Naproxen/esomeprazole magnesium in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis

NSAIDs have been a main stay of arthritis therapy for decades. Some of the adverse events associated with the use of this class of medications include gastrointestinal bleeding, peptic ulcer disease and gastrointestinal symptoms such as dyspepsia and heartburn. Many guidelines exist advising healthcare professionals on how to minimize these risks. Unfortunately, compliance with these guidelines is less than optimal and, even if they are followed by the healthcare professional, patient adherence to this advice is often less than optimal. This article summarizes the published efficacy, safety and patient self-reported outcome results for naproxen/esomeprazole in the treatment of patients with osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

KEYWORDS: ankylosing spondylitis ▪ naproxen/esomeprazole ▪ NSAID gastropathy ▪ NSAIDs ▪ osteoarthritis ▪ rheumatoid arthritis

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Osteoarthritis (OA), rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are three common types of arthritis which are routinely treated with NSAIDs. Guidelines and data regarding the treatment of these three diseases will be briefly discussed.

The American College of Rheumatology (ACR) in 1995 published guidelines for the medical management of OA which were updated in 2000 [1–3]. In these guidelines, the type of pharmacologic therapy recommended was based on a patient's risk factors for serious upper gastrointestinal (GI) and renal toxicity. Risk factors for upper GI (UGI) adverse events (AEs) included age of 65 years or older, oral glucocorticoid therapy, history of peptic ulcer disease, history of UGI bleeding, use of anticoagulants, presence of comorbid conditions, use of high dose or multiple NSAIDs and possibly cigarette smoking and excess alcohol consumption. These guidelines recommended that an individual with GI risk factors be treated with a COX-2 selective inhibitor, a nonselective NSAID plus misoprostol (Cytotec®; NJ, USA), a proton pump inhibitor (PPI) or a nonacetylated salicylate.

In a study of 8843 patients with RA, 200 µg of misoprostol four-times per day reduced the incidence of complicated ulcers, including those with perforation, bleeding and obstruction by 51% [4]. In a 12-week, randomized, placebo (PBO)-controlled, double-blind endoscopy study, 200 µg of misoprostol three-times a day had comparable efficacy in preventing both duodenal and gastric ulcers however 200 µg two-times per day was associated with a significantly lower risk reduction. The higher dose was associated with significant side effects including diarrhea, flatulence and abdominal pain [5].

In a German study of patients with AS, 1081 patients completed a written questionnaire [6]. One quarter of the patients reported severe side effects from their treatment, most commonly abdominal pain, headache, dizziness and nausea. The percentage of patients reporting changing their NSAID due to side effects ranged from 10.5% for celecoxib (CEL; Celebrex®, Pfizer, NY, USA) to 31.4% for indomethacin (Indocin®). Thus, a need exists for effective therapies for OA, RA and AS that are effective but better tolerated in terms of GI AEs and have a convenient dosing schedule.

Overview of the market

Misoprostol, mentioned above, was approved in 1988 to reduce the risk of NSAID-associated gastric ulcers in patients at high risk. It is believed that NSAIDs produce peptic ulceration by preventing the production of prostaglandins in the stomach. Synthetic prostaglandins such as misoprostol given orally 'replace' the prostaglandins whose production is inhibited by NSAIDs and have been shown to protect the lining of the stomach from NSAID-induced ulcers. Two PPIs have also been approved to reduce the risk of NSAID-associated gastric ulcers in patients at risk. Lansoprazole (Prevacid®, Takeda, IL, USA) was approved in 2000 and esomeprazole (ESO; Nexium®, Astra-Zeneca, IL, USA) was approved in 2004. One trial compares

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the efficacy of misoprostol 200 µg four-times per day to lansoprazole 15 mg per day and to PBO in reducing the risk of NSAID-associated gastric ulcers [7]. The mean age was 60 years, 99% of subjects had a history of a gastric ulcer and 19% were taking low-dose aspirin (LDA). Lansoprazole and misoprostol were more effective than PBO in achieving ulcer recurrence-free status at 12 weeks; almost 50% of PBO subjects developed an ulcer by the end of the study. Misoprostol was slightly more effective than lansoprazole for ulcer prevention; however, misoprostol was associated with a significantly higher incidence of AEs (most commonly, diarrhea) compared with lansoprazole, which mitigated any efficacy advantage. Lansoprazole subjects had a lower incidence of daytime abdominal pain, night-time abdominal pain or antacid use compared with misoprostol. A subgroup analysis also observed that lansoprazole was significantly more effective than both misoprostol and PBO in preventing NSAID-associated symptoms of the composite end point of heartburn, abdominal pain and other symptoms [8].

When the COX-2 selective inhibitors were introduced to the market in 1999, it was hypothesized that this class of drugs would have fewer GI AEs. CEL is the only COX-2 selective inhibitor still on the market in the USA. Etoricoxib (Arcoxia®, Merck and Co. Inc., PA, USA) is a COX-2 inhibitor that is available in 70 countries worldwide but not in the USA. Doses are 60 and 90 mg per day for chronic pain and 120 mg/day for acute pain. Current indications include the treatment of OA, RA, AS, psoriatic arthritis, acute pain, chronic low back pain and gout. Approved indications differ by country.

