Drug Class Review
Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Preliminary Scan Report #2

May 2014

Last Report: Update #4 (November 2010)
Last Preliminary Scan: July 2013

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OBJECTIVE

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

Date of Last Update Report

Update #4, November 2010 (searches through June 2010)

Date of Last Preliminary Update Scan Report

July 2013

Scope and Key Questions

1. Are there differences in effectiveness between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
   a. How do oral drugs compare to one another?
   b. How do topical drugs compare to one another?
   c. How do oral drugs compare to topical drugs?
2. Are there clinically important differences in short-term harms (< 6 months) between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
   a. How do oral drugs compare to one another?
   b. How do topical drugs compare to one another?
   c. How do oral drugs compare to topical drugs?
3. Are there clinically important differences in long-term harms (≥ 6 months) between NSAIDs, with or without antiulcer medication, when used chronically in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
   a. How do oral drugs compare to one another?
   b. How do topical drugs compare to one another?
   c. How do oral drugs compare to topical drugs?
4. Are there subgroups of patients based on demographics, other medications (e.g., aspirin), socio-economic conditions, co-morbidities (e.g., gastrointestinal disease) for which one
medication is more effective or associated with fewer harms?

Inclusion Criteria

Populations

Adults with:
- Chronic pain from osteoarthritis
- Rheumatoid arthritis
- Soft-tissue pain
- Back pain
- Ankylosing spondylitis

Interventions

- Oral drugs: celecoxib, diclofenac potassium, diclofenac sodium, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketoprofen extended release, ketoprofen sustained release, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, naproxen delayed release, naproxen sustained release, naproxen sodium, oxaprozin, piroxicam, salsalate, sulindac, tenoxicam, tiaprofenic acid, and tolmetin
- Topical drugs: diclofenac epolamine 1.3% topical patch, diclofenac sodium 1% topical gel, diclofenac sodium 1.5% topical solution, diclofenac sodium 3% topical gel, and topical diclofenac diethylamine 1.16%.

Comparisons

Celecoxib compared with NSAIDs
NSAIDs compared with NSAIDs

Outcomes

Effectiveness outcomes
- Pain
- Functional status
- Discontinuations due to lack of effectiveness.

Harms
- Serious gastrointestinal events (gastrointestinal bleeding, symptomatic ulcer disease, perforation of the gastrointestinal tract, and death)
- Serious cardiovascular events (myocardial infarction, angina, stroke, transient ischemic
attack, cardiovascular death, hypertension, congestive heart failure, and related measures)

- Tolerability and adverse event (discontinuation due to any adverse event; any serious adverse event; the overall rate of adverse events; the rate of gastrointestinal adverse events; the combined rate of adverse events related to renal and cardiovascular function, including increased creatinine, edema, hypertension, or congestive heart failure; and the frequency of, and discontinuations due to, abnormal laboratory tests—primarily elevated transaminases).

**Timing**

Inclusion of randomized controlled trials were limited to only those of at least 4 weeks’ duration

**Study Designs**

- For effectiveness, controlled clinical trials and good-quality systematic reviews
- For harms, controlled clinical trials, good-quality systematic reviews and observational studies

**METHODS**

**Literature Search**

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from January 2013 through May 13, 2014 using terms for included drugs and conditions. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm).

**Study Selection**

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

New Drugs

New drugs identified in this Preliminary Update Scan

Pennsaid (diclofenac sodium 2% topical). Approved on 1/16/14 for the treatment of osteoarthritis of the knee.

New drugs identified in previous Preliminary Update Scan

Vimovo (naproxen and esomeprazole magnesium fixed-dose combination tablet): Approved on 4/30/10 to treat osteoarthritis, rheumatoid arthritis and ankylosing spondylitis

New Indications

New indications identified in this Preliminary Update Scan

None.

New indications identified in previous Preliminary Update Scan

None.

