Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Naproxen/esomeprazole

Proprietary Product Name: Vimovo

Sponsor: AstraZeneca Pty Ltd

November 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Fixed Combination
Decision:	Approved
Date of Decision:	18 October 2011
Active ingredient(s):	Naproxen Esomeprazole (as the magnesium hydrate)
Product Name(s):	Vimovo
Sponsor's Name and Address:	AstraZeneca Pty Ltd Alma Road North Ryde NSW 2113
Dose form(s):	Modified release tablet
Strength(s):	500 mg naproxen, 20 mg esomeprazole
Container(s):	HDPE bottles, blister packs
Pack size(s):	Bottles: 6, 60, 500 Blisters: 10, 30, 100
Approved Therapeutic use:	Vimovo is indicated for patients with an increased risk of gastrointestinal ulceration, who require NSAID therapy for symptomatic management of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis with an inflammatory component AND in whom lower doses of naproxen or other NSAIDS have proven insufficient. If a daily dose of 1 g of naproxen is not required, Vimovo should NOT be used.
Route(s) of administration:	Oral
Dosage:	One tablet twice daily given at least 30 minutes before a meal
ARTG Numbers:	170577, 170578

Product Background

This AusPAR describes the evaluation of an application by AstraZeneca Pty Ltd (the sponsor) to register Vimovo, an oral, fixed dose combination product composed of pH sensitive enteric coated (EC) naproxen 500 mg and immediate release (IR) esomeprazole (as magnesium trihydrate) 20 mg, two well known and established drug substances in widespread clinical use.

Naproxen is a non-steroidal antiinflammatory drug (NSAID) with analgesic, antiinflammatory and antipyretic properties. It is a propionic acid derivative unrelated to salicylates and to the corticosteroid hormones. On the Australian Register of Therapeutic Goods (ARTG) there are a number of different brands of 275 mg tablets available as non-prescription medicines. With regard to prescription medicines, the innovator medicine is Naprosyn as immediate release tablets in strengths of 250 mg, 500 mg and a 25 mg/mL suspension. The innovator is also available as naproxen sustained release (Naprosyn SR) in strengths of 750 mg and 1000 mg.

Naprosyn (immediate release) is indicated for:

The treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, for the symptomatic treatment of primary dysmenorrhoea, for the relief of acute and/or chronic pain states in which there is an inflammatory component and as an analgesic in acute migraine attack.

Naprosyn SR is indicated for:

The treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and for the relief of chronic pain states in which there is an inflammatory component.

Esomeprazole is a proton pump inhibitor and is the S-isomer of omeprazole. It is optically stable *in vivo* with negligible conversion to the R-isomer. In Nexium, the innovator product, it occurs as esomeprazole magnesium trihydrate. Nexium 20 mg and 40 mg tablets are comprised of enteric coated pellets containing esomeprazole. There are also Nexium 10 mg granules for oral suspension comprised of enteric coated pellets containing esomeprazole.

The approved indications for Nexium are extensive and can be listed under 5 main headings:

- Gastro-oesophageal reflux disease (GORD)
- Patients requiring NSAID therapy
- Prevention of rebleeding of gastric or duodenal ulcers following treatment with Nexium IV solution by intravenous infusion
- Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion, and
- In combination with appropriate antibiotics for healing of duodenal ulcer associated with *Helicobacter pylori* and eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer.

From the perspective of this application, the most relevant part of the esomeprazole indication is that to do with patients requiring NSAID therapy. That part of the indication is as follows:

Patients requiring NSAID therapy

- *Short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy*[1]
- *Healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy [the usual dose is 20 mg once daily for 4-8 weeks]*
- *Prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk* [2]

The proposed indication for Vimovo is:

Vimovo is indicated for symptomatic relief in the treatment of OA, RA, and AS in patients at risk for developing NSAID associated gastric and/or duodenal ulcers.

[1] It can be noted under Dosage and Administration that the approved dose is 20 mg once daily and that if symptom control has not been achieved after 4 weeks, the patient should be further investigated. It is also noted that controlled studies did not extend beyond 4 weeks.

[2] It can be noted under Dosage and Administration that the approved dose is 20 mg once daily and that controlled studies did not extend beyond 4 weeks.

The proposed dosing regimen is one tablet (500 mg/20 mg) twice daily given at least 30 minutes before a meal.

Regulatory Status

Similar applications have been submitted in Canada (June 2010), USA (June 2009) and the European Union (EU) (Oct 2009). Vimovo (naproxen/ esomeprazole magnesium) 500/20 mg and 375/20 mg modified release tablets were approved in the USA in April 2010. The approved indications for Vimovo in USA are:

Vimovo is a combination product that contains naproxen and esomeprazole. It is indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID associated gastric ulcers. Vimovo is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen-containing products. Controlled studies do not extend beyond 6 months.

Vimovo (also 500/20 mg and 375/20 mg) was approved in Canada on 13 January 2011. The approved indication is:

Vimovo (naproxen/esomeprazole) is indicated for the treatment of the signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA) and ankylosing spondylitis (AS) and to decrease the risk of developing gastric ulcers in patients at risk for developing NSAID associated gastric ulcers. Vimovo is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed (as with other modified release formulations of naproxen).

For patients with an increased risk of developing cardiovascular (CV) and/or gastrointestinal (GI) adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first (see Contraindications and Warnings and Precautions). Use of Vimovo should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events (see Contraindications and Warnings and Precautions).

Vimovo, as a NSAID, does NOT treat clinical disease or prevent its progression.

Vimovo, as a NSAID, only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

Vimovo (500/20 mg) modified release tablets were approved in the EU on 18 November 2010. This followed all 22 Concerned Member States agreeing with the assessment of the Netherlands Health Authority (MEB), acting as the Reference Member State for the Decentralised Procedure (DCP). The approved indication is:

Symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, in patients who are at risk for developing non-steroidal anti-inflammatory drug (NSAID)-associated gastric and/or duodenal ulcers and where treatment with lower doses of naproxen or of other NSAIDs is not considered sufficient.

The contents of the application submitted in Australia were generally similar to those submitted in other countries with the following two exceptions: (1) the Canadian and US submissions also applied for an additional strength of 375 mg/20 mg, and (2) one of the six biopharmaceutic studies was conducted specifically for this Australian submission and has not been submitted in other markets. This is due to the fact that the Vimovo clinical program (pivotal Phase III as well as bioequivalence studies) relies significantly on comparative studies against EC-Naprosyn (enteric coated naproxen tablets). However, in Australia, naproxen is only available as immediate release tablets (Naprosyn). In order to validate the clinical development program for this submission and as per Australian

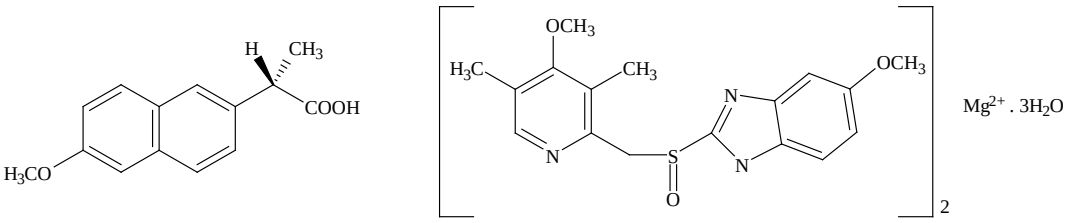
regulatory requirements, a separate bioavailability study (D1120C00035) was conducted to compare bioavailability of the naproxen component of Vimovo with immediate release Naprosyn tablets available in Australia at steady state. This approach was considered acceptable to the TGA.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)



naproxen
$C_{14}H_{14}O_3$ MW = 230.3
CAS # = [22204-53-1]
practically in soluble in water:
{< 0.1 mg/mL}

esomeprazole magnesium trihydrate
$C_{34}H_{36}N_6O_6S_2Mg.3H_2O$ MW = 767.2
CAS # = [217087-09-7]
sparingly soluble in water
{10-33 mg/mL}

Naproxen is manufactured by Divi's Laboratories Limited in India.

A European Directorate on the Quality of Medicines Certificate of Suitability was provided indicating compliance with the European Pharmacopoeia/British Pharmacopoeia monograph for naproxen. The particle size distribution is controlled with limits. The residual solvents of methanol and toluene used in the synthesis are controlled to tighter than International Council on Harmonisation (ICH) guidance.

The esomeprazole hemihydrate is controlled as for the registered Nexium range of products. The particle size distribution is tightly controlled with limits.

Drug Product

The tablet manufacturing process (which involves multiple coating steps) was adequately validated and included appropriate in-process controls.

The delayed release of naproxen is achieved by the presence of an enteric coat. The tablets are well controlled with expiry limits for the esomeprazole and naproxen assays meeting Therapeutic Goods Order 78 requirements.

The expiry limits for degradants of naproxen meet ICH requirements. The expiry limits for degradants of esomeprazole also meet ICH requirements. Appropriate dissolution limits were set.

The only change to the product on storage was an increase in the known and total degradants of esomeprazole and stability data was provided that supported shelf lives of 3 and 2 years, respectively, when stored below 25ºC in high density polyethylene (HDPE) bottles with child resistant caps or in blister packs.

Biopharmaceutics

Introduction

The pivotal Phase III efficacy studies were performed with a tablet termed the 'Phase 3' formulation. Prior to this was a 'Phase 1' formulation and after this is the 'primary stability' formulation. This latter formulation is that proposed for supply in Australia. The differences between the 'Phase 3' and 'primary stability' formulations (*indigo carmine removed from colour coat to change colour from green to yellow, addition of carnauba wax polish and addition of printing in black ink*) are minor and it was accepted that these will not affect bioavailability. The Phase III efficacy studies also used a tablet termed 'EC naproxen'. These were the same as the 'Phase 3' formulation with enteric coated naproxen but without esomeprazole in the active film coat.

Data Provided

To support registration, seven bioavailability studies were provided but only four were evaluated.

Results

DC1120C00035 / QP09B07 compared the proposed 'primary stability' formulation to Naprosyn immediate release tablets purchased in Australia in 24 subjects (23 completed) at steady state. The results indicated bioequivalence of the naproxen response. The time to maximum plasma concentration (T_{max}) was however increased from 1.5 hours (h) to 3.5 h as expected for the proposed delayed release formulation.

PN400-103 investigated the effect of food on the proposed 'primary stability' formulation after single doses. The results indicate that:

- Compared to the fasted state the extent of the bioavailability as indicated by the area under the plasma concentration time curve (AUC) of naproxen is not affected by food. However, the rate of the bioavailability as measured by the maximal plasma concentration (C_{max}) of naproxen is ~15% lower with food or 30 minutes (min) before food but unaffected 60 min before food. Comparing fasted to fed states showed a further delay in T_{max} of 6-14 h.
- Compared to the fasted state the rate and extent of the bioavailability of esomeprazole were decreased by ~75% and ~50% when given with food.
- Compared to the fasted state the point estimates for the rate and extent of the bioavailability of esomeprazole were affected when given 30 min after food. However the confidence intervals were wide and the lack of a food effect cannot be concluded.
- Compared to the fasted state the rate and extent of the bioavailability of esomeprazole were increased by ~50% and ~25% when given 60 min after food.

PN400-102 compared the 'Phase 3' formulation to the 'EC naproxen' formulation (without esomeprazole) and to an enteric naproxen tablet from the US. The results indicated bioequivalence of the naproxen response from the 'Phase 3' formulation and the 'EC naproxen' formulation. The study also indicated that the 'Phase 3' tablet was bioequivalent to the US enteric naproxen tablet with respect to AUC, but not with respect to C_{max} (16% lower with 'Phase 3" formulation) or T_{max} (6 h versus 4 h).

PN400-114 compared the proposed 'primary stability' formulation to a monotherapy enteric naproxen tablet from the US, a monotherapy enteric coated esomeprazole capsule

from the US[3] and these latter two treatments given concomitantly. The results indicated that there are no pharmacokinetic interactions between naproxen and esomeprazole, the enteric coated naproxen formulations are bioequivalent but that the bioavailability (AUC) of esomeprazole from the proposed tablet (where it is immediate release) is only ~50% of that from the enteric coated esomeprazole products.

Advisory Committee Considerations

This application was initially presented to the 136th meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) in January 2011. The PSC had no objections to approval of the submission provided all outstanding issues were addressed to the satisfaction of the TGA (which was the case) and did not require to review this submission again. However, the Committee:

- Supported the issues referred to the Delegate and in particular those in relation to the timing of the dose with regards to food. It was noted that the conditions used in the clinical efficacy studies should be considered most appropriate for registration.
- Considered the lack of bioavailability data comparing the proposed tablet to the enteric coated esomeprazole tablets registered in Australia to be acceptable considering the proposed use of the combination product.
- Recommended that the PI and CMI be amended to include a statement advising patients not to take an extra dose of the product for pain relief. This was brought to the attention of the Delegate.

Quality Summary and Conclusions

Approval of this submission was recommended with respect to chemistry and manufacturing control.

With respect to bioavailability:

- It was accepted that the combination and monotherapy enteric coated naproxen tablets used in the Phase III clinical efficacy studies were bioequivalent with respect to the naproxen response to each other and that the combination formulation proposed for registration will be bioequivalent with respect to both naproxen and esomeprazole to the combination formulation used in the Phase III clinical efficacy studies.
- It was accepted that the naproxen response from the proposed tablet was bioequivalent to that from the naproxen immediate release tablets registered in Australia. There was however an expected delay in T_{max}.
- The esomeprazole response from the proposed tablet will be only ~50% that from the esomeprazole enteric coated tablets registered in Australia. The sponsor states this is not clinically relevant as bioequivalence is not expected or required.

III. Nonclinical Findings

Introduction

No nonclinical studies with Vimovo or the combination of naproxen and esomeprazole were submitted. The sponsor provided the following justification for this omission:

1. The combination is already approved as free combination therapy, and

[3] The TGA has previously evaluated data demonstrating that this capsule is bioequivalent to the 20 mg Nexium tablet registered in Australia.