Nonacetylated salicylates were commonly prescribed before the introduction of the selective COX-2 inhibitors for patients at risk of GI bleeding. Salsalate (no branded product currently being marketed in the USA) and magnesium salicylate (Doan's® pills, Novartis, NJ, USA) are the only commercially available nonacetylated salicylates in the USA. Although these compounds do not interfere with platelet aggregation and can be considered in the management of patients at high risk for NSAID-induced GI events, ototoxicity and CNS toxicity at clinically effective doses limit their use as does the two- to four-times a day dosing.

Multiple products are also available that combine NSAIDs with misoprostol, PPIs or famotidine, a histamine-2 blocker. A product that contains ibuprofen 800 mg/famotidine 26.6 mg (Duexis®, Horizon Pharma, Illinois, USA) was recently approved by the US FDA to relieve the signs and symptoms of RA and OA and to reduce the risk of developing UGI ulcers. This compound was studied in more than 1500 patients with mild-to-moderate pain of arthritis. The primary end point of the REDUCE-1 study was the reduction in incidence of gastric ulcers during the 6-month treatment period. The primary end point of the REDUCE-2 study was the reduction in incidence of UGI (defined as gastric and/or duodenal) ulcers during the 6-month treatment period. In REDUCE-1, the study drug demonstrated a statistically significant reduction in the incidence of gastric ulcers versus treatment with ibuprofen alone (8.7 vs 17.6%). In REDUCE-2, the study drug demonstrated a statistically significant reduction in the incidence of UGI ulcers versus treatment with ibuprofen alone (10.5 vs 20.0%). Misoprostol 200 µg/diclofenac 50/75 mg (Arthrotec®, Pfizer, NY, USA) was approved by the FDA in 1997 to reduce the risk of NSAID-induced gastric ulcers in patients at high risk and lansoprazole/naproxen (NAP; Prevacid® NapraPAC™, Takeda, IL, USA) was approved by the FDA in 2003 to reduce the risk of NSAID-associated gastric ulcers in patients at risk who require an NSAID for treatment of RA, OA and/or AS. NAP/ESO (Vimovo®, Astra-Zeneca, IL, USA) was approved by the FDA in 2010 for relief of the signs and symptoms of OA, RA and AS and to decrease the risk of gastric ulcers in patients at risk.

Introduction to the compound

NAP/ESO is a combination of an enteric-coated (EC) NSAID, NAP and an immediate-release (IR) PPI, ESO. As discussed above, the ACR guidelines suggest the addition of a PPI to an NSAID for the treatment of OA in patients who are at risk of developing an NSAID-induced gastric AE. Unfortunately, adherence to evidence-based guidelines for the prescription of NSAIDs is inadequate as the risk is often underestimated by the prescriber [9]. Even if gastro-protective therapy is prescribed, patient adherence is low for many reasons including dislike of taking one medicine to counteract the potential side effects of another medication, pill burden, cost of multiple copayments for medications and taking a medication to prevent an often asymptomatic condition [10]. To address these unmet needs, a fixed-dose combination of EC NAP 500 mg/375 mg and IR ESO magnesium 20 mg was developed to provide sequential delivery of an NSAID and a PPI in a single pill.

Pharmacodynamics & pharmacokinetics

A Phase I trial evaluated the pharmacokinetics, pharmacodynamics and safety of three different dose formulations of NAP/ESO compared with NAP 500 mg and EC ESO 20 mg daily [11]. The aim of the study was to determine serum levels and time to exposure for these drugs and to determine the dose of IR ESO in the combination product that provides gastric acid suppression similar to EC ESO 20 mg daily. In this randomized, open-label crossover study comprising four treatment periods, 28 healthy adult volunteers received EC NAP 500 mg plus IR ESO 10, 20 and 30 mg (E10, E20, E30) twice daily and non-EC NAP 500 mg plus EC ESO 20 mg daily. On day one of the first treatment period, subjects were randomized to one of the four treatment sequences to receive each of the four treatments for 9 days in a crossover fashion. There was a 12 day or more washout period between treatments. The primary pharmacodynamic end point was the percentage of time over 24 h on day nine of each treatment phase that intra-gastric pH was over 4.0. Intra-gastric pH was measured by a pH probe placed prior to administration of study drug. A pH above 4.0 was chosen as it has been reported that NSAID-associated gastroduodenal damage is reduced substantially if the luminal pH is elevated above 4.0 [12]. Safety assessments were performed for each treatment period including assessment for adverse advents, vital signs, a physical examination, laboratory studies including a complete blood count, urinalysis, and kidney and liver function tests.

