DRAFT

Oregon Health Resources Commission

Non-steroidal Anti-inflammatory Drugs (NSAIDs) Subcommittee Report

Update #3, February 2007

This report is an update of the initial NSAIDs Subcommittee Report of June 2002. All revisions are highlighted.

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Overview for Update #3

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-Managed Prescription Drug Plan. Statute specifically directs the Health Resources Commission (HRC) to advise the Department of Human Services on this Plan.

In January of 2002 the HRC appointed a subcommittee to perform an evidence-based review of the use of non-steroidal anti-inflammatory drugs (NSAIDs). Members of the subcommittee consisted of physicians, pharmacists, physician assistants, nurse practitioners, other health care professionals, consumers and advocates. The subcommittee had seven meetings, two of which were general sessions of orientation and evidence based analysis education. All meetings were held in public with appropriate notice provided.

Subcommittee members worked with Oregon Health and Science University's Evidence-based Practice Center (OHSU-EPC) to develop and finalize key questions for drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity, age, demographics, other medications and co-morbidities.

Using standardized methods, the OHSU-EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The OHSU-EPC's Draft "*Drug Class Review on Non-steroidal Anti-inflammatory Drugs"* was completed the week of April 29, 2002, circulated to subcommittee members and posted on the web. The subcommittee met on May 6 and May 13, 2002 to review the document and any additional evidence. By consensus, the subcommittee members agreed to adopt the EPC report. Time was allotted for public comment, questions and testimony. The subcommittee's final meeting was a teleconference on May 20, 2002 to review and approve the subcommittee report to be submitted to the HRC. All available sources of information, EPC report, which includes information submitted by pharmaceutical manufacturers, and public testimony were considered. The conclusions drawn by the NSAIDs Subcommittee comprise the body of this report.

In January of 2003 the HRC appointed an update committee to perform an evidence-based review of the June 2002 *Non-steroidal Anti-inflammatory Drugs (NSAIDs) Subcommittee Report* for new information or changes in the FDA package inserts. Members of the Update Committee consisted of one HRC member, one OSU pharmacist, one Oregon Health Policy and Research (OHPR)

physician, one OHSU-EPC pharmacist, and two NSAIDS Subcommittee members. The committee had two meetings held in public with appropriate notice provided.

In April 2004 the Health Resources Commission appointed a Standing Update Committee to review new evidence presented in the EPC's Updated Final Report #2 on the NSAID drug class. The Standing Update Committee consists of the HRC Director, one HRC member, one EPC member, one OSU pharmacist, two MDs from subcommittees, and one pharmacist from subcommittees.

In January 2007 the Standing Update Subcommittee met once to consider the *Drug Class Review on Cyclo-oxygenase (COX)-2 Inhibitors and Non-steroidal Anti-inflammatory Drugs (NSAIDs) Update # 3* that was posted on the OHPR website at *www.ohpr.state.or.us*. By consensus, the committee members agreed to adopt the EPC report. Time was allotted for public comment and testimony. All available sources of information from the EPC's report that included information submitted by pharmaceutical manufacturers and public testimony, were considered.

The HRC Standing Update Committee members worked with the OHSU-EPC reviewing the evidence for both effectiveness and safety. Evidence was specifically sought for differences among subgroups of patients based on race, ethnicity, age, demographics, other medications and co-morbidities.

This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services for the plan drug list (PDL). This update report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Standing Update Committee, the NSAIDs Subcommittee, or the HRC. For further information provided during the committee process, readers are encouraged to review the source materials on the website.

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the OHPR website: www.ohpr.state.or.us. You may also request more information or minutes and tapes from committee meetings from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

Alison Little, MD, Assistant Director for Health Projects
Oregon Health & Science University
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There will be a charge for copying and handling in providing documents both from the Office for Oregon Health Policy & Research and from the Center.

Critical Policy:

- *Senate Bill 819*

"The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price."

- *Health Resources Commission*

"Clinical outcomes the most important indicators of comparative effectiveness;

"If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Inclusion Criteria:

- *Scope*

Patients with chronic pain due to osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, soft tissue pain, or back pain. Pain from dysmenorrhea and acute pain, such as from dental procedures and surgery, were excluded. Treatment to prevent development of colorectal polyps was also excluded.

- *Efficacy*

The main efficacy measures are pain, functional status, and discontinuations due to lack of efficacy. Measures vary among studies.

- *Safety and Adverse Effects*

Serious GI events (GI bleeding, symptomatic ulcer disease, perforation of the GI tract, and death).

Serious cardiovascular events (myocardial infarction, heart failure, hypertension, angina, stroke, transient ischemic attack, cardiovascular death, and related measures).

