptan 50 mg versus placebo the NNTs were 6.1, 7.5, and 4.0 for pain-free at two hours and headache relief at one and two hours, respectively. NNTs for sustained pain-free and sustained headache relief during the 24 hours postdose were 9.5 and 6.0, respectively. For sumatriptan 100 mg versus placebo the NNTs were 4.7, 6.8, 3.5, 6.5, and 5.2, respectively, for the same outcomes. Results for the 25 mg dose were similar to the 50 mg dose, while sumatriptan 100 mg was significantly better than 50 mg for pain-free and headache relief at two hours, and for sustained pain-free during 24 hours. Treating early, during the mild pain phase, gave significantly better NNTs for pain-free at two hours and sustained pain-free during 24 hours than did treating established attacks with moderate or severe pain intensity. Relief of associated symptoms, including nausea, photophobia, and phonophobia, was greater with sumatriptan than with placebo, and use of rescue medication was lower with sumatriptan than with placebo. For the most part, adverse events were transient and mild and were more common with the sumatriptan than with placebo, with a clear dose response relationship (25 mg to 100 mg). Sumatriptan was compared directly with a number of active treatments, including other triptans, paracetamol (acetaminophen), acetylsalicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs), and ergotamine combinations.

Conclusion: Oral sumatriptan is effective as an abortive treatment for migraine attacks, relieving pain, nausea, photophobia, phonophobia, and functional disability, but is associated with increased adverse events.

Additional References:

10. Sumavel DosePro Prescribing Information. Zogenix , INC. http://www.zogenix.com/downloads/SV0468.0611_SDP_PI.pdf
11. Rothrock, J., Cady R., Aurora S., Brandes J., Myers J., et al. Needle-free subcutaneous sumatriptan for triptan users requiring a change in migraine therapy: efficacy and impact on patient-related functionality, satisfaction, and confidence. Current Medical Research & Opinion Vol. 27, No. 11, 2011, 2185–2191.
16. 16. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sándor PS. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. Eur J Neurol. 2009 Sep;16(9):968-81.
17. Institute for Clinical Systems Improvement (ICSI) guideline on diagnosis and treatment of headache. Tenth Edition. January 2011. Found at : http://www.icsi.org/headache/headache__diagnosis_and_treatment_of_2609.html