2. There is sufficiently documented human experience of their individual and combined use.

Although the free combination therapy of naproxen and esomeprazole *per se* is not approved in Australia, esomeprazole indications allow for coadministration of naproxen (as a NSAID). Therefore, while completion of nonclinical studies may have been beneficial, particularly as both drugs target the same system (the gastrointestinal [GI] tract), the extensive clinical history of both compounds alone and in combination should be taken into account.

As the pharmacological and toxicological profiles of esomeprazole and omeprazole are similar, nonclinical data for omeprazole are considered relevant for the safety evaluation of esomeprazole. Thus, some data for omeprazole have been included in the nonclinical assessment of Vimovo.

The proposed dosage levels of Vimovo are within the range of those recommended for the individual components. Thus, it is assumed that the safety of the proposed dosage levels has been established in previous nonclinical studies.

The submitted data investigating the degradation of esomeprazole in gastric fluid were generally adequate, although the *in vivo* degradation profile of esomeprazole was not characterised.

Pharmacology

Pharmacodynamic Interactions

Naproxen is a non-selective cyclooxygenase (COX) inhibitor and esomeprazole is a proton pump inhibitor (PPI). Theoretically, these two drugs are not expected to have significant pharmacological interactions. However, the potential for pharmacological interactions will need to be assessed from the clinical data in the absence of nonclinical pharmacological interaction data.

Pharmacokinetics

Pharmacokinetic interactions

Both naproxen and esomeprazole are highly plasma protein bound in humans and slightly less so in animals: *in vitro* plasma protein binding for omeprazole was 87% in rats, 90% in dogs and 95% in humans (binding was presumed to be similar for esomeprazole). Supporting published data are available for naproxen. Thus, plasma protein binding of one could be potentially altered by coadministration of the other. The sponsor stated that there have been no indications of any pharmacokinetic interactions between naproxen and esomeprazole in the clinical situation.

Previous studies showed that esomeprazole is metabolised by cytochrome P450 (CYP) 2C19 and CYP3A4/5. Esomeprazole is also an inhibitor of CYP2C19. Published data indicate that naproxen is metabolised by CYP1A2 and CYP2C9. Thus, the potential for pharmacokinetic interactions on a CYP enzyme level appears to be low.

In the absence of nonclinical pharmacokinetic interaction data, the potential for pharmacokinetic interactions will need to be assessed from the clinical data.

Toxicology

Toxicological interactions

The sponsor provided a discussion on the potential for exacerbation of known toxicities of naproxen and esomeprazole. Non-specific effects on the central nervous system (CNS) (for example, convulsions, ataxia) have been observed at high doses of esomeprazole in acute

toxicity studies in rats, mice and dogs. Published data indicate that similar effects were observed in mice, rats and hamsters with naproxen. The sponsor stated that additive CNS effects may be expected with the combination but effects only occur at plasma concentrations higher than those expected clinically. Although the nonclinical data do not indicate any cause for concern, this issue was referred to the clinical evaluator/Delegate for further comment.

The sponsor stated that no new toxicity or exacerbation of other known toxicities of the individual components would be anticipated. In the absence of nonclinical toxicological interaction data, the potential for toxicological interactions will need to be assessed from the clinical data.

The lack of genotoxicity, carcinogenicity and reproductive toxicity studies is generally acceptable for a fixed combination of previously approved products (the genotoxicity and carcinogenicity of naproxen is discussed further below). As noted in the PI, Vimovo is contraindicated in the third trimester of pregnancy, consistent with the known effects of naproxen on fetal development and parturition.

Genotoxicity and carcinogenicity of naproxen

The sponsor proposed statements in the PI under these subheadings that have not been included in previous PI documents for naproxen or naproxen sodium. Due to the extensive clinical history with naproxen, the nonclinical data are limited and the validity of most assays was unknown. Briefly, naproxen (≤10000 µg/plate) was negative in several bacterial reverse mutation assays. There was no evidence of treatment related tumourigenicity at dietary naproxen doses of 8, 16 or 24 mg/kg/day in a 2 year study in rats (reportedly 0.28 times greater than exposure at the recommended clinical dose, possibly based on mg/m^2). Exposure ratios for the proposed dosage level of naproxen in Vimovo tablets (1000 mg/day, 660 mg/m^2) are 0.07, 0.15 and 0.22, dose respectively. Although this does not reflect the battery of genotoxicity and carcinogenicity studies currently recommended to support the safety of a medicinal product, the long history of clinical use of naproxen should be considered.

Analysis of esomeprazole degradants in gastric fluid

The sponsor submitted a series of studies investigating the effect of esomeprazole on the pH of gastric fluid in rats and dogs, and the *in vitro* degradation profile of esomeprazole in gastric fluid from rats, dogs and humans. The rationale behind these studies was that the esomeprazole in Vimovo tablets is not enteric coated (unlike other registered esomeprazole formulations) and it was unclear whether previous nonclinical studies adequately addressed the safety of any potential degradation products.

Repeated oral (PO) esomeprazole administration was associated with increased pH of gastric fluid from rats (280 mg/kg/day) and dogs (28 mg/kg/day), which may be indicative of pharmacological activity of esomeprazole. Maximum pH values of 8.4 and 7.7 were seen within 5 min and 30 min of dosing in the two respective species. The pH of gastric fluid from both species gradually reduced over time, reaching baseline values (about 3–5) 24 h post-dose.

The high pH of gastric fluid observed within a short period of administration to rats and dogs indicates that the pH sensitive coating of the naproxen component may start to degrade in the stomach, not in the small intestine as intended. This has potential implications for local GI tract toxicity, which may be addressable from clinical data.

One *in vitro* study investigated the degradation profile of esomeprazole in gastric fluid from rats, dogs and humans at pH 2 and 5. Esomeprazole was almost completely degraded within the 60 min incubation time, representing 0.1–0.2% of all species at pH 2 and 4–8%

at pH 5. The profile of degradants detected in all three species was qualitatively and quantitatively similar, with the closest similarity between dogs and humans. The predominant degradants were H168/22 (30-35% in rats, 50–60% in dogs and humans), Ex5 (50–65% in rats, 10–30% in dogs and humans) and unidentified degradant with a relative retention tome 15.55 (1–3% in rats, 9–11% in dogs and humans), H238/85 (1–5%) and AR-H063471 (previously known as Ex1; 0.5–3%). Most other degradants represented <1% of the total population. Differences were observed in the degradation profile with increasing pH; a tendency towards increased proportions of H168/22 and H238/85 and decreased Ex5 was observed. H168/22 is a major metabolite of omeprazole and therefore also a major metabolite of esomeprazole.

The sponsor stated that pH 5 was most representative of the actual pH level in animal stomachs in previous toxicity studies (the same dosage levels were administered as in the studies discussed above), however the fact that pH values of 7 or 8 were observed at the same dosage levels for at least 1–3 h post-dose should also be considered. The degradation profile of esomeprazole at pH values >5 was not investigated. Thus, the *in vitro* degradation profile of esomeprazole at all potentially relevant pH values has not been characterised and it is unclear whether previous toxicity studies have adequately addressed the safety of non-enteric coated esomeprazole. The relationship of the *in vitro* degradation profile to that anticipated *in vivo* is also unknown. Therefore, the sponsor's argument that humans given non-enteric coated esomeprazole are exposed to the same degradation products, in similar relative amounts, as rats and dogs that were treated orally with the non-enteric coated compound in previous toxicity studies with esomeprazole cannot be confirmed. Nevertheless, it appears that rapid degradation of esomeprazole in the stomach with Vimovo tablets is possible, which may have implications for systemic exposure to the active ingredient and therefore relative efficacy. In the absence of relevant supporting nonclinical data, the issue of adequate exposure to esomeprazole with Vimovo tablets was referred to the clinical evaluator/Delegate.

Structure activity relationship (SAR) analysis of the mutagenicity and carcinogenicity potential of several esomeprazole degradants was conducted. The sponsor stated that the degradants analysed may be present at levels above ICH identification and/or qualification thresholds.[4] In the newly submitted study, two degradants gave structural alerts using one of two methodologies, namely H193/61A and H118/87. These two degradants previously tested negative in bacterial reverse mutation assays (although one study has not been evaluated by the TGA); thus, they are not considered to represent a concern, provided levels remain below ICH limits. Neither of these degradants was detected in gastric fluid from rats, dogs or humans.

Nonclinical Summary and Conclusions

No nonclinical studies with Vimovo or the combination of naproxen and esomeprazole were submitted. Thus, the safety assessment of the proposed fixed combination will rely on clinical data.

Oral esomeprazole administration to rats and dogs resulted in increased pH of gastric fluid (values up to 8.4 and 7.7, respectively), which may result in degradation of the pH sensitive coating of the naproxen component of Vimovo tablets in the stomach, rather than the small intestine, which has potential implications for local GI tract toxicity. The *in vitro* degradation profile of esomeprazole in gastric fluid from rats, dogs and humans at lower pH values (but not the maximum observed pH values) was characterised; the relationship

[4] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

of the *in vitro* degradation profile to that anticipated *in vivo* is unknown. Thus, it is unclear whether previous toxicity studies with esomeprazole adequately addressed the safety of degradation products anticipated clinically.

Both active substances have been approved and on the market for many years and there are extensive nonclinical and clinical data available for the individual components. Thus, there are no nonclinical objections to the registration of Vimovo, provided the clinical data adequately demonstrate the safety and efficacy of the combination product, particularly with respect to the potential for local GI tract toxicity as a result of release of naproxen in the stomach.

IV. Clinical Findings

Introduction

The main objectives of the Vimovo clinical development program were as follows:

(1) to document the safety and efficacy of the naproxen component in Vimovo by demonstrating bioequivalence (BE) to marketed formulations of naproxen,

(2) to identify the appropriate dose of the immediate release (IR) esomeprazole component in Vimovo for use in the pivotal Phase III studies and for marketed use,

(3) to demonstrate that the administration of Vimovo twice daily (bd) for 26 weeks to patients who require the use of naproxen for the treatment of arthritis is associated with a significantly lower rate of endoscopically detected gastric ulcers (GUs) and duodenal ulcers (DUs), compared to treatment with EC naproxen alone (Phase III studies - **PN400-301** and **PN400-302**),

(4) to demonstrate that Vimovo administered bd for 12 weeks is non-inferior to Celebrex (celecoxib) in managing pain associated with osteoarthritis (OA) of the knee (two Phase III studies, **PN400-307** and **PN400-309**),

(5) to demonstrate that Vimovo is effective in reducing the risk of GU in a high risk population, compared with Arthrotec (diclofenac 75 mg/misoprostol 200 µg) (Phase III study **PN400-303**), and

(6) to evaluate the safety profile of Vimovo administered bd for up to 52 weeks.

The Vimovo clinical development program (CDP) consisted of 15 completed studies that were included in this submission (8 Phase I pharmacokinetic [PK] studies, 2 Phase I pharmacodynamic [PD] studies and 5 Phase III studies) and one terminated Phase III study (PN400-303). All studies were conducted in the US with the exception of Study **PN400-101** (conducted in Canada) and Study **PN400-108** (conducted in Sweden). Vimovo was referred to as PN400 in the CDP and this nomenclature can be seen in the names of the studies and some of the figures and tables in this AusPAR.

Pharmacokinetics

Introduction

Vimovo was designed as a single combination tablet of 2 distinct formulations: an inner enteric coated (EC) component of 500 mg naproxen and an outer IR film coat of 20 mg esomeprazole (present as 22.3 mg of esomeprazole magnesium trihydrate). The tablet is designed to release the active ingredients in a sequential fashion.

Three formulations were used in the Phase I testing: an initial 'Phase 1' formulation, the 'Phase 3' formulation and the proposed commercial formulation. Only minor film coating formulation changes were made in each case. No formulation changes were made to the

naproxen core and the film coating changes made were not expected to have any effect on formulation quality or performance. The minor formulation changes were not expected to have any effect on formulation quality or performance of Vimovo and the sponsors did not conduct any bridging studies.

The primary goals of the Vimovo biopharmaceutic evaluation were to define the PK profile of IR esomeprazole in Vimovo, to determine the effect of food on the PK profile of Vimovo, and to demonstrate, according to applicable guidelines, the BE of naproxen in Vimovo to:

1) commercially available naproxen (Proxen S [German product], Naprosyn E [Canadian product] and EC Naprosyn [US product]),

2) the naproxen comparator used in the Phase III studies to EC-Naprosyn and

3) its naproxen component (that is, Vimovo without esomeprazole in the film coat).

Absorption, Distribution, Metabolism and Excretion (ADME) profile

The PK profiles of EC naproxen and EC esomeprazole have been well characterised in the original marketing applications for EC Naprosyn and Nexium, respectively and in the scientific literature.

Absorption

At steady state following administration of Vimovo twice daily, peak plasma concentrations of naproxen were reached within a median time of 3 h following both the morning and evening dose; T_{max} of naproxen was slightly longer on the first day of administration (4 and 5 h after morning and evening dose, respectively). Naproxen is rapidly and completely absorbed from the gastrointestinal tract with an *in vivo* bioavailability of 95% and steady state levels of naproxen are reached within 4-5 days.

Following administration of Vimovo twice daily, esomeprazole is rapidly absorbed with peak plasma concentrations reached within a median time of 0.5 to 0.75 h following morning and evening dose on both the first day of administration and at steady state. The peak plasma concentrations of esomeprazole are higher at steady state compared to the first day of dosing of Vimovo.

Effect of food

The Phase I, open label, three way crossover study **D1120C00001** compared the PK and relative bioavailability (BA) in a fasted state of a single oral dose of 500 mg naproxen administered as a combination product Vimovo (500 mg naproxen/20 mg esomeprazole) to the currently marketed naproxen formulations Proxen S (marketed in Germany by Roche Pharma AG) and/or Naprosyn E tablets (marketed in Canada by Hoffman-La Roche Limited) in healthy human volunteers. The secondary objective was to assess and compare the PK and relative bioavailability in a fed state. Part A had a three way crossover design and was performed to assess the relative bioavailability of a single oral dose of 500 mg naproxen administered as Vimovo (Treatment A; test) compared to the marketed formulations Proxen S (Treatment B; reference) and/or Naprosyn E (Treatment C; reference). This study was briefly discussed in *Section II*.