Tolerability and adverse events including discontinuation due to any adverse effects, the overall rate of adverse events, the rate of GI adverse events, and the combined rate of adverse events related to renal and cardiovascular function, including increased creatinine, and edema. Frequency of, and discontinuations due to, abnormal laboratory tests, primarily elevated transaminases (liver tests) was also recorded.

Exclusions:

Endoscopic ulcer

Drugs:

- *COX-2 inhibitor*

Celecoxib (Celebrex)

- *COX-2 preferential NSAIDs*

Etodolac (Lodine; others)
Meloxicam (Mobic)
Nabumetone (Relafen; others)
Salsalate (Disalcid)

- *Non-selective NSAIDs*

Diclofenac (Voltaren; Cataflam)
Diflunisal (Dolobid)
Fenoprofen (Nalfon)
Flurbiprofen (Ansaid)
Ibuprofen (Motrin; Advil; others)
Indomethacin (Indocine, Indocine SR)
Ketoprofen (Oruval)
Ketorolac (Toradol)
Meclofenamate
Naproxen (Naprosyn. Anaprox)
Oxaprozin (Daypro)
Piroxicam (Feldene)
Sulindac (Clinoril)
Tolmetin (Tolectin)

Key Questions:

1. **Are there differences in effectiveness between coxibs and other NSAIDs?**

2. **Are there clinically important differences in short-term safety or adverse effects between coxibs, other NSAIDs, or the combination of a non-selective NSAID plus anti-ulcer medication? Are there clinically important differences in long-term safety or adverse effects between coxibs, other NSAIDs, or the combination of a nonselective NSAID plus antiulcer medication?**

3. **Are there subgroups of patients based on demographics, other medications, or co-morbidities for which one medication is more effective or associated with fewer adverse effects?**

New Findings, November 2006

- Since May 2003 there have been no new NSAID drugs added in the US.
- Using the same search strategy that was used in the original NSAID report, the EPC found 316 new citations of which 62 met criteria and were included in this review. Of these 9 were new random controlled trials and 21 additional systematic reviews.
- Eight studies of refecoxib and valdecoxib included in Update #2 were removed from this update due to the withdrawal of those drugs from the market.
- The main findings summarized in this report are based on the Comparative Effectiveness Review (**CER**) of the Benefits and Safety of Analgesics for Osteoarthritis conduced by the Oregon EPC for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program.[1] The scope of this **CER** overlaps that of this DERP drug class review.

Amended Summary of Results (Changes highlighted)

Comparative Efficacy

1. **ARE THERE DIFFERENCES IN EFFICACY BETWEEN COXIBS AND OTHER NSAIDS?**

   a. Celecoxib vs. non-selective NSAIDs

[1] Chou R. Helfand M, Peterson K, et al. Comparative Effectiveness and Safety of Analgesics for Osteoarthritis: comparative Effectiveness Review: Agency for Healthcare Research and Quality; 2006.

The AHRQ **CER** systematic review found no clear differences in efficacy between celecoxib and non-selective NSAIDs based on results from 7 published trials and two meta-analyses of published and un-published trials. In a large study (**CLASS**) focused largely on adverse effects, a higher proportion of NSAIDS patients withdrew for lack of efficacy.

b. COX-2 preferential vs. non-selective NSAID

In double-blinded trials of a COX-2 preferential NSAID (meloxicam) versus non-selective NSAIDs, generally no differences in efficacy could be demonstrated. In two trials, patients taking non-selective NSAIDs were significantly less likely to withdraw due to lack of efficacy.

Etodolac and non-selective NSAIDs were generally associated with similar rates of withdrawal due to lack of efficacy or improvement in pain in short-term RCTs.

c. Non-selective NSAID vs. non-selective NSAID

Several recent good-quality systematic reviews by the Cochrane Collaboration found no clear differences among non-selective NSAIDs in efficacy.

The Standing Update Committee agrees by consensus that evidence does not demonstrate any difference in efficacy amongst NSAIDs (including celecoxib).

2. ARE THERE CLINICALLY IMPORTANT DIFFERENCES IN SHORT-TERM SAFETY OR ADVERSE EFFECTS BETWEEN COXIBS, OTHER NSAIDS, OR THE COMBINATION OF A NON-SELECTIVE NSAID PLUS ANTI-ULCER MEDICATION? ARE THERE CLINICALLY IMPORTANT DIFFERENCES IN LONG-TERM SAFETY OR ADVERSE EFFECTS BETWEEN COXIBS, OTHER NSAIDS, OR THE COMBINATION OF A NONSELECTIVE NSAID PLUS ANTIULCER MEDICATION?

a. Significant GI events (GI bleeding, hospitalization for GI bleeding, symptomatic ulcer disease, perforation of the GI tract, and death)

1) Celecoxib

CLASS remains the longest-term trial to date. Results from an interim 6 month analysis from the **CLASS** trial and from meta-analyses of short term trials consistently suggest that celecoxib is associated with fewer serious GI complications than nonselective NSAIDs. However, regarding longer-term GI safety, celecoxib, diclofenac and ibuprofen were associated with similar

rates of complicated or symptomatic ulcers after 12 months in the **CLASS** trials.