The intent-to-treat (ITT) population was defined as all randomized participants who had valid pH data for at least one treatment period. Primary pharmacodynamic analyses were based on the per-protocol population – participants in the ITT population who had valid pH data for all four treatment periods. Twenty-eight subjects were randomized to treatment and 27 completed the study. On day nine, the mean percentage of time where the intra-gastric pH was >4.0 over 24 h was 76.5, 71.4, 40.9 and 59.9% for EC NAP/E30, EC NAP/E20, EC NAP/E10 and NAP plus EC E20. Compared with NAP plus EC E20 treatment, this percentage was significantly greater for EC NAP/E30 and NAP/E20 (95% CI: 13.0–26.0 and 7.8–20.7, respectively). Following morning or evening doses on days one and nine, plasma IR ESO concentrations increased with the ESO dose. On day one, quantifiable plasma concentrations of IR ESO were obtained rapidly with all three EC NAP/E treatments at 10 min after the morning dose and at 20–30 min after the evening dose. Following administration of NAP plus EC E20 treatment on days one and nine, measurable plasma concentrations of EC ESO were not available until 0.75–1.5 h postdose in the majority of subjects. On day one, quantifiable plasma concentrations of EC NAP were first detected at approximately 2 h postadministration for all three doses of EC NAP/E. Following non-EC NAP treatment on days one and nine, plasma NAP concentrations were measurable in all subjects at the 10 min postdose sample time.

Most AEs were mild and no subjects reported serious AEs (SAEs) or withdrew from the study due to AEs. The most common AEs reported by 10% or more of the subjects were diarrhea, upper abdominal pain, iron deficiency and headache. The overall incidence of AEs ranged from 29% in the NAP plus EC ESO 20 mg to 50% with EC NAP/IR ESO 30- and 20-mg doses. GI AEs were reported in 29–32% of subjects receiving the EC NAP/IR ESO doses and 18% of subjects receiving NAP plus EC ESO 20 mg. This increase in treatment-related AEs observed with increasing doses of IR ESO in the three different EC NAP/IR ESO formulations suggests that some of these AEs may be related to ESO rather than to EC NAP.

Thus, this study demonstrated that IR ESO 20 or 30 mg in combination with EC NAP twice daily provided gastric acid suppression comparable to EC ESO 20 mg daily. The study also demonstrated that IR ESO combined with EC NAP provided early onset of increased intra-gastric pH before EC NAP was released. IR ESO was rapidly absorbed with relatively high plasma concentrations detected at an earlier postdose time compared with EC ESO (Table 1). These findings confirmed that the sequential-release design of IR ESO with EC NAP is able to rapidly achieve a gastroprotective environment. As EC NAP/IR ESO E10 provided insufficient pH control and EC NAP/IR ESO E30 was associated with more AEs and was not significantly better than EC NAP/IR ESO E20, the latter dosing was selected for further studies to evaluate the analgesic and GI efficacy of this compound.

Clinical gastric ulcer reduction efficacy

Two identical, 6 month, randomized, double-blind parallel-group, controlled, multicenter Phase III studies (301 and 302) were conducted

Table 1. Summary of esomeprazole and naproxen pharmacokinetic parameters on days 1 and 9 (pharmacokinetic population).

Treatment, day and dose	Esomeprazole			Naproxen		
	C_{max} (ng/ml)	t_{max} (h)	AUC† (h·ng/ml)	C_{max} (ng/ml)	t_{max} (h)	AUC† (h·ng/ml)
EC naproxen/E20 (n = 28)						
Day 1, morning	292 (77)	0.50 (0.20–1.50)	350 (113)	44.4 (68)	4.00 (2.00–10.00)	231 (70)
Day 1, evening	96.6 (104)	1.49 (0.33–3.00)	206 (141)	71.5 (26)	14.00 (0.00–14.00)	450 (33)
EC naproxen + E20 (n = 28)						
Day 1, morning	282 (66)	1.50 (1.00–16.00)	540‡ (60)	65.5 (25)	1.50 (0.75–6.00)	409 (16)
Day 1, evening				81.5 (14)	1.50 (0.50–2.50)	685 (10)
EC naproxen/E20 (n = 27)						
Day 9, morning	715 (52)	0.50 (0.17–1.50)	1216 (69)	86.2 (22)	3.00 (0.00–8.05)	607 (19)
Day 9, evening	428 (73)	0.75 (0.33–3.00)	919 (84)	76.8 (18)	10.00 (0.00–14.00)	678 (16)
EC naproxen + EC E20 (n = 28)						
Day 9, morning	435 (48)	1.50 (1.00–14.00)	1046 (54)	90.0 (19)	1.50 (0.50–4.00)	617 (12)
Day 9, evening	–	–	–	86.5 (13)	1.50 (0.75–4.00)	769 (10)

Values are mean (% coefficient of variation) for C_{max} and AUC, and median (range) for t_{max}.
†AUC 0–10, morning or AUC 0–14, evening.
‡n = 26.
AUC: Area under the plasma concentration vs time curve; C_{max}: Peak plasma concentration; E20: EC naproxen 500 mg plus immediate-release esomeprazole 20 mg; EC: Enteric coated; PK: Pharmacokinetic; t_{max}: Time to peak plasma concentration.
Adapted with permission from [11].

in the USA [13]. The primary end point was to determine if NAP/ESO reduced the risk of endoscopic gastric ulcers in patients at risk compared with EC NAP over the 6-month time period. Endoscopies were performed at baseline, 1, 3 and 6 months. Secondary end points were to determine if NAP/ESO reduced the risk of duodenal ulcers and to evaluate the UGI symptoms and tolerability and safety of NAP/ESO compared with EC NAP. An additional end point was to evaluate the incidence of gastric ulcers in the subgroup of subjects taking LDA. A prespecified pooled analysis to assess the effect of LDA use on gastric ulcer incidence in these NSAID users was also conducted. Of note, this study did not evaluate the relative efficacy of these medications in treating the pain associated with arthritis.