New Safety Alerts

New Safety Alerts Identified in this Preliminary Update Scan

None.

New Safety Alerts Identified in previous Preliminary Update Scan

None.
Comparative Effectiveness Reviews

We identified two new comparative effectiveness reviews. The abstracts of these reviews are attached in Appendix A, and links to the full reports are listed below.

Reviews identified in this Preliminary Update Scan

From CADTH:


Reviews identified in previous Preliminary Update Scans


Randomized Controlled Trials Identified since the most recent Full Report

Medline searches for this scan resulted in 96 citations. Of those, there was only one new companion publication (shaded row in Table 1).

From the previous scan, there were six potentially relevant new randomized controlled trials and one new companion publication (Table 1).

Among the new randomized controlled trials, five involved head-to-head comparisons and one was placebo-controlled. Among the head-to-head trials, two involved the new naproxen/esomeprazole magnesium fixed-dose combination product, which has not been included in any previous full update DERP report.

The two companion publications pertained to the CONDOR trial (Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis), which we included in our DERP Update #4 report from November 2010.

Abstracts of all of these trials are attached in Appendix B.

Table 1. New potentially relevant randomized controlled trials

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Comparison</th>
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<td>Cryer 2013 (GI-REASONS)</td>
<td>Celecoxib vs NSAIDs</td>
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<td>Essex 2012</td>
<td>Celecoxib vs naproxen</td>
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<td>Study</td>
<td>Treatment Comparison</td>
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<td>Kellner 2012 <em>(companion to CONDOR, Chan 2010)</em></td>
<td>Celecoxib vs diclofenac plus omeprazole</td>
<td>Subgroup analysis of elderly patients</td>
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<td>Kellner 2013 <em>(companion to CONDOR, Chan 2010)</em></td>
<td>Celecoxib vs diclofenac plus omeprazole</td>
<td>Improvement in arthritic signs and symptoms</td>
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<td>Schmitt 1999</td>
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<td>Activated osteoarthritis</td>
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<td>Cryer 2011/Hochberg 2011</td>
<td>Naproxen/esomeprazole magnesium fixed-dose combination tablet vs celecoxib</td>
<td>Knee osteoarthritis</td>
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<td>Goldstein 2010</td>
<td>Naproxen/esomeprazole magnesium fixed-dose combination tablet vs celecoxib vs naproxen alone</td>
<td>Patients with a history of ulcer</td>
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**Placebo-controlled trials**

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<th>Study</th>
<th>Treatment Comparison</th>
<th>Outcome Measure</th>
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<td>Baraf 2010</td>
<td>Diclofenac sodium topical gel 1% vs placebo</td>
<td>Knee osteoarthritis</td>
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Appendix A. Abstracts of potentially relevant new comparative effectiveness reviews of Nonsteroidal Antiinflammatory Drugs (NSAIDs)

CADTH: Non-steroidal Anti-inflammatory Drugs for Pain: A Review of Safety

Context
Non-steroidal anti-inflammatory drugs (NSAIDs) play an important role in pain management for clinical conditions such as headaches, menstrual disorders, post-operative pain, spinal and soft tissue pain, rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

Technology
NSAIDs reduce pain by blocking cyclooxygenase (COX) enzymes needed to produce prostaglandin. There are two forms of the enzyme: COX-1 and COX-2. Traditional NSAIDs, called “non-selective NSAIDs,” block both forms. NSAIDs that target only the COX-2 form are called “COX-2 selective NSAIDs” or “COX-2 inhibitors.”

Celecoxib (Celebrex) is the only COX-2 inhibitor currently available in Canada.

Issue
Based on their mechanism of action, COX-2 inhibitors are thought to be safer than non-selective NSAIDs in terms of gastrointestinal (GI) bleeding. However, COX-2 inhibitors are associated with an increased risk of major cardiovascular events such as heart attacks and strokes. The COX-2 inhibitor rofecoxib (Vioxx) was removed from the Canadian market in 2004 for this reason. Generic versions of celecoxib will soon be available in Canada.