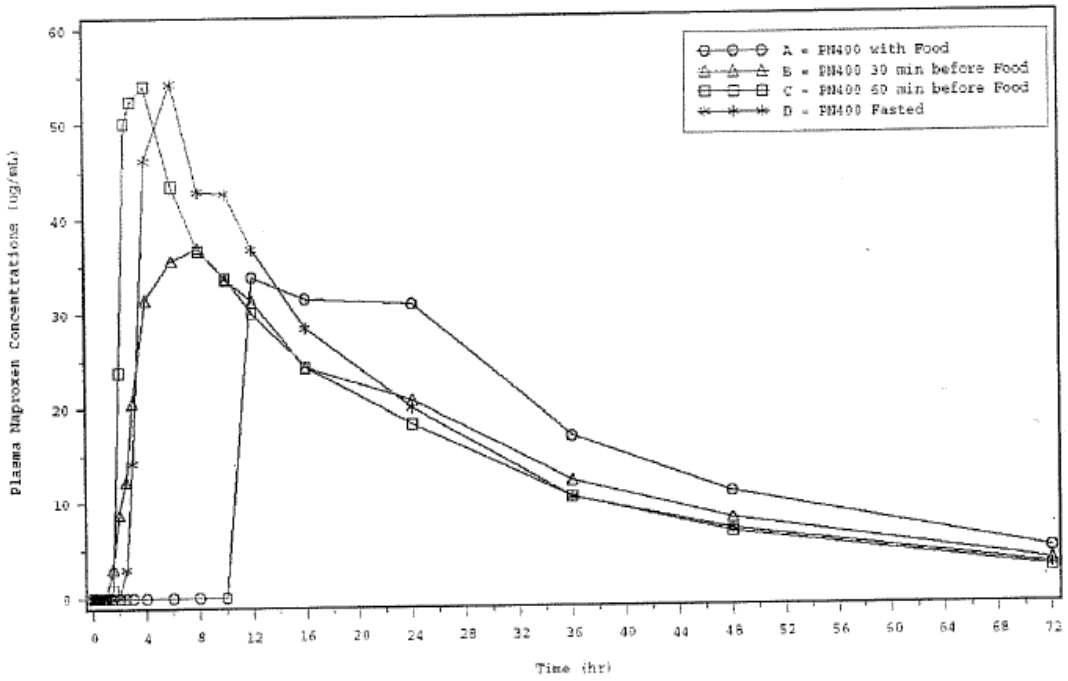
The mean naproxen plasma concentration profiles were similar for the combination product Vimovo (500 mg naproxen/20 mg esomeprazole) and the two currently marketed naproxen formulations Proxen S and Naprosyn E tablets during both fasting and fed conditions. The 90% confidence intervals (CIs) of the geometric mean ratios comparing AUC and C_{max} of the test product (Vimovo) versus the two marketed reference products (Proxen S and Naprosyn E), were all contained within the predefined interval for bioequivalence (0.8 to 1.25) in both the fasting and fed state. The inter-subject variability in the fasting state was 14.8% for AUC and 6.6% for C_{max} and the corresponding intra-

subject variability was 5.9% and 16.8%, respectively. The inter-subject variability was 20.2% for AUC and 13.3% for C_{max} in the fed state and the corresponding intra-subject variability was 6.6% and 17.2%, respectively.

Overall, results from this study demonstrated that Vimovo was bioequivalent to both Proxen S and Naprosyn E in the fasted state, and to Proxen S in the fed state. The absorption of naproxen was prolonged when given with food, as evident by an increase in T_{max} in the fed versus the fasted state. The increase in median T_{max} was 8 h for Vimovo and 7 h for Proxen S. This is consistent with the label for Proxen S, which states that the T_{max} for Proxen S can be more than doubled when administered with a meal.

The Phase I, open label, randomised, four way crossover study **PN400-103** evaluated the effect of food on the bioavailability of naproxen and esomeprazole from the proposed Vimovo tablet. This study was discussed in *Section II*. Following oral administration of Vimovo under fasted conditions (Treatment D), naproxen was absorbed with a median lag time of 1.55 h; median T_{max} occurred at 6 h post dose. When Vimovo was administered with a high fat meal (Treatment A), the absorption lag time was delayed to 10 h post dose and median T_{max} was delayed to 14 h post dose along with a slightly reduced peak concentration. Thus, food intake significantly delayed the absorption of naproxen from a Vimovo tablet (Figure 1). When the dosing time of Vimovo was separated from the test meal by 60 min (Treatment C), there was no effect of food on the rate of absorption or the mean C_{max} value for naproxen. Interestingly, both median delay to T_{max} (T_{lag}) and T_{max} after Treatment C were shorter than those after Treatment D. Some slight food effects were observed when the dosing time of Vimovo was separated from the test meal by 30 min (Treatment B) as shown by the slightly longer median T_{max} and lower mean C_{max} values. The mean area under the plasma concentration time curve from time zero to infinity ($AUC_{0\text{-}inf}$) and the half-life ($t_{1/2}$) estimates of naproxen were comparable among all four treatments. Administration of Vimovo with a high fat meal did not have a significant effect on the extent of absorption of naproxen, although the rate of absorption (C_{max}) was reduced following concomitant administration with a meal.

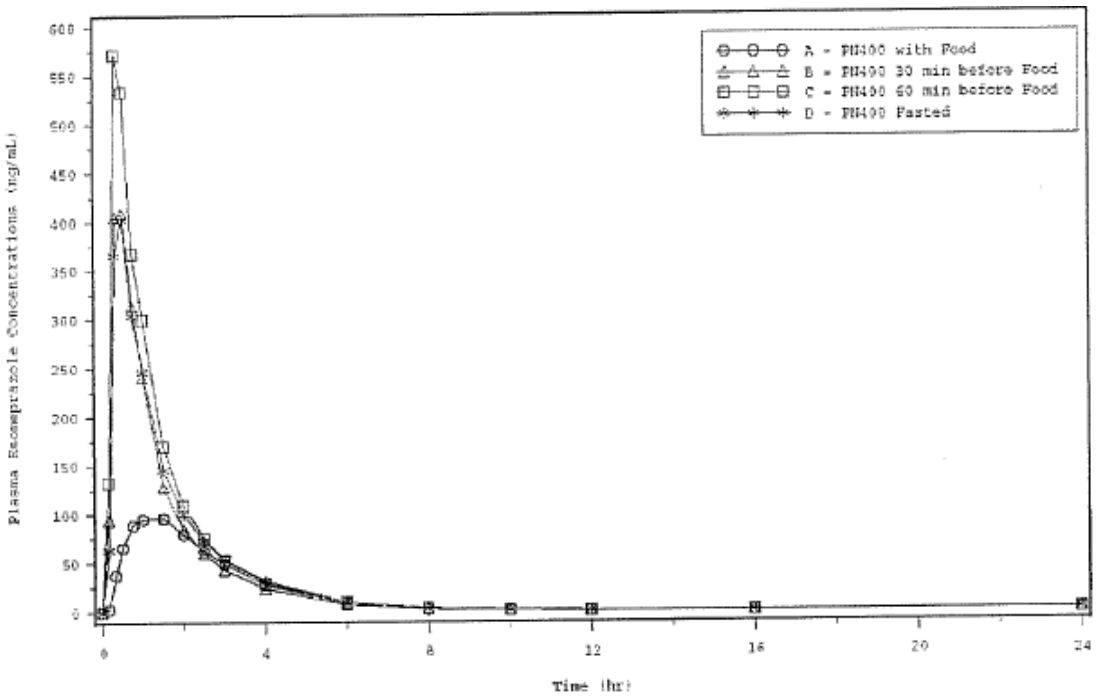
Figure 1: Median plasma naproxen concentrations vs time curves by treatment



Following oral administration of Vimovo under fasted conditions (Treatment D), esomeprazole was rapidly absorbed without a lag time and peak plasma esomeprazole concentration occurred at about 30 min post dose. When the Vimovo was administered with a high fat meal (Treatment A) the median T_{max} was delayed by 1 h and mean C_{max} was reduced by more than 70%, compared to fasted conditions (Treatment D). When the dosing time of Vimovo was separated from the test meal by 30 or 60 min (Treatment B or C, respectively), there was no lag time in absorption and essentially no change in T_{max} as compared to Treatment D. In addition, the mean C_{max} of esomeprazole was comparable between Treatment B and Treatment D and was higher for Treatment C as compared to Treatment D (Figure 2). Esomeprazole was rapidly eliminated from plasma with a mean half-life of about 1 h for all treatments. There was large inter-subject variability in esomeprazole PK parameter estimates, except $t_{1/2}$, for all treatments. Similar to the mean C_{max} values, mean AUCs of esomeprazole were reduced by about 50% when Vimovo was administered with food, were unchanged when Vimovo was administered 30 min before food, and were increased slightly when Vimovo was administered 60 min before food. The analysis of variance (ANOVA) results demonstrate that the 90% CI of the geometric least squares mean (GLSM) ratio (Test/Reference) of $AUC_{0\text{-}inf}$ and C_{max} of esomeprazole for all treatment comparisons fell outside the 0.80 to 1.25 limits, and for Treatment A/D comparison, the 90% CI for each parameter did not contain 1.0, indicating significant food effect on the bioavailability of esomeprazole from Vimovo.

Administration of a high fat meal with Vimovo did not have any effect on the extent of bioavailability of naproxen; however, food significantly delayed the absorption of naproxen and slightly reduced the rate of bioavailability of naproxen. The median T_{max} of naproxen was delayed from 6 to 14 h and the mean C_{max} of naproxen was reduced by about 12% when Vimovo was administered with a high fat meal as compared to administration under fasted conditions. This effect of a high fat meal on delaying naproxen absorption and slightly reducing its C_{max} was not observed when Vimovo was administered 60 min before the meal. In addition, when Vimovo was administered 30 min before a high fat meal, there was minimal effect of food on the naproxen T_{max} or C_{max}.

Figure 2: Median plasma naproxen concentrations vs time curves by treatment



A high fat meal significantly reduced the bioavailability of esomeprazole from Vimovo, resulting in 52% and 75% reductions in esomeprazole $AUC_{0\text{-}inf}$ and C_{max} respectively, as compared to administration under fasted conditions. However, when the Vimovo tablet was administered at 30 or 60 min prior to a high fat meal, there was no meaningful reduction in the extent of esomeprazole bioavailability by food.

Importantly, this study identified that the rate and extent of bioavailability of naproxen or esomeprazole was essentially unaffected when a Vimovo tablet was administered 30 or 60 min before a high fat meal. This dosing instruction was used in the Phase III pivotal clinical trials evaluating the efficacy and safety of Vimovo tablets.

Bioequivalence studies

PN400-102 was a single centre, three way, crossover, randomised bioequivalence study to compare the rate and extent of the bioavailability of naproxen following administration of Vimovo (Treatment A) or the naproxen component of Vimovo (treatment B) to that of enteric coated (EC) Naprosyn 500 mg (Treatment C) in 36 healthy volunteers. The doses of naproxen and esomeprazole contained in Vimovo were chosen because the naproxen 500 mg dose and the esomeprazole 20 mg dose are both approved by the FDA. EC-Naprosyn 500 mg was used as a comparator for naproxen pharmacokinetics because it contains the same naproxen dose in a delayed release formulation as Vimovo. This study was reported in *Section II*.

Following oral administration of a Vimovo tablet or a tablet of the naproxen component of Vimovo, naproxen was slowly absorbed with a median lag time of 2.0 or 2.1 h, respectively which was similar to that following administration of a tablet of EC-Naprosyn 500 mg. The peak plasma concentration was observed at 6 h following treatments A and B and 4 h following EC-Naprosyn. The $t_{1/2}$ was comparable in all 3 treatment groups (mean of 19-20 h). The ANOVA results showed that the 90% CI of the geometric least squares mean (LSM) ratio (Test/Reference) for all key PK parameters ($AUC_{0\text{-}inf}$, the area under the plasma concentration time curve from time zero for a dosing period t [$AUC_{0\text{-}t}$] and C_{max}) of naproxen fell within the 0.80 to 1.25 limits to claim bioequivalence between Treatment B and Treatment C, and between Treatment A and Treatment B. In addition, the 90% CI of

the geometric LSM ratio, Treatment A vs Treatment C, for naproxen $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ fell within the 0.80 to 1.25 limits. However, the lower bound of the 90% CI of the geometric LSM ratio, Treatment A vs Treatment C, for naproxen Cmax fell below the limit of 0.80. This indicates that Treatment A is bioequivalent to Treatment C in terms of naproxen $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$, but had slightly (about 16%) lower naproxen C_{max} than Treatment C.

The intra-subject variabilities for C_{max} and AUC0-inf of naproxen were estimated to be 21.9% and 10.4%, respectively.

The Vimovo tablet was bioequivalent to EC-Naprosyn 500 mg in terms of the extent of naproxen bioavailability (as determined by $AUC_{0\text{-}inf}$), but not the rate of bioavailability (as determined by C_{max}). Compared to EC-Naprosyn 500 mg, the Vimovo tablet had a somewhat prolonged naproxen T_{max} and T_{lag}. The somewhat lower C_{max} value after administration of a Vimovo tablet was consistent with the slightly prolonged T_{max} and T_{lag} of naproxen for the Vimovo tablet as compared to EC-Naprosyn 500 mg tablet. Several subjects had unusually delayed T_{max}, that is, occurring at 16 to 36 h post dose, across the three treatments, however, there were slightly more subjects with such prolonged T_{max} following treatment with Vimovo as compared to following treatment with EC-Naprosyn 500 mg tablet, that is, 4 vs 2 subjects. The blood sampling for PK was less frequent beyond 12 h post dosing (sampling intervals were 4 h or more) as the T_{max} for naproxen was expected 2-12 h post dose. These longer blood sampling intervals may have contributed to the unusually late T_{max} values in this small number of subjects. Therefore, as an exploratory analysis, ANOVA was repeated to compare naproxen C_{max} values between treatments in those subjects with T_{max} values less than 16 h, which showed bioequivalence between all 3 treatments in terms of C_{max}. Overall, demonstration of bioequivalence in terms of naproxen $AUC_{0\text{-}inf}$ and C_{max} between EC-Naprosyn 500 mg and the naproxen component of Vimovo validated use of the naproxen component of Vimovo as a comparator in the Phase III controlled trials.