The Standing Update Committee concluded by consensus that for a composite endpoint of serious gastrointestinal events and symptomatic ulcers, celecoxib offers a short-term advantage over nonselective NSAIDs, but this has not been conclusively demonstrated in longer-term (> 6 months) studies.

2) COX-2 preferential NSAIDs versus other NSAIDs

Evidence that etodolac, meloxicam and nabumetone prevent ulcer complications compared to non-selective NSAIDs is weaker than that for celecoxib. The only evidence related to the risks of serious adverse events associated with etodolac comes from two observational studies of unknown durations. These suggest that etodolac was associated with similar PUB rates relative to non-use or naproxen.

The main endpoint used in meta-analyses performed on trials of both of these agents was perforation, ulceration or bleeding (PUB) rates. There was a decrease in PUB rates in nabumetone compared to non-selective NSAID; no conclusions could be drawn about meloxicam. The meta-analyses were flawed because quality of the included studies was not assessed, and end-points were less well defined, raising questions about the validity of the conclusions drawn. Another double-blind trial of meloxicam and diclofenac reporting 12 week PUB rates in RA patients that has been recently published showed no difference between these drugs; but as with the meta-analysis, the lack of a more stringent endpoint than PUB rates provides insufficient evidence to make any judgment about the safety of meloxicam.

The Standing Update Committee agrees by consensus that the evidence does not support the conclusion that COX-2 preferentials are superior to other NSAIDs in preventing ulcer complications.

3) Combination of a non-selective NSAID plus anti-ulcer medication

Misoprostol:

One good-to-fair-quality trial (**MUCOSA**) found that misoprostol prevented symptomatic ulcers and ulcer complications among patients taking non-selective NSAIDs compared to placebo. Misoprostol was associated with a

high rate GI adverse effects, and led to a significantly higher rate of discontinuation of the drug than NSAID plus placebo.

> ***The Standing Update Committee agrees by consensus that misoprostol plus a nonselective NSAID is superior to placebo plus a nonselective NSAID in preventing symptomatic ulcers and ulcer complications, but with a high discontinuation rate due to diarrhea.***

Proton pump inhibitors (PPIs) and H-2 receptor antagonists:

A Cochrane review summarized four trials of PPIs and seven trials of H-2 receptor antagonists. Strong evidence showed that PPIs and double-dose H-2 receptor antagonists reduce the risk of endoscopic gastric and duodenal ulcers. It could not be shown whether symptomatic ulcers or clinical ulcer complications are reduced. There are no head-to-head trials comparing PPIs and H-2 receptor antagonists.

No head-to-head comparisons of high-dose H2-receptor blockers to PPIs have been done. A trial comparing lansoprazole and misoprostol in patients who had a history of NSAID-induced ulcer showed higher withdrawals for misoprostol but equal efficacy on an intention-to-treat basis.

In one good study of patients with recent GI bleeding, there was no significant difference between celecoxib and diclofenac plus omeprazole; however, there was a high risk of recurrent GI bleeding in both groups.

> ***The Standing Update Committee agrees by consensus that:***
> - ***Although PPIs and H2-receptor antagonists with NSAIDs reduce endoscopic ulcers, insufficient evidence is available to conclude whether serious ulcer complications are reduced.***
> - ***Studies indicate that patients with recent gastrointestinal bleeding, whether on NSAIDs alone, NSAIDs with anti-ulcer regimen, or COX-2 inhibitors have a significant risk of recurrent GI bleeding.***

b. Cardiac Events

One trial (**CLASS**) found that celecoxib had no statistically significant effect on the rate of cardiovascular events at 6 months compared with diclofenac and ibuprofen overall and for the subgroup that did not use aspirin. Validity of

these results is questionable; duration of the study may not have been long enough to show an increased incidence of cardiovascular events.

The two most recent meta-analyses found MI rates or combined rates of thromboembolic cardiovascular events higher for patients receiving celecoxib (200 or 400 mg twice daily, or 400 mg qd) compared to placebo (RR 2.1; 95% CI 1.2,3.8 or RR 1.5; 95% CI 1.0, 2.2, respectively).[2,3] Most of the MIs observed in trials of celecoxib were recorded from two large long-term placebo-controlled trials of celecoxib for polyp prevention (**APC**[4] and **PreSAP**[5]) that involved up to 3 years of follow-up and randomized a total of almost 3,600 patients. In the **APC** trial absolute risk of nonfatal MI for celecoxib compared to placebo was 0.9% and was 0.6% in **PreSAP**. Although the relative risk was statistically significant, the absolute risk remained very small.