A review of the comparative safety of NSAIDs will help inform decisions on their use for the management of pain.

Methods
A limited literature search was conducted of key resources, and titles and abstracts of the retrieved publications were reviewed. Full-text publications were evaluated for final article selection according to predetermined selection criteria (population, intervention, comparator, outcomes, and study designs).

Key Messages

- The COX-2 inhibitor, celecoxib, appears to be associated with:
  - a cardiovascular risk similar to diclofenac and ibuprofen, and a higher risk than naproxen
  - a GI bleeding risk similar to diclofenac, and a lower risk than ibuprofen and naproxen.
- Among non-selective NSAIDs:
  - diclofenac may be associated with a higher cardiovascular risk than ibuprofen or naproxen
naproxen may be associated with a lower cardiovascular risk than diclofenac, ibuprofen, or indomethacin.

• Interpret these results with caution as:
  o study durations were short (generally less than three months)
  o studies used different NSAID doses.

Results
The literature search identified 275 citations, with an additional 8 articles identified from other sources. Of these, 13 were deemed potentially relevant and 6 met the criteria for inclusion in this review — 5 systematic reviews and 1 health technology assessment.

Abstracts for comparative reviews from previous update:


Structured Abstract

Objectives:
To update a previous report on the comparative benefits and harms of oral non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) for osteoarthritis.

Data Sources:
Ovid MEDLINE (1996–January 2011), the Cochrane database (through fourth quarter 2010), and reference lists.

Review Methods:
We included randomized trials, cohort studies, case-control studies, and systematic reviews that met predefined inclusion criteria. For each study, investigators abstracted details about the study population, study design, data analysis, followup, and results, and they assessed quality using predefined criteria. We assessed the overall strength of each body of evidence using predefined criteria, which included the type and number of studies; risk of bias; consistency; and precision of estimates. Meta-analyses were not performed, though pooled estimates from previously published studies were reported.

Results:
A total of 273 studies were included. Overall, we found no clear differences in efficacy for pain relief associated with different NSAIDs. Celecoxib was associated with a lower risk of ulcer complications (RR 0.23, 95% CI 0.07 to 0.76) compared to nonselective NSAIDs. Coprescribing of proton pump inhibitors, misoprostol, and H2-antagonists reduce the risk of endoscopically detected gastroduodenal ulcers compared to placebo in persons prescribed NSAIDs. Celecoxib
and most nonselective, nonaspirin NSAIDs appeared to be associated with an increased risk of serious cardiovascular (CV) harms. There was no clear association between longer duration of NSAID use or higher doses and increased risk of serious CV harms. There were no clear differences between glucosamine or chondroitin and oral NSAIDs for pain or function, though evidence from a systematic review of higher-quality trials suggests that glucosamine had some very small benefits over placebo for pain. Head-to-head trials showed no difference between topical and oral NSAIDs for efficacy in patients with localized osteoarthritis, lower risk of gastrointestinal (GI) adverse events, and higher risk of dermatological adverse events, but serious GI and CV harms were not evaluated. No head-to-head trials compared topical salicylates or capsaicin to oral NSAIDs.

Conclusions:
Each of the analgesics evaluated in this report was associated with a unique set of risks and benefits. Choosing the optimal analgesic for an individual with osteoarthritis requires careful consideration and thorough discussion of the relevant tradeoffs.
Appendix B. Abstracts of potentially relevant new randomized controlled trials of Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Head-to-Head Trials


OBJECTIVES: Because of the limitations of randomized controlled trials (RCTs) and observational studies, a prospective, randomized, open-label, blinded endpoint (PROBE) study may be an appropriate alternative, as the design allows the assessment of clinical outcomes in clinical practice settings. The Gastrointestinal (GI) Randomized Event and Safety Open-Label Nonsteroidal Anti-inflammatory Drug (NSAID) Study (GI-REASONS) was designed to reflect standard clinical practice while including endpoints rigorously evaluated by a blinded adjudication committee. The objective of this study was to assess if celecoxib is associated with a lower incidence of clinically significant upper and/or lower GI events than nonselective NSAIDs (nsNSAIDs) in standard clinical practice.