Inclusion criteria were *Helicobacter pylori* negative patients with OA, RA, AS or any other condition expected to require daily NSAID use over a 6-month period of time. Subjects were either age 50 years or older or age 18–49 years who had a documented history of an uncomplicated gastric or duodenal ulcer in the past 5 years. Exclusion criteria were gastric or duodenal ulcer on baseline endoscopy, history of hypersensitivity or allergy to any PPI or NSAID, any uncontrolled medical condition, history of alcohol or drug abuse or prior GI disease or surgery. Subjects were not allowed to take another NSAID (other than LDA), bisphosphonates or anticoagulants (excluding LDA) during the treatment phase. PPIs, sucralfate and histamine-2 blockers had a washout period of 2 weeks prior to baseline and misoprostol had a 1-week washout prior to screening. After the washout period a baseline endoscopy was performed and subjects without an ulcer at baseline were randomized. Subjects were randomized to either NAP/ESO (500/20 mg) or EC NAP (500 mg) taken twice daily before meals for 6 months and were stratified by LDA use (less than or equal to 325 mg/day). Acetaminophen and liquid antacid were allowed for rescue pain management and relief of UGI symptoms.

UGI symptoms and tolerability were measured using patient self-reported questionnaires including: Severity of Dyspepsia Assessment (SODA), Overall Treatment Evaluation-Dyspepsia (OTE-DP) and assessment of heartburn. SODA was administered at baseline and 1, 3 and 6 months and heartburn severity was also assessed at these visits. The OTE-DP questionnaire was administered at the 6-month visit. Safety was assessed by recording the incidence of AEs, treatment-related AEs and SAEs. Laboratory studies including a complete blood count and liver and renal function tests were performed at screening and/or baseline and at 1, 3 and 6 months.

All efficacy analyses were performed on the ITT populations (all randomized subjects who received one or more doses of study drug and met inclusion criteria). Planned supportive analyses were performed on the per-protocol population – those subjects with no major protocol violations and treatment compliance of 70% or greater. Subgroup analyses included age (less than 60 years of age or 60 years of age and older), history of ulcer in the past 5 years (yes/no) and use of LDA (yes/no).

In study 301, of the 635 subjects screened, 438 subjects were randomized, 434 subjects were treated and 333 subjects completed the study. In study 302, 639 subjects were screened, 423 subjects were randomized, 420 subjects were treated and 304 subjects completed the study. The mean age of subjects was approximately 61 years in study 301 and 60 years in study 302 and two-thirds of the subjects in both studies were female. Approximately 23% of subjects were taking LDA and more than 80% of the subjects had OA. Baseline demographics and characteristics were similar between the two groups except that there was a numerically greater proportion of subjects with RA in the NAP/ESO group compared with the EC NAP group in study 301.

In both studies, the cumulative incidence of gastric ulcers over 6 months was significantly lower in the subjects randomized to NAP/ESO compared with those randomized to EC NAP (study 301: 4.1 vs 23.1%, $p < 0.001$; study 302: 7.1 vs 24.3%, $p < 0.001$). This was calculated to be a relative risk reduction of 82.3% for study 301 and 70.8% for study 302. A significant difference was seen as early as month one and was maintained throughout the 6 month study (FIGURE 1). The cumulative incidence of duodenal ulcers was also significantly lower in the subjects randomized to NAP/ESO compared with those randomized to EC NAP (study 301: 0.05 vs 5.1%, $p = 0.003$; study 302: 1.0 vs 5.7%, $p = 0.007$). This translated to a relative risk reduction of 90.1% in study 301 and 82.4% in study 302. In a pooled analysis of both studies, the cumulative incidence of gastric ulcers in LDA users was also significantly lower in the NAP/ESO group compared with the EC NAP group (FIGURE 2).

The most common UGI AEs occurring in 10% or more of subjects in either treatment group were erosive gastritis, gastritis, dyspepsia and erosive duodenitis. In the ITT population, the incidence of predefined NSAID-associated UGI AEs was significantly lower in the NAP/ESO group compared with the EC NAP group in both studies (study 301: 52.3 vs 69.0%, $p < 0.001$; study 302: 54.3 vs 71.9%, $p < 0.001$). A significantly lower proportion of subjects discontinued the study due to UGI AEs (including duodenal ulcer) in the NAP/ESO