In the Phase I, two way, crossover, randomised bioequivalence study **PN400-105**, the mean values of C_{max}, $AUC_{0\text{-}inf}$ and $t_{½}$ of naproxen were comparable between the two formulations following a single dose of Vimovo (375 mg naproxen/20 mg esomeprazole) and EC-Naprosyn 375 mg. The ANOVA results demonstrated that the 90% confidence interval of the GLSM ratio (Vimovo 375 mg/EC-Naprosyn 375 mg) of all key PK parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max}) of naproxen fell within the 0.80 to 1.25 limits to claim bioequivalence between Vimovo 375 mg and EC-Naprosyn 375 mg. Following oral administration of Vimovo 375 mg, esomeprazole was rapidly absorbed with mean peak plasma concentrations occurring at about 0.5 h post dose, followed by rapid elimination with a mean half-life of 1.04 h. The PK profiles of esomeprazole from administration of a single dose of Vimovo 375 mg showed large inter-subject variability. Overall, results from this study demonstrated bioequivalence between Vimovo 375 mg and EC-Naprosyn 375 mg in terms of naproxen pharmacokinetics. The sponsor has not applied for approval of the 375 mg/20 mg dose strength in this submission.

PN400-111 was an open label, single centre, two period crossover study conducted in 18 healthy subjects to assess the intra-subject variability in esomeprazole pharmacokinetics following a single dose and after repeat bd doses of Vimovo. The intra-subject variability in esomeprazole pharmacokinetics after repeat bd doses of Vimovo may be different from that after a single dose of Vimovo, because esomeprazole bioavailability is dependent on its pharmacological effect, that is, inhibition of gastric proton pumps with repeat esomeprazole dosing leads to higher intragastric pH and reduced acid degradation of esomeprazole.

Following oral administration of Vimovo, esomeprazole was rapidly absorbed. Peak esomeprazole concentrations occurred, on average, at about 20 to 30 min post dose on

Day 1 or Day 10 in each period. Following repeated bd doses of Vimovo, esomeprazole concentrations on Day 10 were much higher than those on Day 1 in both periods, with Day 10 to Day 1 C_{max} ratio of 3.17 and AUC_{0-24} ratio of 5.26 in Period 1; and Day 10 to Day 1 C_{max} ratio of 2.78 and AUC_{0-24} ratio of 4.22 in Period 2. Mean Day 1 C_{max} and AUC values in Period 2 were slightly higher than the corresponding values in Period 1. However, mean Day 10 C_{max} and AUC values in Period 2 were slightly lower than the corresponding values in Period 1. These differences were primarily due to the larger accumulation ratios (Day 10 vs Day 1) observed in Period 1. Plasma esomeprazole was rapidly eliminated with a mean half-life estimates of 0.99 and 0.95 h on Day 1 in Periods 1 and 2, respectively. The mean half-life estimates were slightly longer on Day 10 following repeated doses, 1.53 and 1.31 h for Periods 1 and 2, respectively.

The Phase I, randomised, four way crossover bioequivalence study **PN400-114** was conducted to assess the relative bioavailability of naproxen and esomeprazole from a single dose of Vimovo (containing 500 mg delayed release naproxen and 20 mg IR esomeprazole) and each of its components administered together and alone in 40 healthy volunteers. This study was reported in *Section II*. The delayed release naproxen component in Vimovo is a formulation which releases naproxen at pH >5.5, similar to EC-Naprosyn 500 mg. Thus, in this study Vimovo was compared to a commercially available dosage form of EC naproxen (EC Naprosyn 500 mg). However, for esomeprazole, only an enteric coated formulation, not an immediate release formulation is commercially available (Nexium 20 mg) for use as the esomeprazole component of Vimovo.

Following oral administration of Vimovo, there was delayed absorption of naproxen, with a median lag time of 1.50 h and a median T_{max} occurring at 5.25 h post dose. This delayed absorption characteristic for naproxen from Vimovo was similar to that observed following administration of EC naproxen alone or EC naproxen combined with EC esomeprazole. However, median naproxen T_{max} for Vimovo treatment was slightly longer than that of the other treatments containing EC naproxen, 5.25 h vs 3.5 or 4 h. Consequently, the mean naproxen C_{max} for Vimovo treatment was also slightly (~10%) lower than those for the other two treatments. The mean AUC_{0-t}, AUC_{0-inf} and $t_{1/2}$ estimates of naproxen were comparable among all 3 treatments. The ANOVA results demonstrate that the 90% confidence interval (CI) of the GLSM ratio (Test/Reference) of AUC_{0-inf}, AUC_{0-t}, and C_{max} of naproxen for all treatment comparisons fell within the 0.80 to 1.25 limits. These results indicate that Vimovo is bioequivalent to EC naproxen given alone or in combination with EC esomeprazole.

Following oral administration of Vimovo (Treatment A), esomeprazole was rapidly absorbed without any lag time, and median esomeprazole T_{max} occurred at about 30 min post dose. As expected, there was 0.75 h median lag time in esomeprazole absorption from the EC esomeprazole product (Treatments B and D). The mean C_{max} of esomeprazole from administration of Vimovo (containing immediate release esomeprazole) was slightly lower than that from administration of EC esomeprazole. The mean AUC_{0-inf} of esomeprazole from administration of Vimovo was almost half of that from administration of EC esomeprazole. Esomeprazole was rapidly eliminated from plasma with a mean half-life of about 1 h for all treatments. There was large inter-subject variability in esomeprazole C_{max} and AUC values, but not $t_{1/2}$, for all treatments. All mean PK parameter estimates of esomeprazole following administration of EC esomeprazole in Treatment B and Treatment D were similar. Based on the point estimates and 90% CI, AUC_{0-inf} and AUC_{0-t} of esomeprazole for Treatment A (IR esomeprazole in Vimovo) were about 50% lower than those of Treatment B or D (that is, EC esomeprazole). The lower bound of the 90% confidence interval (CI) of the GLSM ratio (Test/Reference) of esomeprazole C_{max} for all treatment comparisons fell below 0.80. The esomeprazole C_{max} for Treatment A (Vimovo) was statistically significantly lower than that from Treatment D (EC

esomeprazole) by 28.5%. When EC esomeprazole was coadministered with EC naproxen, esomeprazole C_{max} was reduced by about 17%.

Overall, Vimovo was bioequivalent to EC naproxen in terms of naproxen C_{max} and $AUC_{0\text{-}inf}$. The extent of bioavailability ($AUC_{0\text{-}inf}$) of esomeprazole from a single dose of an IR formulation was about 50% of that from an enteric coated formulation in the presence and absence of naproxen.

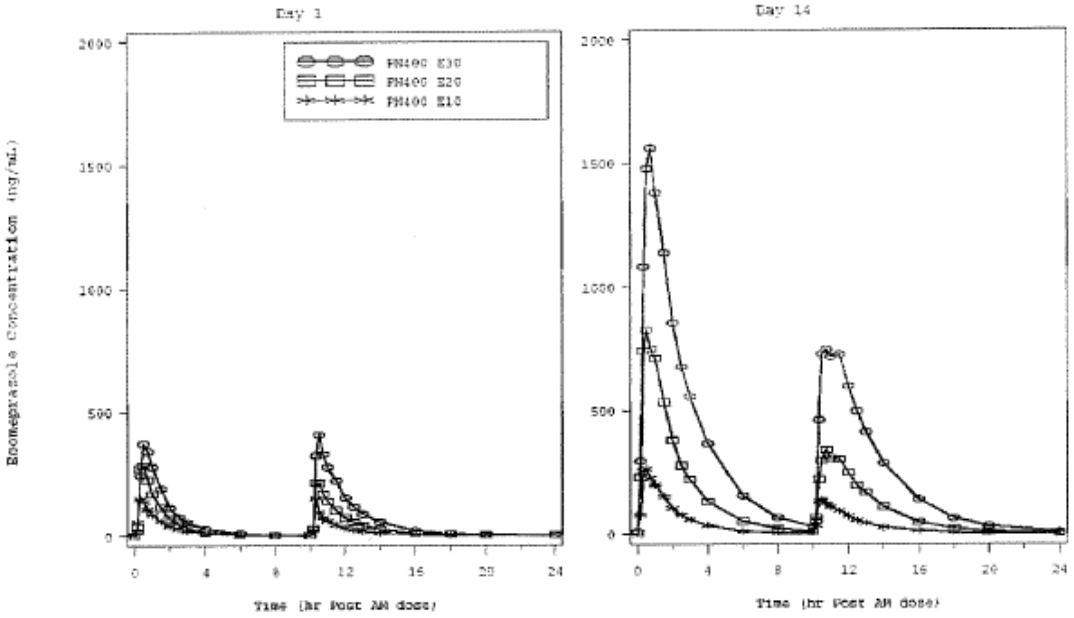
The TGA had indicated that they required some additional pharmacokinetic data given as there is no enteric coated naproxen formulation in the Australian market. Hence, the Phase I, single centre, two treatment, two period, two sequence, randomized crossover steady state relative bioavailability study **D1120C00035** compared the steady state pharmacokinetics of naproxen in two tablet formulations given twice daily (Vimovo versus Naprosyn containing naproxen 500 mg). This study was discussed in *Section II*. Vimovo was designed as a delayed release formulation for the naproxen active substance, while the reference product (Naprosyn) is an IR naproxen formulation. It was decided that, in order to satisfy the TGA's requirement for a pharmacokinetic comparison between Vimovo and a naproxen product sold in Australia, this non delayed release comparator would be used; this difference in selected comparator formulation would be partly addressed by conducting a steady state study rather than a single dose study, which is appropriate for a product that will be used in chronic pain. The two formulations were bioequivalent with respect to rate/extent of absorption of naproxen as assessed in terms of the maximal plasma concentration at steady state (C_{ssmax})(90% CI: 0.923 to 1.052), the minimal plasma concentration (C_{min}) (90% CI: 0.985 to 1.146), the average plasma concentration at steady state C_{ssavg} (0.978 to 1.087) and $AUC_{0\text{-}t}$ (0.978 to 1.087). However, there was a statistically significant difference in the minimal plasma concentration at steady state C_{ssmin} (1.086 to 1.261) although this was not considered a relevant parameter for assessment of delayed release naproxen given that the C_{min} was observed immediately after the dose and not before the next dose (as in case of the IR naproxen). The T_{max} was also significantly greater with Vimovo (containing delayed release naproxen) compared to Naprosyn (p=0.0002) as would be expected when comparing delayed release formulation with an immediate release formulation.

Dose proportionality and time dependency

In study **PN400-101**, following repeat twice daily doses of Vimovo treatments, plasma esomeprazole concentrations were measurable in the majority of subjects on Day 14 from pre-dose throughout the 24 h sampling time for Treatment A (Vimovo with esomeprazole 30 mg [Vimovo/E30]) and from 10 min up to 20 h post AM dose (or 10 h post PM dose) for Treatment B (Vimovo with esomeprazole 20 mg [Vimovo/E20]), and from 10 min up to 4 h post either AM or PM dose for Treatment C (Vimovo with esomeprazole 10 mg [Vimovo/E10]). Thus, there was dose related duration of measurable plasma esomeprazole concentrations over the 24 h daily interval. Following repeat twice daily doses, C_{max} and AUC values of esomeprazole were higher on Day 14 than on Day 1 for each Vimovo treatment. There was a greater increase in C_{max} and AUC values from Day 1 to Day 14 after the AM dose than after the PM dose, and the increased esomeprazole exposure following repeat doses was dose dependent. The results showed that on Day 1 after the AM or PM dose, C_{max} and AUC values of esomeprazole increased almost proportionally to esomeprazole dose in the Vimovo treatments. However, on Day 14 after the AM or PM dose, C_{max} and AUC values of esomeprazole increased more than dose proportionally. This is primarily due to the dose dependent increase in the bioavailability and extent of accumulation in plasma exposure to esomeprazole following repeat doses of Vimovo treatments. The magnitude of the increased bioavailability of esomeprazole after repeat dosing of Vimovo tablets reflects both reduced acid degradation due to continuing proton

pump inhibition and decreased systemic clearance of esomeprazole due to substrate induced inhibition of CYP2C19. The greater deviation from dose proportionality in plasma exposure to esomeprazole was observed as the dose increased from 20 to 30 mg. Plasma esomeprazole concentrations after the PM dose were similar to those after the AM dose on Day 1, but on Day 14 esomeprazole concentrations after the PM dose were lower than those after the AM dose in each treatment. In addition, the mean/median concentrations of esomeprazole were higher on Day 14 than on Day 1, especially after the AM dose. The extent to which plasma esomeprazole levels increased following repeat doses of Vimovo also increased with dose (Figure 3).