METHODS: This was a PROBE study carried out at 783 centers in the United States, where a total of 8,067 individuals aged >= 55 years, requiring daily NSAIDs to treat osteoarthritis, participated. The participants were randomized to celecoxib or nsNSAIDs (1:1) for 6 months and stratified by Helicobacter pylori status. Treatment doses could be adjusted as per the United States prescribing information; patients randomized to nsNSAIDs could switch between nsNSAIDs; crossover between treatment arms was not allowed, and patients requiring aspirin at baseline were excluded. The primary outcome was the incidence of clinically significant upper and/or lower GI events.

RESULTS: Significantly more nsNSAID users met the primary endpoint (2.4% (98/4,032) nsNSAID patients and 1.3% (54/4,035) celecoxib patients; odds ratio, 1.82 (95% confidence interval, 1.31-2.55); P = 0.0003). Moderate to severe abdominal symptoms were experienced by 94 (2.3%) celecoxib and 138 (3.4%) nsNSAID patients (P=0.0035). Other non-GI adverse events were similar between treatment groups. One limitation is the open-label design, which presents the possibility of interpretive bias.

CONCLUSIONS: Celecoxib was associated with a lower risk of clinically significant upper and/or lower GI events than nsNSAIDs. Furthermore, this trial represents a successful execution of a PROBE study, where therapeutic options and management strategies available in clinical practice were incorporated into the rigor of a prospective RCT.


OBJECTIVE: To assess the efficacy and tolerability of celecoxib versus naproxen in patients with osteoarthritis (OA) of the knee.

METHODS: This 6-month, randomized, double-blind, double-dummy trial was conducted at 47 centres in the USA. Patients with OA of the knee were randomized to receive 200 mg
celecoxib orally once daily or 500 mg naproxen orally twice daily. The primary endpoint was defined as a 20% improvement from baseline to 6 months in Western Ontario and McMaster Universities (WOMAC) OA total score.

RESULTS: A total of 586 out of 589 randomized patients received at least one dose of celecoxib (n=294) or naproxen (n=292). The primary endpoint (6-month response rate) was achieved by 52.7% and 49.7% of patients in the celecoxib and naproxen treatment groups, respectively. Significantly fewer discontinuations due to gastrointestinal adverse events occurred in patients receiving celecoxib than in those receiving naproxen (4.1% versus 15.1%, respectively).

CONCLUSIONS: Over the 6-month study period, celecoxib provided similar improvements in OA symptoms to naproxen. In addition, celecoxib provided better upper gastrointestinal tolerability than naproxen.


OBJECTIVE: To compare the safety and efficacy of celecoxib versus diclofenac slow release (SR) plus omeprazole in elderly arthritis patients.

RESEARCH DESIGN AND METHODS: Patients aged>=65 years, with osteoarthritis and/or rheumatoid arthritis, at high gastrointestinal (GI) risk who participated in the CONDOR trial (Celecoxib vs. Omeprazole and Diclofenac in Patients With Osteoarthritis and Rheumatoid Arthritis) were included in this subanalysis. CONDOR was a 6-month prospective, double-blind, randomized, parallel-group, multicenter, international study comparing treatment with celecoxib 200mg twice daily (BID) versus diclofenac SR 75mg BID plus omeprazole 20mg daily.

MAIN OUTCOME MEASURES: The primary end point was a composite of Clinically Significant Upper and Lower GI Events adjudicated by an independent blinded expert committee. Efficacy was determined by the Patient's Global Assessment of Arthritis.