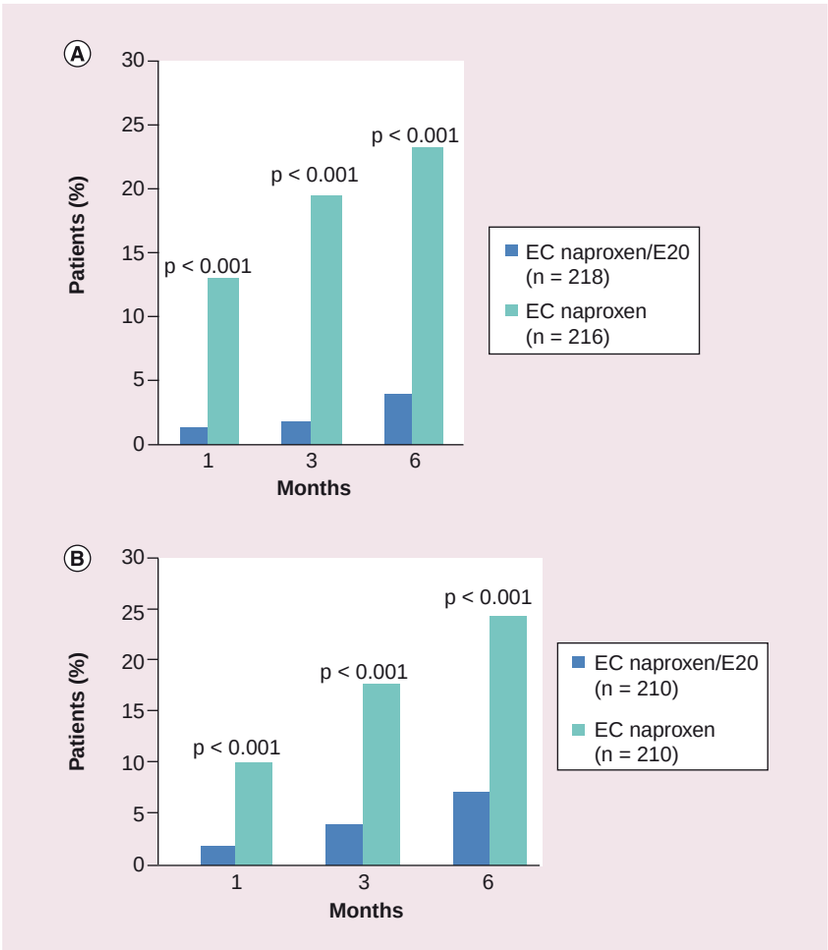

Figure 1. Cumulative observed incidence of gastric ulcers at 1, 3 and 6 months. (A) Study 301 and **(B)** study 302.
E20: EC naproxen 500 mg plus immediate-release esomeprazole 20 mg; EC: Enteric coated.

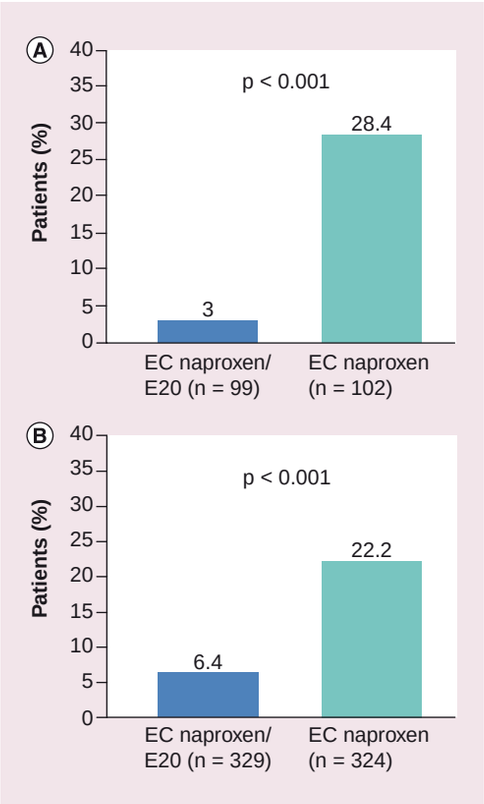

Figure 2. Pooled cumulative observed incidence of gastric ulcers at month 6.
(A) Low-dose aspirin users and **(B)** low-dose aspirin nonusers.
E20: EC naproxen 500 mg plus immediate-release esomeprazole 20 mg; EC: Enteric coated.

groups compared with the EC NAP groups (study 301: 3.2 vs 12.0%, p < 0.001; study 302: 4.8 vs 11.9%, p = 0.009).

Subjects randomized to NAP/ESO reported significantly better UGI tolerability compared with those assigned to EC NAP in terms of OTE-DP response, SODA scores and proportion of heartburn-free subjects. Those subjects who experienced an improvement in upper abdominal pain and/or discomfort and were assigned to NAP/ESO, reported that the degree of change was at least moderately better or more compared with EC NAP (study 301: 86.0 vs 69.2%: study 302: 79.8 vs 61.9%). Of those subjects who reported a deterioration in symptoms, the proportion that stated the degree of change to be at least moderately worse or more was numerically similar or greater in the EC NAP groups compared with the NAP/ESO groups (study 301: 60.0 vs 61.1%: study 302: 74.3 vs 62.5%). In study 301, SAEs related to study treatment were duodenal ulcer hemorrhage (n = 1) and noncardiac chest pain (n = 1), both in the EC NAP groups. There were no treatment-related SAEs in study 302 or deaths in either study.