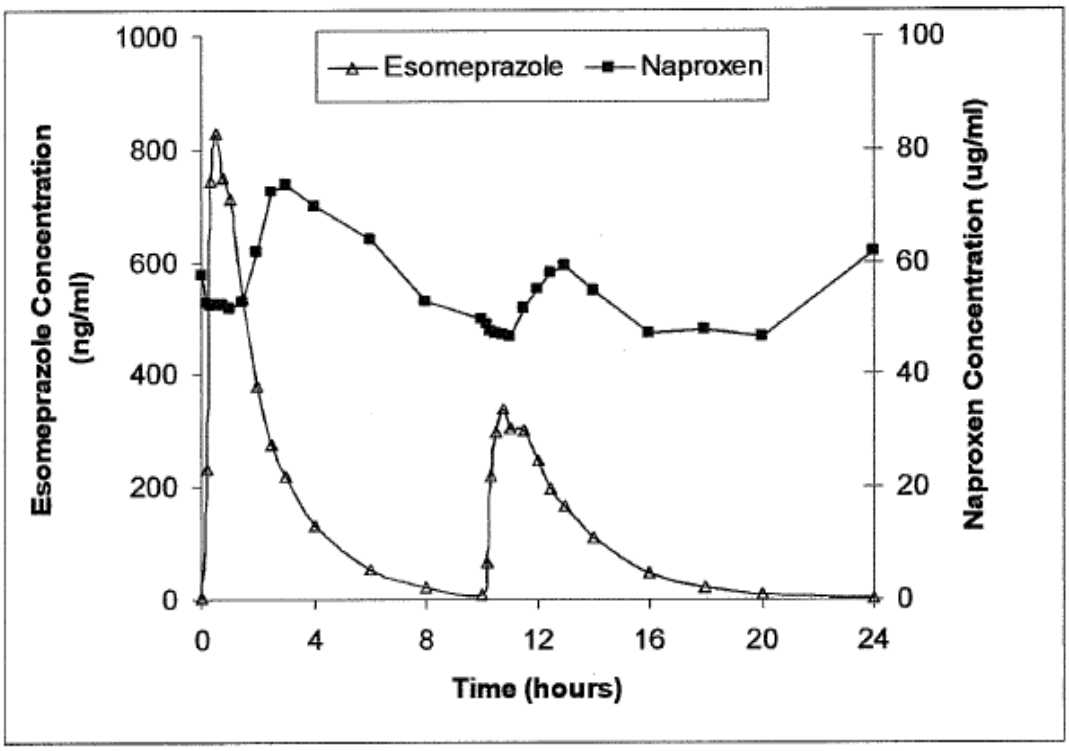
Figure 3: Mean esomeprazole plasma concentration vs time curves for all Vimovo treatments on Day 1 and Day 14



In general, mean plasma concentration vs time profiles of naproxen were comparable between the three Vimovo treatments and the EC naproxen treatment on either Day 1 or Day 14, with some intersubject variability due to the parallel group study design. The delayed release characteristics in the naproxen plasma profiles were obvious following each treatment, especially after the AM dose on Day 1 or Day 14. Plasma naproxen profiles following the PM dose on either Day 1 or Day 14 demonstrated secondary absorption peaks with plasma concentrations continuing to increase from 18 to 24 h post AM dose (that is, 8 to 14 h post PM dose). Mean plasma naproxen concentrations on Day 14 were higher than those on Day 1 for each treatment. As expected, absorption of naproxen was delayed following oral administration of Vimovo tablets due to the pH sensitive coating on the naproxen core which prevents naproxen release in the stomach (that is, at pH <5). Median T_{max} values ranged from 2.5 to 5.0 h across treatments, dose time and dosing days. Mean C_{max} and AUC values of naproxen after the AM or PM dose were comparable among the 3 treatments with Vimovo and the treatment with EC naproxen on both Day 1 and Day 14. Following repeat dose administration of Vimovo or EC naproxen, C_{max} and AUC values of naproxen on Day 14 were greater than those on Day 1. The GLSM ratios (Day 14 to Day 1) for naproxen the area under the plasma concentration time curve from time zero to 24 h (AUC_{0-24}) were1.36-1.38 across the 4 treatments, and the ratios for naproxen $C_{max,am}$ and $C_{max,pm}$ were 1.26-1.37 and 0.96-1.10, respectively, across treatments. This extent of accumulation following repeat doses of naproxen containing formulations is consistent with the half-life estimates of naproxen and twice daily dosing frequency. Most importantly, peak plasma concentrations of esomeprazole, following dosing with all 3 of

the immediate release esomeprazole doses (10, 20 and 30 mg) preceded peak plasma concentrations of naproxen (Figure 4).

Figure 4: Mean Day 14 plasma concentrations of esomeprazole and naproxen from the Vimovo treatment group



In study **PN400-104**, esomeprazole concentrations on Day 9 were much higher than those on Day 1 following each treatment. The magnitude of differences in esomeprazole concentrations (Day 9 vs Day 1) increased with the esomeprazole dose level in Vimovo. The difference in plasma esomeprazole concentration between Day 9 and Day 1 was not as great after administration of EC esomeprazole in EC E20 + naproxen as that after administration of the proposed combination tablet of Vimovo/E20.

Immediate release esomeprazole was rapidly absorbed from the Vimovo tablets with plasma concentrations measurable at 10 min post dose on Day 1. The AM dose following an overnight fast was absorbed faster and to a greater extent than the PM dose. After repeat bd Vimovo doses, plasma esomeprazole concentrations increased substantially as compared to those after the first day of dosing. The magnitude of this increased exposure to esomeprazole after repeat doses was dose dependent. At steady state (Day 9), esomeprazole AUC_{0-10} was higher for Vimovo/E20 than for EC E20 + naproxen and C_{max} values following the AM dose of Vimovo/E20 on Day 9 were twice as high as EC esomeprazole 20 mg on Day 9.

The steady state naproxen plasma profiles were comparable among the three Vimovo treatments, indicating that the esomeprazole in Vimovo did not affect the PKs of naproxen; plasma profiles of naproxen following Vimovo exhibited delayed absorption characteristics, consistent with the formulation design.

Intra- and inter-individual variability

In study PN400-111, there was much smaller inter-subject variability in esomeprazole half-life values as compared to C_{max} and AUC values, generally less than 30% on Day 1 and about 35 to 45% on Day 10 for both periods. There was very large inter-subject (or

between-subject) variability in C_{max} and AUC values on both Day 1 and Day 10 of each period, ranging from 69% to 138% for C_{max} and 104% to 168% in AUC values across study days and periods based on natural log transformed parameter values. Based on results of ANOVA, the intra-subject variability (within group coefficient of variation; CV_w) in esomeprazole C_{max} was 62% and 48% on Day 1 and Day 10, respectively; and intra-subject variability in AUC values was 50% and 69% on Day 1 and Day 10, respectively. This high intra-subject variability in esomeprazole PK values is greater than that reported in the literature for commercially available, enteric coated omeprazole, that is, 38% for C_{max} and 20% for AUCs (Hussein 2007).[5] In addition to high intra-subject variability, the inter-subject variability in esomeprazole C_{max} and AUC values was also very large, following both single and repeat doses of Vimovo, but was similar to that reported in previous Phase I studies with Vimovo. The large intra- and inter-subject variability in PK values found with esomeprazole is likely due to the IR nature of the formulation, subjecting esomeprazole to a variable amount of gastric acid degradation between study days. A decline in the first pass metabolism and systemic clearance of esomeprazole with repeat esomeprazole dosing, secondary to inhibition of CYP2C19 activity (Hassan-Ali 2000), also likely contributed to the increased bioavailability of esomeprazole with repeat dosing.[6]

Pharmacokinetics in special populations

Studies in special populations have not been conducted with the proposed combination Vimovo. Naproxen administered as Vimovo is bioequivalent (BE) to commercial formulations of naproxen. While the PK profile of IR esomeprazole is different from commercially available EC esomeprazole (Nexium), the pharmacological properties are consistent with the known properties of Nexium. It seems unlikely that coadministration of Vimovo would impact the known behaviour of the two active ingredients, administered alone, in patients whose metabolic status is altered by age, renal impairment, or hepatic impairment. Accordingly, the current prescribing information for the reference drugs was used to address the use of Vimovo in special populations.

Interactions

No new drug interaction studies were conducted with Vimovo. However, drug interactions with the individual components of the combination tablet (esomeprazole and naproxen) are well established and adequately represented in the proposed PI for Vimovo.

Exposure relevant for safety evaluation

The pharmacokinetics of Vimovo were not evaluated in the target patient population.

The pharmacokinetics of Vimovo have not been determined in patients with renal/hepatic impairment. There are no specific PK data in patients over 65 years. However, the pharmacokinetics of individual components (naproxen and esomeprazole) are well established in the in the target patient population as well as the special patient populations and appropriate precautions are included in the proposed Vimovo product information.

Evaluator's overall conclusions on pharmacokinetics

Three formulations were used in the Phase I testing: an initial 'Phase 1 formulation', the 'Phase 3' formulation and the proposed commercial formulation. Only minor film coating formulation changes were made in each case. No formulation changes were made to the

[5] Hussein RF, Lockyer M, Hammami MM. Bioequivalence assessment of two capsule formulations of omeprazole in healthy volunteers. Arzneimittel-Forschung 2007; 57: 101-105.

[6] Hassan-Alin M, Andersson T, Bredberg E, Röhss K. Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects. Eur J Clin Pharmacol 2000; 56: 665-670.

naproxen core and the film coating changes made were not expected to have any effect on formulation quality or performance. The minor formulation changes were not expected to have any effect on formulation quality or performance of Vimovo and the sponsors did not conduct any bridging studies. Importantly, bioequivalence was established between the Phase III formulation (Studies PN400-102 and PN400-108), the proposed marketing formulation (Study PN400-114) and commercial formulations of naproxen.

Based on naproxen exposures, Vimovo is bioequivalent to a Vimovo tablet without IR esomeprazole in the film coat, that is, containing only enteric coated naproxen. In addition, Vimovo is bioequivalent to commercially available naproxen (Proxen S, Naprosyn E, and EC Naprosyn). In Australia, none of the enteric coated naproxen formulations are available and only the immediate release Naprosyn is approved. The bioequivalence of the immediate release Naprosyn with delayed release naproxen core in the Vimovo tablet was demonstrated in term of extent of exposure to naproxen; T_{max} was significantly greater with Vimovo (containing delayed release naproxen) compared to Naprosyn as would be expected when comparing delayed release formulation with an immediate release formulation.

The PK profiles of naproxen and esomeprazole in Vimovo are consistent with the sequential delivery design of the tablet: esomeprazole is released rapidly, followed by delayed release of naproxen.

Esomeprazole AUCs observed with Vimovo at steady state are greater than those reported with EC esomeprazole 20 mg but lower than those reported with EC esomeprazole 40 mg.

The effect of food on the BA of naproxen and esomeprazole in Vimovo suggests that Vimovo should be taken at least 30 min prior to meals.

There is no evidence of a PK interaction between the 2 compounds when combined in Vimovo. No new drug interaction studies were conducted with Vimovo. However, drug interactions with the individual components of the combination tablet (esomeprazole and naproxen) are well-established and adequately represented in the proposed PI for Vimovo

Pharmacodynamics

Introduction

Two studies in 104 healthy volunteers evaluated the effect of three Vimovo dose combinations, consisting of a fixed delayed release naproxen dose (500 mg) combined with different immediate release esomeprazole doses (10, 20 and 30 mg) on the risk of naproxen associated gastroduodenal injury (determined by combined gastric and duodenal Grade 3 or 4 lesions (study PN400-101) and effects on percent of time intragastric pH>4.0 (study PN400-104).

Mechanism of action

Naproxen was selected as the NSAID of choice for Vimovo because of its long recognized efficacy and safety profile as an antiarthritic. Compared to other selective and non-selective NSAIDs (except aspirin), naproxen does not seem to increase the risk of cardiovascular thromboembolic events such as myocardial infarction (Hippisley-Cox 2005, Kearney 2006, McGettigan 2006, Singh 2006).[7,8,9,10]

[7] Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclooxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ 2005; 330: 1366-72.

[8] Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclooxygenase- 2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 2006; 332: 1302-8.

Esomeprazole was selected as the PPI of choice because of its superior acid inhibiting properties compared to other marketed PPIs and in view of its proven efficacy in risk reduction of NSAID associated gastric ulcers (Scheiman 2006).[11]

Since NSAID associated gastropathy may involve local and systemic features, Vimovo was designed as a multilayer, coordinated delivery tablet combining an immediate release (non-enteric coated) esomeprazole magnesium layer and a delayed-release naproxen core.

The pH sensitive coating prevents naproxen release at pH levels below 5, providing protection against possible local gastric toxicity of naproxen. As a result, the protective agent, esomeprazole is deployed prior to the dissolution of the NSAID.

Primary pharmacology

The clinical pharmacology of naproxen and esomeprazole have been well characterised in the original marketing applications for EC naproxen (EC-Naprosyn) and Nexium, respectively, and in the scientific literature. Naproxen is an NSAID with analgesic and antipyretic properties. The mechanism of action of the naproxen anion, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetise inhibition. Esomeprazole is a proton pump inhibitor (PPI) that suppresses gastric acid secretion by specific inhibition of the H+/K+- ATPase in the gastric parietal cell. Esomeprazole is protonated and converted in the acidic compartment of the parietal cell, forming the active inhibitor achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. Esomeprazole has been studied and approved for the treatment and prophylaxis of NSAID induced GI damage. The esomeprazole component of Vimovo is released in the stomach prior to the dissolution of naproxen in the small intestine. The enteric coating prevents naproxen release at pH levels below 5.5.

The open label, investigator blinded, randomised, parallel group study PN400-101 evaluated the effect of three Vimovo dose combinations, consisting of a fixed delayed release naproxen dose (500 mg) combined with different immediate release esomeprazole doses (10, 20 and 30 mg) on the risk of naproxen associated gastroduodenal injury (determined by combined gastric and duodenal Grade 3 or 4 lesions) in 80 healthy volunteers. Endoscopies were performed on Day -1 and Day 15 by the same gastroenterologist who was blinded to study treatment. All areas of the gastric and duodenal bulb were examined and the numbers of haemorrhages, erosions, and ulcers in each location were recorded. A composite score for each subject was calculated using the Lanza grading system (Lanza 1988)[12]:

[9] McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenases: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase- 2. JAMA 2006; 296: 1633–44.

[10] Singh G, Fort JG, Goldstein JL et al for the SUCCESS-I Investigators. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESSI study. Am J Med 2006; 119: 255-66.