RESULTS: A total of 2446 patients aged>=65 years were included in the intent-to-treat (ITT) population (n=1219 celecoxib; n=1227 diclofenac). Eight patients in the celecoxib group and 52 in the diclofenac group were adjudicated as having Clinically Significant Upper and Lower GI events (adjusted odds ratio: 6.27; p<0.0001). Clinically significant reductions in hemoglobin (>=2g/dL) and/or hematocrit (>=10%) were observed in 23 patients in the celecoxib group and in 76 in the diclofenac group (relative risk: 3.22 [95% confidence interval: 2.04-5.07]; p<0.0001). Incidence of moderate-to-severe abdominal symptoms and discontinuation of treatment due to GI adverse events (AEs) were lower in the celecoxib group. The Patient's Global Assessment of Arthritis score least squares mean change from baseline to final visit and percentage of patients rating treatment efficacy as good/very good at baseline and final visit were similar in both groups.

LIMITATIONS: The dose of celecoxib used is consistent with the European label for the management of osteoarthritis and may not reflect what is commonly prescribed in current clinical practice in the United States. The data were obtained in a clinical trial setting where patients were enrolled based on specific inclusion and exclusion criteria;
as such, the patients may not be broadly representative of the patient population in a general practice setting.

CONCLUSIONS: Efficacy was comparable in the two treatment groups. There were fewer endpoints as well as fewer GI AEs reported in patients treated with celecoxib compared with diclofenac. These data may help physicians in their treatment decisions for elderly patients with arthritis.


OBJECTIVE: Compare effectiveness of celecoxib versus diclofenac plus omeprazole in improving arthritis signs and symptoms in patients at high gastrointestinal (GI) risk who were enrolled in the CONDOR (Celecoxib vs Omeprazole and Diclofenac in Patients With Osteoarthritis and Rheumatoid Arthritis) trial.

METHODS: CONDOR was a 6-month, prospective, double-blind, triple-dummy, parallel-group, randomized, multicenter trial comparing celecoxib 200 mg twice daily versus diclofenac slow release (SR) 75 mg twice daily plus omeprazole 20 mg daily. Patients were Helicobacter pylori negative, had osteoarthritis (OA) or rheumatoid arthritis (RA), were aged >60 years, were with or without a history of gastroduodenal ulceration, or were >18 years with previous gastroduodenal ulceration. Patients' Global Assessment of Arthritis was determined at each study visit.

RESULTS: A total of 4484 patients were randomized to treatment (2238 celecoxib, 2246 diclofenac SR) and included in the intention-to-treat analyses. Least squares mean (LSM) (standard error [SE]) for Patients' Global Assessment of Arthritis was 3.219 (0.017) and 3.221 (0.017) at baseline for celecoxib and diclofenac SR (p=0.90). Improvement in both groups was similar in months 2, 4, and 6; at month 1 the LSM (SE) was 2.647 (0.017) and 2.586 (0.017) for celecoxib and diclofenac (p=0.0025). LSM difference (SE) from baseline to final visit demonstrated an improvement of 0.75 (0.02) in celecoxib-treated patients and 0.77 (0.02) in diclofenac SR-treated patients (p=0.42).

CONCLUSIONS: Celecoxib and diclofenac plus omeprazole were shown to have similar efficacy in patients with OA and/or RA at increased GI risk who were enrolled in the CONDOR trial.

TRIAL REGISTRY: Trial was registered under ClinicalTrials.gov identifier NCT00141102.


This double-blind, randomised, multicentre study investigated the efficacy and safety of two different dosages of a diclofenac sodium dual release capsule (150 mg or 75 mg once daily) in comparison to a standard treatment with enteric coated tablets (50 mg t.i.d.) and placebo in patients with activated osteoarthritis. Pain relief as the main efficacy variable was measured through 24 hours by means of a Visual Analogue Scale at baseline and on five assessment days during the 12 weeks of treatment. Efficacy was
observed in all treatment groups with a statistically significant difference between the verum groups and placebo. The overall safety and tolerability of the active treatments was good. For the 75 mg group, a lower incidence of liver and biliary system-related side effects was reported. Considering efficacy, safety, and compliance aspects, the once daily administration of diclofenac sodium 75 mg dual release capsule is the appropriate dosage regimen for mid- and long-term treatment of osteoarthritis.