Long-term safety

A 12-month open-label, multicenter, Phase III study was performed with the primary objective to evaluate the long-term safety of NAP/ESO (500/20 mg) in patients at risk of developing NSAID-associated gastric ulcers [14]. The inclusion criteria were the same as the other Phase III studies except that anticipation of the need for 12 months of NSAID therapy was required. Exclusion criteria were similar as well except that narcotics were allowed as rescue therapy but no more than six episodes during the treatment phase. Safety assessments were performed at baseline, 1, 3, 6, 9 and 12 months.

Overall, 239 subjects were enrolled and included in the overall safety population; 143 subjects were considered to have completed the study but only 135 subjects received treatment for 348 study days. The demographics and baseline characteristics were similar to the other Phase III studies with 30% of the subjects LDA users.

The overall incidence of AEs was approximately 70% and was similar for both the safety and 12-month completer populations. Dyspepsia was the most common treatment-emergent AE in the overall safety population (7.9%) and upper respiratory tract infections (URIs) were the most frequent in the 12-month completers (9.6%). Other common treatment-emergent AEs reported by 5% or more of the subjects included nausea and constipation in the overall safety population and contusion and back pain in the 12-month completer population. GI AEs were reported by 35.6% of the subjects in the overall safety population and in 30.4% of the 12-month completers. In the overall safety population, AEs led to study discontinuation in 18.8% of subjects and GI AEs led to withdrawal of 19 subjects (7.9%). Only one subject in the overall safety population experienced an SAE that was considered to be possibly treatment related; the subject developed hematemesis and was withdrawn from the study. There were no deaths during the study.

GI AEs were reported by 33.5% of subjects younger than 65 years of age and by 39.7% of subjects 65 years of age or older in the overall safety population and by 28.3 and 34.9% of subjects, respectively, in the 12-month completer population. In the overall safety population, dyspepsia (8.7%) was the most common AE

among subjects aged less than 65 years of age and arthralgia (9%) was the most common AE among subjects aged 65 years or older. In the 12-month completer population, URI (10.9%) and back pain (11.6%) were the most frequent AEs in the younger and older age groups, respectively.

The cumulative incidence of predefined NSAID-associated UGI AEs leading to discontinuation was approximately 5.7%. Predefined NSAID-associated UGI AEs occurred in 18.8% of the subjects in the overall safety population and in 16.3% of subjects in the 12-month completer population. The most common AEs (combined incidence of cardiovascular, hemorrhage, and unknown death, nonfatal myocardial infarction and nonfatal stroke) reported by at least 3% of the subjects in either population were dyspepsia, upper abdominal pain, nausea and hypertension. Predefined cardiovascular AEs occurred in 6.3% of the overall safety population and in 5.2% of the 12-month completer population.

GI AEs were reported by 28.4% of the LDA users and 38.8% of LDA nonusers in the overall safety population and by 22.5 and 33.7%, respectively, in the 12-month completer population. Diarrhea was the most frequent AE in the overall safety population (8.1%) and in the 12-month completer population (10.0%) in the LDA users. URI and back pain were also reported in 10.0% of LDA users in the 12-month completer population. Dyspepsia (10.3%) and URI (9.5%) were the most commonly reported AEs in the non-LDA users in the overall safety and 12-month completer populations, respectively.

Increases of more than 20 mmHg in systolic and diastolic blood pressures at any study visit were observed in 24.7 and 6.3%, respectively, in the overall safety population. Physical examinations did not reveal any unexpected safety findings. Clinically abnormal hematology values were observed in four subjects. Blood chemistry abnormalities occurred in 17 subjects. Clinically significant ECG abnormalities were reported for three subjects in the overall safety population by month 12 or the final visit.

Clinical OA pain efficacy

Two randomized, double-blind, PBO-controlled 12-week identical Phase III studies (307 and 309) were performed that compared the efficacy, safety and tolerability of NAP/ESO with CEL 200 mg and PBO in treating patients with OA of the knee [15]. Three coprimary efficacy end points were mean change from baseline to week 12 in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, WOMAC function and Patient Global Assessment of Osteoarthritis Visual Analog Scale (PGA-VAS) scores. The primary objective was to demonstrate noninferiority of NAP/ESO versus CEL 200 mg for the treatment of the signs and symptoms of OA of the knee. UGI tolerability was assessed by the modified SODA, heartburn severity questionnaire and the incidence of predefined NSAID-associated UGI AEs and the proportion of patients discontinuing treatment due to any AE or predefined NSAID-associated UGI AE. Safety assessment end points also included the overall incidence of AEs.

Inclusion criteria included subjects age 50 years or older with at least a 6 month history of symptomatic, clinically diagnosed OA of the knee (ACR functional class 1, 2 or 3) who had received a stable dose of selective or nonselective NSAIDs or other oral analgesics for 6 weeks or more. Exclusion criteria included concomitant use of any other NSAID oral or topical (except LDA less than or equal to 325 mg/day) or use of a gastroprotective agent during the study. Rescue use of acetaminophen (3 g or less per day) and use of an oral antacid to treat UGI symptoms were allowed during the study. The subjects were not allowed to take any narcotic analgesics.

