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: January 2012
Date of Last Review: February 2007
PDL Class: Analgesics: NSAIDS
Source Document: HRC Report

Current Preferred Agents:

Diclofenac
Diclofenac DR
Etodolac
Flurbiprofen
Ibuprofen
Indomethacin
Ketoprofen
Ketorolac tromethamine*
Meloxicam
Nabumetone
Naproxen
Naproxen DR
Oxaprozin
Salsalate
Sulindac

*with quantity limit

Current Non-Preferred Agents:

Celecoxib (Celebrex®)
Piroxicam
Mefenamic acid
Tolmetin
Fenoprofen
Diflunisal
Meclofenamate

Topical Agents
Diclofenac topical (Flector patch®)
Diclofenac topical (Voltaren®, Voltaren gel®)

Combination Agents:
Diclofenac/misoprostol (Arthrotec®)

Previous Recommendations:

- 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.
- In patients with hypertension there is a risk of further elevation of blood pressure with all NSAIDs

PA Criteria/QL:

PA: Non-preferred NSAIDS require a PA to ensure use is for covered diagnoses
Quantity Limit: Restricts ketorolac to short-term use (5 days every 60 days) per the FDA black boxed warning

New Systematic Reviews:

The Oregon Evidence-based Practice Center (EPC) for the Drug Effectiveness Review Project (DERP) produced an updated report on the Drug Class Review of Nonsteroidal Antiinflammatory Drugs (NSAIDS) in November 2010.[1] The full report can be found on the Evidence-based Practice Center website:

http://derp.ohsu.edu/about/final-document-display.cfm and the final executive summary can be found on the Oregon Pharmacy and Therapeutics website: http://pharmacy.oregonstate.edu/drug_policy/meetings. It compared the effectiveness and harms of oral and topical NSAIDs in the treatment of chronic pain from five diagnoses: osteoarthritis (OA), rheumatoid arthritis (RA), soft tissue pain, anklylosing spondylitis, and back pain.

Key Questions:

1. Are there differences in effectiveness between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from OA, RA, soft-tissue pain, back pain, or anklylosing spondylitis?
2. Are there clinically important differences in short-term harms between NSAIDs?
3. Are there clinically important differences in long-term harms (≥6 months) between NSAIDs?
4. Are there subgroups of patients based on demographics, other medications, socio-economic conditions, co-morbidities for which one medication is more effective or associated with fewer harms?

Conclusions:

1. There was high-strength evidence that there are no significant differences between oral NSAIDs for efficacy, including celecoxib.
2. No significant differences were found between oral NSAIDS, topical NSAIDs, or between oral and topical NSAIDs for short-term (less than 6 months) pain relief.
3. There is high-strength evidence that celecoxib seems to offer a short-term advantage over nonselective NSAIDs in regard to gastrointestinal adverse events but there is insufficient long-term evidence.
4. Celecoxib does not appear to have a higher risk of cardiovascular events compared to nonselective NSAIDs, but evidence is primarily from short-term studies.
5. There is moderate strength evidence that all non-selective NSAIDs, except naproxen, are associated with increased risks of CV events similar to that seen with COX-2 inhibitors. Naproxen appears to be risk-neutral.
6. There is high-strength evidence that all non-selective oral NSAIDS have similar risk of short-term and long-term gastrointestinal complications, but the partially selective NSAID nabumetone appears to be gastroprotective.
7. For comparisons among different topical diclofenac products, only low-strength, indirect evidence was available indicating that diclofenac 1.5% topical solution and 1.0% topical gel had similar significant improvements in pain, functional outcome measures, and response rate
8. Compared with oral NSAIDs, high-strength evidence showed that diclofenac 1.5% solution resulted in similar improvements in efficacy but with significantly improved gastrointestinal tolerability.
9. There is low-strength evidence that suggests there may be lower risks of serious gastrointestinal, cardiovascular, and renal adverse events in elderly patients with celecoxib compared to diclofenac or ibuprofen.

Limitations:

- Majority of trials are short term duration and little evidence exists on the comparative effectiveness of NSAIDs that is truly effectiveness
- No trials that directly compared the effectiveness or efficacy between different topical NSAIDs were found
- Insufficient evidence was available to evaluate any differences in effects based on ethnicity/race, gender, or socioeconomic status.

Methods:

Search Strategy

An Ovid MEDLINE search was conducted since the literature search performed for the DERP report and used the following search terms:

NSAIDS; anti-inflammatory agents, non-steroidal; diclofenac; etodolac; flurbiprofen; ibuprofen; ketoprofen; ketorolac tromethamine; meloxicam; nabumetone; naproxen; oxaprozin; salsalate; sulindac; arthritis; osteoarthritis; osteoarthritis, hip; osteoarthritis, spine; osteoarthritis, knee; arthritis, rheumatoid; ankylosing spondylitis; back pain; soft tissue pain. The search was limited to controlled trials conducted with humans in English language publications from 2010 to present.

Results:

The MEDLINE search retrieved 80 full citations. After a full review of citations and abstracts, no new head-to-head using FDA approved agents were identified. The majority of the RCTs identified compared available NSAIDS with opiates, DMARDs, dietary supplements, herbal agents and NSAIDS not approved for use in the U.S. Other exclusions were for wrong study type (observational, case study), or for the wrong endpoint (C-reactive protein levels, cartilage turnover).