[11] Scheiman JM, Yeomans ND, Talley NJ et al. Prevention of ulcers by esomeprazole in at-risk patients using non-selective NSAIDs and COX-2 inhibitors. Am J Gastroenterol 2006; 101: 1-10.

[12] Grading of Stomach and Duodenal Lesions (Lanza 1988): Grade Number of Erosions, Haemorrhages, and Ulcers:
0= No visible lesions;
1= 1 erosion or haemorrhages;
2= 2-10 erosions or haemorrhages;
3 = 11-25 erosions or haemorrhages;
4 = >25 erosions or haemorrhages or any ulcer

Any ulcers were measured and the largest diameter recorded. An ulcer was defined as a mucosal break of at least 3 mm in diameter (measured by close application of open endoscopic biopsy forceps) with depth (Lanza 1988).[12] Photographs of the gastric and duodenal bulb of each subject were obtained during the Day 15 endoscopy. The percentage of subjects with a Grade 3 or Grade 4 Lanza score on Day 15 was greater with EC naproxen (74%) than with any of the Vimovo treatments (20-30%). Treatment differences in the distribution of Lanza scores were statistically significant in each pairwise comparison with EC naproxen. The Vimovo/E20 treatment had a higher percentage of subjects with no visible GI lesions (40% of subjects with Lanza 1988 Score = 0) compared to all other treatments (range 5.3-15%); the treatment difference between Vimovo/E20 and EC naproxen for Grade 0 Lanza score was significant ($p<0.05$) (Table 1). Furthermore, 6 subjects in the EC Naproxen group presented with duodenal or stomach ulcers on Day 15 compared to none in the Vimovo treatment groups.

Table 1: Lanza scores Day 15 – stomach and duodenum combined

	PN 400/E30 N=20	PN 400/E20 N=20	PN 400/E10 N=20	EC Naproxen N=19
Lanza Score, n (%)				
0 (no visible lesions)	3 (15.0)	8 (40.0)	2 (10.0)	1 (5.3)
1 (1 hemorrhage or erosion)	1 (5.0)	2 (10.0)	1 (5.0)	0
2 (2-10 hemorrhages or erosions)	12 (60.0)	5 (25.0)	11 (55.0)	4 (21.1)
3 (11-25 hemorrhages or erosions)	4 (20.0)	3 (15.0)	5 (25.0)	5 (26.3)
4 (>25 hemorrhages or erosions, or an ulcer)	0	2 (10.0)	1 (5.0)	9 (47.4)
Lanza Score = 3 or 4 at Day 15/Early Withdrawal	4 (20.0)	5 (25.0)	6 (30.0)	14 (73.7)
p-value [1] compared to EC Naproxen	0.001	0.004	0.010	--

[1] Fisher's Exact test

The Phase I, randomised, parallel group study PN400-104 was conducted to provide dose ranging data on pharmacodynamics (percent of time intragastric pH>4.0; consistent with the prescribing information for Nexium) and safety of three Vimovo dose combinations, consisting of a fixed naproxen 500 mg dose and esomeprazole doses of 10, 20 or 30 mg. EC esomeprazole (20 mg) + EC naproxen 500 mg, taken together as separate tablets, were used as the active control. However, a non-EC naproxen formulation was inadvertently used instead of the protocol planned EC naproxen.

From a previous sponsor study, the within-subject standard deviation of percent time intragastric pH > 4.0 was 10%. The present study planned to enrol 28 subjects with the aim to have 24 evaluable subjects for analysis. A total of 24 subjects provided 80% power to reject the null hypothesis that the difference between each of the Vimovo treatments and the active control treatment in percent time intragastric pH > 4.0 over 24 h is ≤8% using a pairwise t-test with a 1-sided significance level of 0.05.

On Day 9, Vimovo/E30 and Vimovo/E20 treatment resulted in a greater percent time with intragastric pH > 4.0 than treatment with EC E20 + naproxen. Vimovo/E10 had the lowest percent time with intragastric pH > 4.0 and was also the most variable treatment as evidenced by the high percentage coefficient of variation (%CV). The %CV of the Vimovo/E10 treatment arm was about three times that of the other treatment groups. The overall pH profiles on Day 9 showed an esomeprazole dose related effect on intragastric pH beyond the influence of food intake. The effect on intragastric pH profiles was similar between Vimovo/E30 and Vimovo/E20, with each of these treatments reflecting a slower return of gastric contents to lower pH levels after food intake than either the Vimovo/E10 or EC E20 + naproxen treatments. The initial Day 9 pH measurements from all treatments showed that the mean intragastric pH after an overnight fast was between 2.0 and 3.0 which was higher than the initial pH (between 1.0 and 2.0) on Day 1.

There was only a minimal effect of any of the study treatments on intragastric pH, beyond the effect of food, throughout the first 24 h on the first day of treatment.

Analysis of percent time of pH > 3.0 and > 5.0 on Day 9 resulted in a similar pattern statistically as that of the primary endpoint of percent time pH > 4 on Day 9 for the "per protocol" (PP) population, with Vimovo/E30 and Vimovo/E20 showing a greater acid reducing capacity than EC E20 + naproxen, which had a greater capacity than Vimovo/E10, based on LSM differences and 95% CIs.

Since Vimovo is dosed twice daily, the individual time intervals corresponding to this dosing regimen, that is 0-10 h and 10-24 h, were analysed for percent time intragastric pH >4.0 on Day 9. The results indicate that for the 0-10 h period, Vimovo/E30 treatment resulted in a greater percent time with intragastric pH > 4.0 (84%) than treatment with EC E20 + naproxen (71%). While Vimovo/E20 also had a high percent time intragastric pH > 4.0 (79%), the results were not statistically significantly different from the EC E20 + naproxen treatment. As expected with bd dosing, both Vimovo/E30 and Vimovo/E20 had greater percent time intragastric pH > 4.0 (71% and 66%, respectively) compared to treatment with EC E20 + naproxen (47%) for the 10-24 h treatment interval. The Vimovo/E10 treatment had a lower percent time intragastric pH > 4.0 compared to treatment with EC E20 + naproxen for both the 0-10 h (52%) and the 10-24 h (33%) treatment interval.

Relationship between plasma concentration and effect

In study PN400-101, there was a reduction in gastroduodenal injury with all three doses of esomeprazole in Vimovo based on Lanza scores in healthy volunteers following 14 days treatment. The reduction in gastroduodenal injury with Vimovo compared to EC naproxen based on percentages of subjects with Grade 3 or 4 Lanza scores, showed an insignificant esomeprazole dose dependent trend. However, maximum gastroprotective effect appeared to be present at the proposed dose of 500/20 mg.

In study PN400-104, the relationship between the mean total plasma exposure to esomeprazole, that is, AUC_{0-24} on Day 9 (representing steady state exposure), and the mean percent time with intragastric pH > 4.0 on Day 9 (the primary PD endpoint) was evaluated. The maximum effect (E_{max}) was estimated to be 90.4% of time with intragastric pH > 4.0 over the daily interval at steady state. The AUC_{0-24} value required to achieve half (or 50%) of the maximal response was estimated to be 713 ng*hr/mL. Following Vimovo/E20, the PD response had achieved about 80% of the maximal response, which was only slightly less than that (85% of E_{max}) achieved by Vimovo/E30.

The plasma profiles of esomeprazole and naproxen and the intragastric pH profiles (that is, PK and PD profiles) obtained on Day 9 were consistent with the sequential release design of Vimovo. Repeat doses of the immediate release esomeprazole in Vimovo/E30

and Vimovo/E20 resulted in faster onset of increased intragastric pH (at about 1 h post dose) than the EC esomeprazole in EC E20 + naproxen, which was at about 1.5 h post dose.

In fact, with the bd regimen of Vimovo/E20, given 1 h before a meal, the intragastric pH was maintained at above 4.0 for greater than 70% of time over a 24 h period, which would encompass any rise in plasma naproxen concentrations throughout the day. In contrast, immediate release naproxen taken together with EC esomeprazole (E20) produced peak naproxen concentrations that preceded the increase in intragastric pH.

Taken together, the PK and PD data in this study support the sequential release design concept of Vimovo, that is, combining immediate release esomeprazole and delayed release naproxen in one dosage form to produce early onset of increased intragastric pH at steady state before naproxen is absorbed.

Evaluator's overall conclusions on pharmacodynamics

In Study PN400-101, the percentage of subjects with a Grade 3 or Grade 4 Lanza score (stomach and duodenum combined) on Day 15 was significantly greater ($p<0.01$) with EC naproxen than with any of the Vimovo treatments (naproxen 500 mg with esomeprazole 10, 20 and 30 mg) with a possible dose related trend in scores. In Study PN400-104, administration of Vimovo containing 20 or 30 mg esomeprazole resulted in a higher percent time with intragastric pH >4.0 compared to Vimovo/E 10 (the latter also having the highest variability in this response) after 9 days of bd dosing. Based on pH control and low inter-subject variability, Vimovo/E20 was selected for studies in subjects at risk for NSAID associated gastric ulcers. All formulations were well tolerated. The proposed PI accurately reflects the pharmacodynamic findings for Vimovo.

Efficacy

Introduction

All clinical studies were multinational, well conducted and complied with Good Clinical Practice guidelines with adequate ethical approval.

Five Phase III studies were conducted to demonstrate efficacy of Vimovo for the proposed indication. These included two pivotal, 6 month, active controlled studies (PN400-301 and PN400-302) that compared GU occurrence in patients who took Vimovo bd and those who took EC naproxen 500 mg bd. Two noninferiority, 3 month, Phase III supportive studies (PN400-307 and PN400-309) were designed to show that Vimovo was similar to Celebrex (celecoxib), a widely used COX-2 inhibitor, in the treatment of signs and symptoms of OA of the knee.

The 12 month open label safety study **PN400-304** was conducted to evaluate long term safety of Vimovo but also provided supportive efficacy data in terms of upper gastrointestinal (UGI) tolerability. An additional efficacy study, PN400-303, was initiated at the request of the FDA in a population at high risk for developing NSAID associated GUs, defined as those patients who had a documented history of a serious UGI event such as bleeding, perforation, or obstruction. This subpopulation represents a small fraction of the overall population at risk for developing NSAID associated GUs. This study compared Vimovo to Arthrotec and was discontinued due to slow enrolment after consultation with the FDA.

Dose response studies

The selection of the 20 mg esomeprazole dose was supported by results of dose ranging studies in healthy subjects (PN400-101 and PN400-104). In study PN400-101, after 2 weeks of bd dosing, Vimovo containing an esomeprazole dose of 20 mg resulted in a higher percentage of subjects with no visible GI lesions (40% of subjects with Lanza Score

of 0) compared to Vimovo formulations containing 10 mg or 30 mg of esomeprazole or naproxen alone (range 5.3-15%). In study PN400-104, after 9 days of bd dosing, both Vimovo containing esomeprazole 20 mg and 30 mg treatments resulted in a greater percent time with intragastric pH > 4.0 (71.4% and 76.5% time with gastric pH > 4.0, respectively) than treatment with EC esomeprazole 20 mg plus naproxen 500 mg (56.9%) and Vimovo containing esomeprazole 10 mg (40.6%). Given the similar pH control of Vimovo containing esomeprazole 20 mg as Vimovo with esomeprazole 30 mg and the fact that EC esomeprazole 20 mg has been shown efficacious in reducing ulcer occurrence in NSAID users, Vimovo containing esomeprazole 20 mg was selected for Phase III studies in subjects at risk for developing NSAID associated gastric ulcers. No dose response studies were conducted for the naproxen component of the Vimovo combination tablet.

Main (Pivotal) studies

Pivotal studies comparing Vimovo with EC-Naproxen alone (PN400-301 and PN400-302)

Methods, objectives and study treatments

Studies PN400-301 and PN400-302 were identical, 6 month, randomised, double blind, parallel group, active controlled, multicentre, outpatient studies conducted concurrently at sites throughout the US. Study PN400-301 was conducted from 11 September 2007 to 3 September 2008 at 59 centres in the USA. Study PN400-302 was conducted from 21 September 2007 to 29 September 2008 at 70 centres in USA.

The primary objective of each study was to demonstrate that Vimovo is effective in reducing the occurrence of gastroduodenal ulcers, dyspepsia and heartburn in subjects at risk for developing NSAID associated gastric ulcers. Each study included 2 treatment groups: the Vimovo group received 1 Vimovo tablet bd, and the EC naproxen group received 1 naproxen tablet bd, given 30-60 min before breakfast and dinner. To maintain the double blind design in the pivotal Phase III studies, the comparator product was a 500 mg EC naproxen tablet (identical to Vimovo tablets, but without esomeprazole in the film coat) to match the Vimovo tablet. Bioequivalence of the comparator to EC-Naprosyn 500 mg was already confirmed in Study PN400-102.

Randomisation ratios were 1:1 and stratified by low dose aspirin (LDA) use as the impact of LDA on the gastric mucosa could bias efficacy outcomes. The randomization code was produced under the direction of sponsors by a third party using a validated system that automated the random assignment of treatment groups to randomization numbers.

The 6 month study duration was considered adequate to compare GU occurrence between treatments, effects of the combination drug on discontinuations due to UGI adverse events (AEs) and other features of tolerability and safety.

Medications allowed during the study were paracetamol, incidental use of liquid antacid, LDA, antiplatelet agents, inhaled steroids for asthma, corticosteroids, methotrexate, monoclonal antibody for rheumatoid arthritis and intra-articular injections (but not of NSAIDs). Medications not allowed at any time during the study were any NSAID other than LDA during the treatment phase (during the screening phase, use of any NSAID, or preferably paracetamol, was allowed), any PPI, H_2 receptor antagonist or sucralfate, misoprostol containing products such as Arthrotec, anticoagulants, investigational drugs, ulcerogenic medications (such as alendronate and risedronate) and non-NSAID analgesics for any of the indications studied. Episodic use of narcotics for treatment of acute pain or breakthrough pain was allowed for no more than 5 consecutive days and for no more than 3 episodes during the treatment phase.