After a 7–14 day washout period, subjects who experienced a flare of their OA defined as a WOMAC pain score of greater than or equal to 40 at baseline, mean change in WOMAC pain score of 15 mm or more compared with baseline and worsening PGA of OA by one or more points using a 5-point Likert scale. Subjects were randomized 2:2:1 to receive NAP/ESO (500/20 mg) twice daily, CEL 200 mg once daily or PBO. Study drug was taken 30–60 min by mouth before the morning and evening meals for 12 weeks. In study 307, 619 subjects were randomized and 521 subjects completed the study. In study 309, 615 subjects were randomized and 489 subjects completed the study. Baseline demographics and characteristics were similar among treatment groups in both studies.

Improvements in WOMAC pain, WOMAC function and PGA-VAS from baseline to week 12 were observed in both studies as measured by the least squares mean changes from baseline for each treatment group. A two-sided 95% CI for the treatment differences

(NAP/ESO minus CEL; NAP/ESO minus PBO; and CEL minus PBO) was calculated. Noninferiority of NAP/ESO versus CEL was established only if the upper bound of a 95% CI was less than or equal +10 mm for both pain and function subscales and if the lower bound was more than or equal -10 mm for PGA-VAS. The prespecified noninferiority margin between NAP/ESO and CEL was met for all three coprimary end points in both studies. In study 307, both active treatments were significantly better than PBO for all three coprimary end points. In study 309, NAP/ESO was significantly better than PBO for all three coprimary end points but improvements with CEL versus PBO did not reach statistical significance (TABLE 2).

Although dyspepsia-related pain was mild at baseline as reflected by low modified SODA scores, improvements were observed across all three treatment groups in both studies at week 12. There was no significant difference between NAP/ESO and CEL in either study. Subjects who received NAP/ESO reported significantly more heartburn-free days than those treated with CEL in both studies. The overall incidence of AEs was approximately 50% and was similar among groups in both studies. The most frequently reported treatment-emergent AEs were GI disorders, including diarrhea and dyspepsia (TABLE 3). SAEs occurred in 2% or fewer subjects in the active treatment groups. One case of anaphylaxis in a subject

Table 2. Noninferiority analysis of Western Ontario and McMaster Universities Osteoarthritis Index pain, function and Patient Global Assessment of Osteoarthritis Visual Analog Scale at week 12.

	NAP/ESO (n = 246)	CEL (n = 242)	PBO (n = 124)	NAP/ESO–CEL	NAP/ESO–CEL	CEL–PBO
Study 307						
WOMAC pain, n	226	221	108			
LS mean change from baseline to week 12	-42	-41.8	-35.6	-0.2	-6.4	-6.1
95% CI				-4.8, 4.3	-12.0, -0.7	-11.8, -.05
WOMAC function, n	226	332	209			
LS mean change from baseline to week 12	-36.4	-36.3	-30.6	-0.1	-5.8	-5.7
95% CI				-4.6, 4.4	-11.3, -0.2	-11.2, -0.1
PGA-VAS, n	242	230	119			
LS mean change from baseline to week 12	21.2	21.6	14.4	-0.5	6.8	7.2
95% CI				-5.1, 4.1	1.1, 12.4	1.6, 12.9
	(n = 241)	**(n = 244)**	**(n = 122)**			
Study 309						
WOMAC pain, n	213	220	106			
LS mean change from baseline to week 12	-44.2	-42.9	-38.4	-1.3	-5.9	-4.6
95% CI				-5.9, 3.3	-11.6, -0.1	-10.3,1.2
WOMAC function, n	213	220	106			
LS mean change from baseline to week 12	-38.9	-36.8	-32.3	-2.1	-6.6	-4.5
95% CI				-6.8, 2.6	-12.4, -0.8	-10.3, 1.3
PGA-VAS, n	235	234	115			
LS mean change from baseline to week 12	c29	25.6	21.4	3.5	7.6	4.2
95% CI				-1.4, 8.3	1.7, 13.6	1.8, 10.2

CEL: Celecoxib; LS: Least squares; NAP/ESO: Naproxen/esomeprazole; PBO: Placebo; PGA-VAS: Patient Global Assessment of Osteoarthritis Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.
Adapted with permission from [14].

Table 3. Summary of predefined NSAID-associated upper gastrointestinal adverse effects and discontinuations as a result of upper gastrointestinal adverse effects or any adverse effect.