BACKGROUND. Non-steroidal anti-inflammatory drugs are associated with poor upper gastrointestinal (UGI) tolerability and increased ulcer risk, but patient adherence to gastroprotective co-therapy is frequently inadequate. A fixed-dose combination of enteric-coated naproxen 500 mg and immediate-release esomeprazole magnesium 20 mg was evaluated: efficacy is reported by Hochberg et al. (Curr Med Res Opin 2011;27:1243-53); tolerability findings are reported here. PATIENTS AND METHODS. In two 12-week double-blind, placebo-controlled, multicenter, phase III studies (PN400-307 and PN400-309), patients aged >= 50 years with symptomatic knee osteoarthritis randomly (2:2:1) received naproxen/esomeprazole magnesium BID, celecoxib 200 mg QD, or placebo. Tolerability end-points included: modified Severity of Dyspepsia Assessment (mSODA); heartburn severity; and UGI adverse events (AEs). RESULTS. Overall, 619 (PN400-307) and 615 (PN400-309) patients were randomized; mSODA scores improved (baseline to week 12) in each group, with no significant treatment differences between naproxen/esomeprazole magnesium and celecoxib (95% CIs: PN400-307: -0.4, 1.9; PN400-309: -1.8, 0.6). Naproxen/esomeprazole magnesium-treated patients reported significantly more heartburn-free days versus celecoxib (95% CIs: PN400-307: 2.1, 12.7; PN400-309: 2.5, 13.4). UGI AE incidence (PN400-307: 17.3%; PN400-309: 20.3%) was similar between treatment groups. UGI AEs resulted in few discontinuations (< 4%, either study). CONCLUSIONS. Naproxen/esomeprazole magnesium has comparable UGI tolerability to celecoxib in patients with osteoarthritis.


OBJECTIVE: To demonstrate that a fixed-dose combination of enteric-coated naproxen 500mg and immediate-release esomeprazole magnesium 20mg has comparable efficacy to celecoxib for knee osteoarthritis.

RESEARCH DESIGN AND METHODS: Two randomized, double-blind, parallel-group, placebo-controlled, multicenter phase III studies (PN400-307 and PN400-309) enrolled patients aged >=50 years with symptomatic knee osteoarthritis. Following an osteoarthritis flare, patients received naproxen/esomeprazole magnesium twice daily, celecoxib 200mg once daily, or placebo for 12 weeks.

CLINICAL TRIAL REGISTRATION: NCT00664560 and NCT00665431.
MAIN OUTCOME MEASURES: Three co-primary efficacy endpoints were mean change from baseline to week 12 in Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain and function subscales, and Patient Global Assessment of osteoarthritis using a visual analog scale (PGA-VAS).

RESULTS: In Study 307, 619 patients were randomized and 614 treated. In Study 309, 615 patients were randomized and 610 treated. Both naproxen/esomeprazole magnesium and celecoxib were associated with improvements (least squares mean change from baseline to week 12) in WOMAC pain (Study 307: -42.0 and -41.8, respectively; Study 309: -44.2 and -42.9, respectively), WOMAC function (Study 307: -36.4 and -36.3, respectively; Study 309: -38.9 and -36.8, respectively), and PGA-VAS (Study 307: 21.2 and 21.6, respectively; Study 309: 29.0 and 25.6, respectively). A prespecified non-inferiority margin of 10mm between naproxen/esomeprazole magnesium and celecoxib was satisfied for each co-primary endpoint at week 12 in both studies. Significant improvements were observed with naproxen/esomeprazole magnesium versus placebo in both studies (p<0.05). Celecoxib was significantly different from placebo in Study 307 (p<0.05); however, the improvements were not significant in Study 309. Acetaminophen use and patient expectation of receiving active treatment (80% probability) may have contributed to a high placebo response observed.