Hence, the study protocol was well designed to exclude the use of any concomitant medications that are known to either cause or treat ulcers or other UGI symptoms, and also excluded medications that might alter the underlying arthritic process.

Study participants (inclusion and exclusion criteria)

The pivotal studies included patients who had chronic inflammatory arthritis that would require daily use of NSAIDs for at least next 6 months and were considered to be at risk of GI toxicity from the chronic use of NSAIDS; specific diagnoses required for entry into the study included OA, rheumatoid arthritis (RA), alkylosing spondylitis (AS) or any other medical condition that would require the daily use of NSAIDs for the 6 month study period. Other main inclusion criteria were patients 18-49 years of age had to have a history of a documented, uncomplicated gastric or duodenal ulcer (a mucosal break of at least 3 mm in diameter with depth, without any concurrent bleeding, clot or perforation) within the past 5 years or patients who were 50 years of age or older were eligible to be randomised regardless of their ulcer history.

The main exclusion criteria were:

- A positive breath test for H. pylori or a positive screening endoscopy that revealed an ulcer ≥3 mm diameter with any depth.
- Pregnant or lactating females
- Hypersensitivity or intolerance to esomeprazole (or other PPIs) or any NSAIDs
- Presence of uncontrolled acute or chronic medical illness
- Coagulation disorders including use of anticoagulants
- Severe cardiovascular or psychiatric illness
- Intake of prohibited concomitant medications
- Clinically significant laboratory abnormalities
- History of malignancy (treated or untreated) within the past 5 years, with the exception of successfully treated basal cell or squamous cell carcinoma of the skin.

Compliance was assessed by the investigator and/or study personnel at each visit using tablet counts and information provided by the subject. The importance of study drug compliance was reiterated to the subject at each visit and by telephone every month. Treatment compliance for each visit and overall was categorized as < 50%, 50% to < 70%, and ≥ 70% and summarized by treatment group.

Efficacy endpoints and statistical considerations

The primary efficacy endpoint was the incidence of gastric ulcers at any time throughout 6 months of treatment. An ulcer was defined as a mucosal break of at least 3 mm in diameter (measured by close application of open endoscopic biopsy forceps) with unequivocal crater depth. Endoscopies were performed at Screening, Visit 2 prior to randomization and at 1, 3 and 6 months during the treatment period. Every reasonable effort was made to have the same endoscopist perform all endoscopies for a given subject.

Key secondary efficacy/tolerability endpoints included the following:

- Proportion of subjects with pre-specified NSAID associated UGI AEs or duodenal ulcers[13];
- Proportion of subjects discontinuing from the study due to pre-specified NSAID associated UGI AEs or due to duodenal ulcers;
- Proportion of subjects developing duodenal ulcers throughout 6 months of study treatment.

[13] Duodenal ulcer was a study endpoint and not reported as an AE.

Non-key secondary efficacy/tolerability endpoints included the following:

- Proportion of subjects with heartburn[14] resolution;
- Response on OTE-DP[15] rating;
- Mean change from Baseline for each of the SODA[16] sub-sections;
- Proportion of subjects discontinuing from the study due to any AE or duodenal ulcers (tolerability endpoint).

Other efficacy endpoints included:

- Incidence of gastroduodenal ulcers at any time throughout 6 months of treatment by LDA use (Yes/No) at randomization and
- Incidence of gastroduodenal ulcers at any time throughout 6 months of treatment

All efficacy and tolerability analyses were performed based on the "intent to treat" (ITT) population (all randomized subjects who received at least one dose of study drug and had no ulcer detected by endoscopy at the screening visit). In addition, analyses of the primary efficacy endpoint and the key secondary efficacy and tolerability endpoints were performed using the PP population (all subjects in the ITT population who did not violate the protocol in any major way that would have impacted the evaluation of efficacy and had at least 70% overall treatment compliance) as a supportive analysis. No centres were pooled for analysis purposes, as analyses were not adjusted for centre differences.

The cumulative proportion of subjects developing gastric ulcers at 6 months was analysed using a Cochran-Mantel-Haenszel (CMH) test stratified by use of LDA (Yes/No) at randomization. In addition, the proportion of subjects developing gastric ulcers was estimated using the Kaplan-Meier method. Time to gastric ulcer was calculated from the first day of study drug dispensed to the day of confirmed gastric ulcer or was censored at the last day endoscopic assessment or date of withdrawal (the last date a subject was seen at the investigative site) if no gastric ulcer developed. To confirm the robustness of primary analysis results, a sensitivity analysis was performed in which premature withdrawals without a confirmed gastric ulcer were classified as developing a gastric ulcer at 6 months if the subject developed a duodenal ulcer or discontinued due to a pre-specified UGI AE randomization (Yes/No), and age group (< 60, or ≥ 60 years) as covariates. The primary analysis was performed on data from the following subgroups in the ITT population if the number of subjects in a subgroup was appropriate:

[14] Heartburn symptoms were assessed as: none= no symptoms, mild= awareness of symptom, but easily tolerated, moderate= discomforting symptom sufficient to cause interference with normal activities (including sleep), severe= incapacitating symptom, with inability to perform normal activities (including sleep). Heartburn was defined as a burning feeling rising from the stomach or lower part of the chest towards the neck.

[15] The Overall Treatment Evaluation – Dyspepsia (OTE-DP) has been developed based on, and is considered a derivative work of, the Global Ratings of Change Questionnaire, which was originally developed at McMaster University. It consists of the question: "Since treatment started, has there been any change in your upper abdominal pain and/or discomfort?" Responses may be rated as "better", "the same", or "worse".

[16] The Severity of Dyspepsia Assessment (SODA) questionnaire is a self-administered, multi-dimensional measure of dyspepsia-related health. Dyspepsia and related GI symptoms, including burping/belching, heartburn, bloating, passing gas, sour taste, nausea and bad breath, are commonly reported by patients taking NSAIDs and significantly impact treatment effectiveness, cost and quality of life. Concepts measured within the 3 scales that comprise the SODA instrument are dyspepsia pain intensity, non-pain symptoms, and satisfaction with dyspepsia-related health. The SODA contains 17 questions and can be completed in 5 minutes. It uses a 7-day recall period for questions in the pain intensity and non-pain symptoms domains.

- Use of LDA (Yes/No);
- Age (< 60, or ≥ 60 years);
- History of gastric or duodenal ulcer within the previous 5 years (Yes/No);
- Race (White, Black, Other);
- Gender
- Ethnicity
- Smoking Status (Yes/No).

Treatment comparisons were performed for the following key secondary efficacy and tolerability endpoints in a sequential order as shown below:

(1) The proportion of subjects with pre-specified NSAID associated UGI AEs or duodenal ulcers,
(2) The proportion of subjects discontinuing from the study due to NSAID associated UGI AEs or due to duodenal ulcers and
(3) The proportion of subjects developing duodenal ulcers throughout 6 months of study treatment.

The determination of sample size was based on the assumption that 15% of subjects treated with naproxen would have a gastric ulcer over the 6 month study, compared to 5% of subjects treated with Vimovo. The computation used a Fisher's exact test with a 2-sided significance level of 5% and 90% power to detect the difference between naproxen and Vimovo to determine that the sample size in each group was 200. The exact basis for these assumptions was not clearly stated in the study report. However, the cumulative incidence of gastroduodenal ulcers with conventional NSAID use has been reported to be as high as 25-30% at 3 months and 45% at 6 months, while that of placebo is 3-7% (Bias 2004, Laine 1999, Hawkey 2000, Hawkey 2003, Simon 1999).[17,18,19,20,21]

From a previous study (PN200-301) comparing a previous formulation [PN 200] (naproxen 500 mg/ omeprazole 20 mg tablet) and naproxen 500 mg tablet, the proportions of subjects with UGI AEs were 51% for PN 200 and 71% for naproxen; the proportions of subjects discontinuing from the study due to UGI AEs or due to duodenal ulcers were 4.9% for PN 200 and 17.7% for naproxen; the incidences of duodenal ulcers at any time throughout 6 months of treatment were 0.5% for PN 200 and 8.9% for naproxen. Based on the results presented above which were used as assumptions for this study, 200 subjects per arm provided at least 90% power with a two-sided significance level of 5% to detect the treatment difference between Vimovo and naproxen for each of the three key secondary endpoints using Fisher's exact test. The hierarchical fixed sequence testing approach was used to adjust for multiple comparisons of the key secondary endpoints.

[17] Bias P, Buchner A, Klesser B, Laufer S. The gastrointestinal tolerability of the LOX/COX inhibitor, licofelone, is similar to placebo and superior to naproxen therapy in healthy volunteers: results from a randomized, controlled trial. Am J Gastroenterol 2004; 99: 611-8.
[18] Laine L, Harper S, Simon T et al. A randomized trial comparing the effect of rofecoxib, a Cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Gastroenterology 1999; 117: 776-83.
[19] Hawkey CJ. Risk of ulcer bleeding in patients infected with Helicobacter pylori taking non-steroidal anti-inflammatory drugs. Gut 2000; 46: 310-11.
[20] Hawkey CJ, Laine L, Simon T, Quan H, Shingo S, Evans, on behalf of the Rofecoxib Rheumatoid Arthritis Endoscopy Study Group. Incidence of gastroduodenal ulcers in patients with rheumatoid arthritis after 12 weeks of rofecoxib, naproxen, or placebo: a multicentre, randomised, double blind study. Gut 2003; 52: 820–826
[21] Simon LS, Weaver AL, Graham DY et al. Antiinflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis. A randomized controlled trial. JAMA 1999; 282: 1921-8.

Efficacy, safety and tolerability variables assessed in the pivotal studies were appropriate and similar to commonly used end points in clinical trials of PPIs and NSAIDs.

Results of pivotal study PN400-301

Patient disposition, baseline patient characteristics, treatment compliance

Overall, 438 patients were randomised of which 434 (218 Vimovo and 216 EC naproxen) received at least one dose of study treatment and were included in the ITT analysis population. More patients in the Vimovo group completed the study compared to those on EC naproxen (82.6% vs 69.5%) and there were more discontinuations due to AEs, withdrawal of consent and duodenal ulcer in the EC naproxen group (Table 2).

Table 2: PN400-301 subject accountability and disposition

	PN 400 N=218	DR Naproxen N=220	Total N=438
	n (%)	n (%)	n (%)
Randomized, N	218 (100)	220 (100)	438 (100)
Treated (Safety population)	218 (100)	216 (98.2)	434 (99.1)
ITT Population	218 (100)	216 (98.2)	434 (99.1)
PP Population	203 (93.1)	201 (91.4)	404 (92.2)
Completed study [1]	180 (82.6)	153 (69.5)	333 (76.0)
Completed study without gastric ulcer	171 (78.4)	103 (46.8)	274 (62.6)
Prematurely Discontinued	38 (17.4)	67 (30.5)	105 (24.0)
Adverse event	14 (6.4)	24 (10.9)	38 (8.7)
Withdrew consent	13 (6.0)	25 (11.4)	38 (8.7)
Lost to follow-up	5 (2.3)	2 (0.9)	7 (1.6)
Duodenal ulcer	1 (0.5)	10 (4.5)	11 (2.5)
Other	5 (2.3)	6 (2.7)	11 (2.5)

Source: Table 14.1.1

[1] Includes subjects who completed 6 months of treatment or who discontinued due to gastric ulcer.

Major protocol violations were identified for 9 (4%) randomized subjects in each treatment group; the majority of protocol violations pertained to subjects with no post-baseline endoscopy (15 subjects). The PP population excluded 15 subjects from each treatment group of the ITT population. Subjects excluded were those with major protocol violations and subjects with study drug compliance < 70% or unknown (13 Vimovo subjects and 11 naproxen subjects). Eight subjects had more than 1 violation leading to exclusion from the PP population.

The majority of subjects (≥ 94%) in both treatment groups had ≥ 70% compliance overall from baseline to Month 1, Month 3 and end of study. The majority of patients were female (69%), White (84%), non-smokers (86%) with mean age of 61 years (2%, 46% and 52% were <50years, 50-59 years and >60 years old). Approximately 25% of patients in each group were using LDA at randomization. About 6% reported having had a gastric and/or duodenal ulcer within the last 5 years. Osteoarthritis was the most frequently reported reason for NSAID use. There were small differences in the distribution of underlying

aetiologies between the two treatment groups. Most of the "other" indications for NSAID use were back pain, chronic back pain, low back pain (in 49 subjects). In the ITT population, the 2 treatment groups were similar with regard to baseline demographics and characteristics of ulcer history and NSAID use. These patients were representative of the target patient population for Vimovo.

Primary efficacy results

The cumulative observed incidence of gastric ulcers throughout 1, 3 and 6 months was significantly lower with Vimovo treatment than naproxen (p<0.001 at all time points) (Table 3). Significant separation between treatment groups was observed as early as 1 month and was maintained throughout 6 months of therapy; the cumulative gastric ulcer rate at 6 months was 4% with Vimovo and 23% with naproxen.

Table 3: Analysis of cumulative observed incidence of gastric ulcers at 1, 3 and 6 months (ITT population)

Number (%)	PN 400 N=218	DR Naproxen N=216	p-Value[1]
	n (%)	n (%)	
0-1 Month			
Gastric ulcer	3 (1.4)	28 (13.0)	<0.001
95% CI	(0.3-4.0)	(8.8-18.2)	
Gastric ulcer-free[2]	215 (98.6)	188 (87.0)	
Maintained gastric ulcer-free	200 (91.7)	160 (74.1)	
Discontinued gastric ulcer-free	15 (6.9)	28 (13.0)	
0-3 Months			
Gastric ulcer	4 (1.8)	42 (19.4)	<0.001
95% CI	(0.5 – 4.6)	(14.4 – 25.4)	
Gastric ulcer-free[2]	214 (98.2)	174 (80.6)	
Maintained gastric ulcer-free	182 (83.5)	121 (56.0)	
Discontinued gastric ulcer-free	32 (14.7)	53 (24.5)	
0-6 Months			
Gastric ulcer	9 (4.1)	50 (23.1)	<0.001
95% CI	(1.9 – 7.7)	(17.7 – 29.4)	
Gastric ulcer-free[2]	209 (95.9)	166 (76.9)	
Maintained gastric ulcer-free	171 (78.4)	103 (47.7)	
Discontinued gastric ulcer-free	38 (17.4)	63 (29.2)	

Source: Table 14.2.1.1. CI = confidence interval [1]P-value for ulcer occurrence is from a CMH test stratified by low-dose aspirin use, at randomization, as reported on the concomitant medications CRF page. [2]ulcer status as determined by last known endoscopic examination.