	Study 307			Study 309		
	NAP/ESO (n = 247)	***CEL (n = 244)***	***PBO (n = 124)***	***NAP/ESO (n = 243)***	***CEL (n = 245)***	***PBO (n = 122)***
Patients with any UGI AE, n (%)	41 (16.6)	41 (16.9)	24 (19.4)	46 (18.9)	53 (21.6)	25 (20.5)
UGI AEs reported by ≥3% of patients, n (%)†						
Dyspepsia	13 (5.3)	19 (7.8)	14 (11.3)	28 (11.5)	33 (13.5)	16 (13.1)
Nausea	12 (4.9)	6 (2.5)	6 (4.8)	5 (2.1)	9 (3.7)	3 (2.5)
Upper abdominal pain	10 (4.0)	9 (3.7)	2 (1.6)	10 (4.1)	12 (4.9)	6 (4.9)
Vomiting	5 (2.0)	2 (0.8)	4 (3.2)	3 (1.2)	4 (1.6)	0 (0.0)
Discontinuations due to UGI AEs	3 (1.2)	4 (1.6)	3 (2.4)	2 (0.8)	9 (3.7)	3 (2.5)
Discontinuations due to any AE	18 (7.3)	16 (6.6)	7 (5.6)	16 (6.6)	22 (9.0)	5 (4.1)

†Any treatment group of either study.
AE: Adverse event; CEL: Celecoxib; NAP/ESO: Naproxen/esomeprazole; PBO: Placebo; UGI: Upper gastrointestinal.
Adapted with permission from [14].

randomized to CEL in study 307 was felt possibly treatment related. There were no deaths in either study.

Regulatory affairs

NAP/ESO is currently approved in 23 countries in the EU, in Canada and in the USA.

Conclusion

NAP/ESO provides the efficacy of NAP in OA, RA and AS and has shown clinical efficacy in reducing the pain associated with OA of the knee. Its GI safety profile is superior to EC NAP in all variables measured-fewer gastric ulcers, fewer duodenal ulcers, fewer GI complaints and fewer drug discontinuations. Even when taken in combination with LDA, this safety profile remains. Long-term treatment for 12 months was not associated with any new safety issues. Compared to CEL, NAP/ESO has comparable efficacy in the treatment of OA of the knee and comparable UGI tolerability. Thus, NAP/ESO offers an effective, well-tolerated alternative to currently available therapy for patients who require NSAID therapy and are at risk of NSAID-associated ulcers.

Future perspective

Based on pay-for-performance, a healthcare provider will be rewarded if a patient taking an NSAID does not develop GI AEs or complaints that require therapeutic intervention. This favorable outcome depends on several factors including healthcare provider awareness and acceptance of the potential AE, prescribing medications that place the patient at lower risk of GI AEs and ensuring patient compliance and adherence. One possible solution to this dilemma is to develop combination products such as NAP/ESO and based on this assumption, more combination products will be developed and marketed in the future. The challenge for the healthcare provider and the patient is to convince the insurer to pay for these combination products that often contain one or two generic medications. Another solution would be to develop medications for OA, RA, AS and other pain conditions requiring chronic therapy that have fewer side effects. Unfortunately, drug development has been slow to achieve this goal. NAP/ESO is the first new oral NSAID approved by the FDA for OA, RA and AS pain since 2000. Hopefully with better understanding of the pathophysiology of pain in OA, RA and AS, new therapies will be developed with convenient administration and equal or greater efficacy and fewer AEs.

Financial & competing interest disclosure

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Executive summary

Mechanism of action

- Naproxen/esomeprazole (Vimovo®) is a fixed-dose combination of immediate-release (IR) esomeprazole (20 mg) and enteric-coated naproxen (375 and 500 mg).

Pharmacokinetic properties

- Quantifiable plasma concentrations of IR esomeprazole are obtained at 10 min after the morning dose and at 20–30 min after the evening dose.
- Quantifiable plasma concentrations of enteric-coated (EC) naproxen were first detected at approximately 2 h postdosing.
- The mean percentage of time where intra-gastric pH was greater than 4.0 over a 24-h period was 71.4%. It is understood that NSAID-associated gastroduodenal damage can be substantially reduced by elevating the luminal pH above 4.0.
- The pharmacokinetic parameters and plasma profiles of IR esomeprazole and EC naproxen in addition to the intra-gastric pH profiles are consistent with the qualities needed to rapidly achieve a gastroprotective environment.

Clinical efficacy

- IR naproxen/esomeprazole has similar efficacy to celecoxib and superior efficacy to placebo for the treatment of signs and symptoms of osteoarthritis of the knee over a 12-week treatment period.

Safety & tolerability

- Compared to EC naproxen, IR naproxen/esomeprazole significantly reduced the incidence of gastric ulcers, regardless of concomitant low-dose aspirin use, in at-risk patients requiring long-term NSAID therapy.
- IR naproxen/esomeprazole significantly reduces the incidence of duodenal ulcers.
- IR naproxen/esomeprazole is associated with improved upper gastrointestinal (UGI) tolerability as assessed by the incidence of UGI adverse events and resulting discontinuation.
- IR naproxen/esomeprazole has comparable UGI tolerability and similar safety profile to celecoxib in patients with OA of the knee over a 12-week treatment period.

Drug interactions

- There were no drug-to-drug interactions between IR esomeprazole and EC naproxen when coadministered as a fixed-dose combination as the dose level of IR esomeprazole in the combination product did not affect the steady-state plasma exposure to naproxen.

Dosage & administration

- Available as the fixed-dose combination tablet to be administered twice daily before meals.

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