Results from a fair-quality systematic review of 138 short-term RCTs suggest that some of the nonselective NSAIDs such as ibuprofen and diclofenac are associated with similar risks of cardiovascular events compared to celecoxib. In indirect analyses, naproxen was risk neutral for cardiovascular events relative to placebo, and other nonselective NSAIDs were associated with similar risks.

By consensus, the Standing Update Committee agrees:

- ***the evidence regarding increased risk of cardiovascular events with celecoxib compared to placebo is statistically significant, but the differences are of minimal clinical significance.***
- ***non-selective NSAIDs were risk neutral relative to placebo.***

c. Renal toxicity

[2] Kearney PM, Baigent c, Godwin J, et al. Do selective cyclo-ogenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomized trials. BMJ 2006;332:1302-8.
[3] Caldwell B, Aldington S, Eatherall M et al. Risk of cardiovascular events and celecoxib: a systematic review and meta-analysis. Journal of the Royal society of Medicine. 2006;99:132-40.
[4] Solomon SD, McMurray JV, Pfeffer MA et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. NEJM 2005;352:1071-80.
[5] Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. NEJM 2006;355:885-95.

The renal and hypertensive effects of COX-2 inhibitors and non-selective NSAIDs are not shown to be different. Two head-to-head trials found higher rates of renal complications with rofecoxib than with celecoxib. This difference may have been a dose effect.

d. Liver toxicity

Liver function data was insufficient to draw any conclusions about liver toxicity

3. ARE THERE SUBGROUPS OF PATIENTS BASED ON DEMOGRAPHICS, OTHER MEDICATIONS, OR CO-MORBIDITIES FOR WHICH ONE MEDICATION IS MORE EFFECTIVE OR ASSOCIATED WITH FEWER ADVERSE EFFECTS?

A post-hoc analysis that stratified patients as to whether they were taking low-dose aspirin prophylaxis for cardiac protection showed celecoxib to be superior for the composite end-point in patients not taking aspirin. For patients taking aspirin the benefit of celecoxib was obviated.

One meta-analysis of trials of celecoxib versus NSAIDs focused on efficacy in elderly patients. Celecoxib 200 mg and 400 mg and naproxen 1000 mg were similar in efficacy.

In most of the published trials, a majority of subjects were women. No publications focusing on the differential efficacy or safety of COX-2 inhibitors in African Americans, Hispanics, or other ethnic minorities were found.

A risk analysis in the United Kingdom revealed that serious GI complications from NSAIDs increased with age from 1:2100 under age 45 to 1:110 over age 75.

The Standing Update Committee agrees by consensus:

- ***The evidence does not support a difference between celecoxib and other NSAIDs for efficacy or safety with respect to age, gender, race or ethnicity.***
- ***For patients taking aspirin the benefit of celecoxib in reducing serious gastrointestinal events was obviated.***
- ***In patients with recent GI bleeding all NSAIDs should be used with caution because of the high risk of recurrent bleeding.***
- ***In patients with hypertension there is risk of further elevation of blood pressure with all NSAIDs.***

Conclusion

In a series of public meetings with the opportunity for public questions, comment and testimony, the NSAIDs Update Committee and Subcommittee of the Health Resources Commission reviewed the medical evidence comparing COX-2 inhibitors and other NSAIDs. All available sources of information including OHSU's Evidence-based Practice Center report, *Drug Class Review on Non-steroidal Anti-Inflammatory Drugs (NSAIDs),* and additional information presented in public testimony were considered.

Using all of these sources of information, the subcommittee and update committee arrived at the following conclusions about the comparative effectiveness and safety of non-steroidal anti-inflammatory drugs as supported by analysis of the medical literature:

The Standing Update Committee found by consensus that:

- ***There is no evidence to demonstrate a significant difference in efficacy amongst NSAIDs including celecoxib.***
- ***There are concerns about adverse cardiac events of celecoxib as compared to naproxen, but data is inconclusive at the present time to draw definitive conclusions.***
- ***There is no evidence that celecoxib is superior to other NSAIDs in preventing ulcer complications***
- ***There is raised concern that for patients taking aspirin the benefit of celecoxib in preventing serious gastrointestinal events was obviated.***
- ***Caution should be used in treating patients with recent GI bleeding with all NSAIDs because of the high risk for re-bleeding.***
- ***Misoprostol plus a nonselective NSAID is superior to placebo plus a nonselective NSAID in preventing symptomatic ulcers and ulcer complications, but with a high discontinuation rate due to diarrhea.***
- ***In patients with hypertension there is risk of further elevation of blood pressure with all NSAIDs***

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Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer Commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The Commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the Commission subject to approval by a majority of the Commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.