CONCLUSIONS: Naproxen/esomeprazole magnesium has comparable efficacy to celecoxib for the management of pain associated with osteoarthritis of the knee over 12 weeks.


BACKGROUND: Gastroprotective co-therapy may reduce the risk of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcers, but adherence is suboptimal.

AIM: To compare the incidence of gastric ulcers with PN 400 [enteric-coated (EC) naproxen 500 mg and immediate-release esomeprazole 20 mg], or EC naproxen.

METHODS: Two randomized, double-blind, multicentre studies (PN400-301, PN400-302). Patients [stratified by low-dose aspirin (< or =325 mg) use] aged > or =50 years or 18-49 years with a history of ulcer, received PN 400 BID (301, n = 216; 302, n = 210) or EC naproxen 500 mg BID (301, n = 216; 302, n = 210) for 6 months. The primary endpoint was the cumulative incidence of endoscopic gastric ulcers.

RESULTS: The cumulative incidence of gastric ulcers was significantly lower with PN 400 vs. EC naproxen (301: 4.1% vs. 23.1%, P < 0.001; 302: 7.1% vs. 24.3%, P < 0.001). PN 400 was associated with a lower combined incidence of gastric ulcers vs. EC naproxen in low-dose aspirin users (n = 201) (3.0% vs. 28.4%, P < 0.001) and non-users (n = 653) (6.4% vs. 22.2%, P < 0.001). The incidence of, and discontinuations due to, upper gastrointestinal (UGI) AEs was significantly lower with PN 400 relative to EC naproxen (P < 0.01, both studies).
CONCLUSIONS: PN 400 significantly reduces the incidence of gastric ulcers, regardless of low-dose aspirin use, in at-risk patients, and is associated with improved UGI tolerability relative to EC naproxen (ClinicalTrials.gov, NCT00527782).
Placebo-Controlled Trials


Background Topical nonsteroidal anti-inflammatory drugs (NSAIDs) may provide an alternative to oral NSAIDs to relieve pain from osteoarthritis (OA), reducing systemic exposure. This 12-week, randomized, double-blind, parallel-group, multicenter trial examined the efficacy and safety of topical diclofenac sodium 1% gel (DSG) for symptomatic knee OA. Methods Eligible patients were aged >= 35 years with symptomatic Kellgren-Lawrence grade (KLG) 1 to 3 OA in 1 or both knees for >= 6 months. Patients meeting entry criteria applied DSG 4 g or vehicle 4 times daily to the symptomatic knee(s). Primary endpoints were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function subscales and global rating of benefit at week 12. Pain on movement at week 4 was an additional primary endpoint for European regulatory purposes. Secondary endpoints included primary outcomes at weeks 1, 4, and 8; WOMAC stiffness subscale; spontaneous pain; global rating of disease; and global evaluation of treatment. Subanalyses were performed according to KLG, the number of knees treated, and age. Results Four hundred twenty patients were randomly assigned to DSG (n = 208) or vehicle (n = 212). At week 12, DSG provided significantly greater reductions in WOMAC pain (52.6% vs 43.1%; P = 0.008) and physical function (49.7% vs 39.4%; P = 0.004) versus vehicle and provided significant improvements in most secondary endpoints. Treatment-related adverse events (AEs) were infrequent (DSG, 7.7%; vehicle, 4.2%), with application site dermatitis being the most common AE (DSG, 4.8%; vehicle, 0%). No treatment-related gastrointestinal or serious AEs occurred with DSG. Conclusion Topical DSG treatment provided effective pain relief and functional improvement of OA in 1 or both knees and was well tolerated, irrespective of disease severity or patient age.