New FDA-approved drugs:

No new molecular entities were approved but two fixed-dose combination products were FDA approved and one new formulation/delivery system of ketorolac was approved in May 2010.

1. **Sprix®** (ketorolac tromethamine) is a new nasal spray formulation indicated for short-term (5 days or less) management of moderate to moderately severe pain. It carries the same black box warning as the oral and IV formulations. Ketorolac nasal spray was approved based on two randomized placebo-controlled trial of adults treated post-operatively from elective abdominal or orthopedic surgery for 48 hours. The primary efficacy outcome was summed pain intensity difference over 6 hours. Patients in both studies were also treated with morphine PCA on an as-needed basis. These studies only demonstrated efficacy compared to placebo in the inpatient setting for postoperative pain and therefore it is difficult to extrapolate to use in the outpatient setting

Treatment Group	N	Single-dose summed pain intensity difference score (mean score)	P-Value	Mean morphine use (mg) during hours 0-48	P-Value[#]
Brown, et al.[2]	300				
Intranasal ketorolac 30mg	199	83.3 ± 10.6	< 0.007	51.4 ± 2.75	<0.001
Placebo	101	37.2 ± 12.9	--	77.4 ± 5.28	
Singla, et al.[3]	321				
Intranasal ketorolac 30mg	214	117.4 ± 7.7	<0.032	23	=0.041
Placebo	107	89.9 ± 10.6		31	
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2. **Vimovo®** (naproxen/esomeprazole) is a new oral combination product indicated for pain relief in patients with osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis and to decrease the risk of stomach ulcers in patients at risk of developing a NSAID induced gastric ulcer. Approval was based on four randomized, double-blind, placebo-controlled studies. Two of these were 12-week studies to determine efficacy of naproxen/esomperazole in treating the signs and symptoms of OA of the knee compared to placebo and celecoxib.[4] Patients receiving naproxen/esomeprazole had significantly better results compared to placebo as measured by the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale and a Patient Global Assessment score. The study results did not find naproxen/esomeprazole to be noninferior to celecoxib but did compared to placebo.
   There were also two randomized, double-blind studies performed comparing the incidence of gastric ulcer formation compared to placebo and naproxen EC 500mg BID.[5] The incidence of cumulative gastric ulcers at 6 months was significantly lower for the naproxen/esomperazole group vs. naproxen EC (Study 301: 4.1% vs. 23.1%, $p<0.001$; Study 302: 7.1% vs. 24.3%, $p<0.001$).

3. **Duexis ®** (ibuprofen/famotidine) is a new oral combination product indicated for the relief of signs and symptoms of RA and OA and to decrease the risk of developing gastric ulcers. Ibuprofen/famotidine was evaluated in two phase III, randomized, double-blind trials of 24 weeks in duration comparing ibuprofen/famotidine three times daily to ibuprofen 800mg three times daily.[6, 7] The primary outcome was the incidence of endoscopic gastroduodenal ulcers. The incidence of endoscopic gastroduodenal ulcers with Duexis was 11%, compared to 21.9% with ibuprofen alone. These trials were not published and they therefore cannot be assessed for quality or risk of bias.

New FDA Indications:
None identified.

New FDA safety alerts:
None identified.

New Guidelines:
None identified.

Recommendations:
1. No further research or review needed.
2. Consider Sprix nasal spray for PDL placement pending price comparison and restrict to a 5-day quantity limit.
3. Add new combination products to Proton Pump Inhibitor clinical pa similar to PrevPac.

References:

1. Peterson K, McDonagh M, Thakurta S, et al. Drug Class Review: Nonsteroidal antiinflammatory drugs (NSAIDs). Update 4 final report. Available at: http://derp.ohsu.edu/about/final-document-display.cfm.

2. Brown C, Moodie J, Bisley E, Bynum L. Intranasal ketorolac for postoperative pain: a phase 3, double-blind, randomized study. *Pain Med*. 2009;10(6):1106-1114.

3. Singla N, Singla S, Minkowitz HS, Moodie J, Brown C. Intranasal ketorolac for acute postoperative pain. *Curr Med Res Opin*. 2010;26(8):1915-1923.

4. Hochberg MC, Fort JG, Svensson O, Hwang C, Sostek M. Fixed-dose combination of enteric-coated naproxen and immediate-release esomeprazole has comparable efficacy to celecoxib for knee osteoarthritis: two randomized trials. *Current Medical Research and Opinion*. 2011;27(6):1243-1253.

5. Goldstein JL, Hochberg MC, Fort JG, et al. Clinical trial: the incidence of NSAID-associated endoscopic gastric ulcers in patients treated with PN 400 (naproxen plus esomeprazole magnesium) vs. enteric-coated naproxen alone. *Alimentary Pharmacology & Therapeutics*. 2010;32(3):401-413.

6. Weinblatt M. Efficacy, safety, and tolerability of HZT-501, including users of low-dose aspirin, a single tablet combination of ibuprofen-famotidine: results of two phase 3 trials (abstract). *Arthritis Rheum.* 2010;62:945.

7. The Medical Letter on Drugs and Therapeutics. A fixed-dose combination ibuprofen and famotidine (Duexis). *Med Lett Drugs Ther*. 2011;53(1376):85-86.