These primary efficacy results in the ITT population were robust and supported by similar results in the PP population; the sensitivity analysis including subjects with a gastric or duodenal ulcer or who discontinued due to a pre-specified NSAID associated UGI AE also showed statistically significant lesser 6 month incidence of GU in Vimovo group compared with naproxen (7% vs 35%, p<0.001).

Compared to 32 naproxen treated subjects (14.8%), 5 subjects on Vimovo (2.3%) had gastric ulcers of at least 5 mm. Most of the gastric ulcers were located in the antrum.

Similarly only 1 subject (0.5%) on Vimovo had duodenal ulcers of at least 5 mm compared with 9 subjects (4.2%) in the naproxen treatment group.

Secondary efficacy results

In the ITT population, a significantly smaller proportion of subjects in the Vimovo group had pre-specified NSAID associated UGI AEs and/or duodenal ulcers compared with naproxen (52% vs 69%, p<0.001). The rate of discontinuation from the study due to a pre-specified NSAID associated UGI AEs or duodenal ulcer was also significantly lower with Vimovo than with naproxen (3% vs 12%, p<0.001). The cumulative observed incidence of duodenal ulcers throughout 6 months was also significantly lower with Vimovo treatment than with naproxen (0.5% vs 5%, p=0.003) (Table 4).

Table 4: Analysis of cumulative observed incidence of duodenal ulcers at 1, 3 and 6 months (ITT population)

Number (%)	PN 400 N=218	DR Naproxen N=216	p-Value[1]
	n (%)	n (%)	
0-1 Month			
Duodenal ulcer	1 (0.5)	9 (4.2)	0.010
95% CI	(0.0 – 2.5)	(1.9 – 7.8)	
Duodenal ulcer-free	217 (99.5)	207 (95.8)	
Maintained duodenal ulcer-free	200 (91.7)	157 (72.7)	
Discontinued duodenal ulcer-free[2]	17 (7.8)	50 (23.1)	
0-3 Months			
Duodenal ulcer	1 (0.5)	11 (5.1)	0.003
95% CI	(0.0 – 2.5)	(2.6 – 8.9)	
Duodenal ulcer-free	217 (99.5)	205 (94.9)	
Maintained duodenal ulcer-free	182 (83.5)	121 (56.0)	
Discontinued duodenal ulcer-free[2]	35 (16.1)	84 (38.9)	
0-6 Months			
Duodenal ulcer	1 (0.5)	11 (5.1)	0.003
95% CI	(0.0 – 2.5)	(2.6 – 8.9)	
Duodenal ulcer-free	217 (99.5)	205 (94.9)	
Maintained duodenal ulcer-free	171 (78.4)	103 (47.7)	
Discontinued duodenal ulcer-free[2]	46 (21.1)	102 (47.2)	

Source: Table 14.2.7.1 CI = confidence interval. [1]P-value for ulcer occurrence is from a CMH test stratified by low-dose aspirin use, at randomization, as reported on the concomitant medications CRF page. [2]Includes subjects with gastric ulcers, since they were treated as completers

From an early time point (Month 1), Vimovo treatment demonstrated a significantly higher heartburn resolution rate than naproxen (65.1% vs 39.9%, p<0.001) and this was maintained at 3 and 6 months. The OTE-DP assessment showed significantly more improvement in the Vimovo group compared with the naproxen group (p<0.001) with a higher percentage of "better" response and a lower percentage of "worse" response in the Vimovo group. All three domains of the SODA questionnaire (pain intensity, non-pain and

satisfaction domains) showed significantly greater improvements with Vimovo compared with naproxen.

The discontinuation rate due to any AE (including duodenal ulcer) was significantly lower with Vimovo than with naproxen (7% vs 16%, p=0.004).

There was no significant difference between treatment groups in percentage of subjects who used paracetamol (73% vs 81%), although Vimovo patients who used paracetamol reported intake of higher median number of tablets compared with naproxen (66 vs 56 tablets). Similarly, fewer subjects in the Vimovo treatment group reported antacid use (64% vs 70%) and, for those who did, similar amounts were used (median of 12 in each group).

Results of pivotal study PN400-302

Patient disposition, baseline patient characteristics, treatment compliance

Overall, 423 patients were randomised of which 420 (210 patients in each group) received at least 1 dose of study treatment and were included in the ITT analysis population. The proportion of patients completing the study was similar (72% each) in the Vimovo and naproxen groups; there were more discontinuations due to AEs and duodenal ulcer in the naproxen group, while incidence of withdrawal of consent was higher in the Vimovo group (Table 5).

Table 5: PN400-302 subject accountability and disposition

	PN 400 N=212	DR Naproxen N=211	Total N=423
	n (%)	n (%)	n (%)
Randomized, N	212 (100)	211 (100)	423 (100)
Treated (safety population)	210 (99.1)	210 (99.5)	420 (99.3)
ITT population	210 (99.1)	210 (99.5)	420 (99.3)
PP Population	180 (84.9)	180 (85.3)	360 (85.1)
Completed study [1]	151 (71.2)	153 (72.5)	304 (71.9)
Completed study without gastric ulcer	136 (64.2)	102 (48.3)	238 (56.3)
Prematurely Discontinued	61 (28.8)	58 (27.5)	119 (28.2)
Adverse event	20 (9.4)	30 (14.2)	50 (11.8)
Withdrew consent	24 (11.3)	8 (3.8)	32 (7.6)
Lost to follow-up	6 (2.8)	7 (3.3)	13 (3.1)
Duodenal ulcer	2 (0.9)	8 (3.8)	10 (2.4)
Other	9 (4.2)	5 (2.4)	14 (3.3)

Source: Table 14.1.1

[1] Includes subjects who completed 6 months of treatment or who discontinued due to gastric ulcer.

Major protocol violations were identified for 28 (Vimovo=12, naproxen=16) randomised patients and all of these violations pertained to subjects with no post-baseline endoscopy. In addition, 3 of the 28 subjects did not take study drug.

The PP population excluded 30 subjects from each treatment group of the ITT population Subjects excluded were those with major protocol violations and subjects with study drug

compliance < 70% or unknown (26 Vimovo subjects and 22 naproxen subjects). Thirteen subjects had more than 1 violation leading to exclusion from the PP population.

The majority of subjects (88%) in both treatment groups had ≥ 70% compliance overall from baseline to Month 1, Month 3 and end of study. The majority of patients were female (65%), White (89%), non-smokers (82%) with mean age of 61 years (3%, 44% and 53% were <50years, 50-59 years and >60 years old). Approximately 22-24% of patients in each group were using LDA at randomization. About 9-11% reported having had a gastric and/or duodenal ulcer within the last 5 years. Osteoarthritis was the most frequently reported reason for NSAID use. There were small differences in distribution of underlying aetiologies between the two treatment groups. Most of the "other" indications for NSAID use were back pain, chronic back pain, low back pain (in 49 subjects). In the ITT population, the 2 treatment groups were similar with regard to baseline demographics and characteristics of ulcer history and NSAID use with the exception that there were slightly more Blacks (12% vs 8%) and patients aged > 60 years (47% vs 43%) in the Vimovo group compared with naproxen. These patients were representative of the target patient population for Vimovo.

Primary efficacy results

The cumulative observed incidence of gastric ulcers throughout 1, 3 and 6 months was significantly lower with Vimovo treatment than naproxen ($p<0.001$ at all time points) (Table 6). Significant separation between treatment groups was observed as early as 1 month and was maintained throughout 6 months of therapy; the cumulative gastric ulcer rate at 6 months was 7.1% with Vimovo and 24.3% with naproxen. Only 8 subjects on Vimovo (3.8%) had gastric ulcers of at least 5 mm compared to 36 naproxen treated subjects (17.1%). Most of the gastric ulcers were located in the antrum. Similarly, only 2 subjects on Vimovo (1%) had duodenal ulcers of at least 5 compared with 9 subjects in the naproxen treatment group (4.8%).

Table 6: Analysis of cumulative observed incidence of gastric ulcers at 1, 3 and 6 months (ITT population)

Number (%)	PN 400 N=210	DR Naproxen N=210	p-Value[1]
	n (%)	n (%)	
0-1 Month			
Gastric ulcer	4 (1.9)	21 (10.0)	<0.001
95% CI	(0.5 – 4.8)	(6.3 – 14.9)	
Gastric ulcer-free[2]	206 (98.1)	189 (90.0)	
Maintained gastric ulcer-free	178 (84.8)	160 (76.2)	
Discontinued gastric ulcer-free	28 (13.3)	29 (13.8)	
0-3 Months			
Gastric ulcer	10 (4.8)	37 (17.6)	<0.001
95% CI	(2.3 – 8.6)	(12.7 – 23.5)	
Gastric ulcer-free[2]	200 (95.2)	173 (82.4)	
Maintained gastric ulcer-free	149 (71.0)	126 (60.0)	
Discontinued gastric ulcer-free	51 (24.3)	47 (22.4)	
0-6 Months			
Gastric ulcer	15 (7.1)	51 (24.3)	<0.001
95% CI	(4.1 – 11.5)	(18.6 – 30.7)	
Gastric ulcer-free[2]	195 (92.9)	159 (75.7)	
Maintained gastric ulcer-free	136 (64.8)	102 (48.6)	
Discontinued gastric ulcer-free	59 (28.1)	57 (27.1)	

Source: Table 14.2.1.1. CI = confidence interval. [1]P-value for ulcer occurrence is from a CMH test stratified by low-dose aspirin use, at randomization, as reported on the concomitant medications CRF page
[2]ulcer status as determined by last known endoscopic examination.

These primary efficacy results in the ITT population were robust and supported by similar results in the PP population; the sensitivity analysis including subjects with a gastric or duodenal ulcer or who discontinued due to a pre-specified NSAID associated UGI AE showed similar results with a 6 month incidence of 12% for Vimovo and 36% for naproxen (p<0.001).

Secondary efficacy results

In the ITT population, a significantly smaller proportion of subjects had prespecified NSAID associated UGI AEs and/or duodenal ulcers with Vimovo than with naproxen (54% vs 72%, p<0.001). The rate of discontinuation from the study due to a pre-specified NSAID associated UGI AEs or duodenal ulcer was also significantly lower with Vimovo than with naproxen (5% vs 12%, p=0.009). The cumulative observed incidence of duodenal ulcers throughout 6 months was also significantly lower with Vimovo treatment than with naproxen (1.0% vs 5.7%, p=0.007) (Table 7).

Table 7: Analysis of cumulative observed incidence of duodenal ulcers at 1, 3 and 6 months (ITT population)

Number (%)	PN 400 N=210	DR Naproxen N=210	p-Value[1]
	n (%)	n (%)	
0-1 Month			
Duodenal ulcer	2 (1.0)	6 (2.9)	0.168
95% confidence CI	(0.1 – 3.4)	(1.1 – 6.1)	
Duodenal ulcer-free	208 (99.0)	204 (97.1)	
Maintained duodenal ulcer-free	178 (84.8)	160 (76.2)	
Discontinued duodenal ulcer-free[2]	30 (14.3)	44 (21.0)	
0-3 Months			
Duodenal ulcer	2 (1.0)	11 (5.2)	0.013
95% CI	(0.1 – 3.4)	(2.6 – 9.2)	
Duodenal ulcer-free	208 (99.0)	199 (94.8)	
Maintained duodenal ulcer-free	149 (71.0)	126 (60.0)	
Discontinued duodenal ulcer-free[2]	59 (28.1)	73 (34.8)	
0-6 Months			
Duodenal ulcer	2 (1.0)	12 (5.7)	0.007
95% CI	(0.1 – 3.4)	(3.0 – 9.8)	
Duodenal ulcer-free	208 (99.0)	198 (94.3)	
Maintained duodenal ulcer-free	136 (64.8)	102 (48.6)	
Discontinued duodenal ulcer-free[2]	72 (34.3)	96 (45.7)	

Source: Table 14.2.7.1 CI=confidence interval. [1] P-value for ulcer occurrence is from a CMH test stratified by low-dose aspirin use, at randomization, as reported on the concomitant medications CRF page. [2]Includes subjects with gastric ulcers, since they were treated as completers

From an early time point (Month 1), Vimovo treatment demonstrated a significantly higher heartburn resolution rate than naproxen (62% vs 48%, p=0.003) and this was maintained at 3 and 6 months. The OTE-DP assessment showed significantly more improvement in the Vimovo group compared with the naproxen group (p<0.001), with a higher percentage of "better" response and a lower percentage of "worse" response in the Vimovo group. All 3 domains of the SODA questionnaire (pain intensity, non-pain and satisfaction domains) showed significantly greater improvements with Vimovo compared with naproxen.

The discontinuation rate due to any AE (including duodenal ulcer) was significantly lower with Vimovo than with naproxen (11% vs 18%, p=0.029).

There was no significant difference between treatment groups in percentage of subjects who used paracetamol (70% vs 74%). Significantly fewer subjects in the Vimovo treatment group used antacid (56% vs 66%, p=0.021), and for those who did, fewer doses were used.

Pivotal non-inferiority studies comparing Vimovo with celecoxib

Methods, objectives and study treatment

Studies PN400-307 and PN 400-309 were identical, 6 month, randomised, double blind, placebo controlled, parallel group, active controlled, multicentre, outpatient studies

conducted concurrently at sites throughout the US. Study PN400-307 was conducted from 8 April 2008 to 3 December 2008 at 79 centres in the USA. Study PN400-309 was conducted from 9 April 2008 to 30 December 2008 at 82 centres in USA.

The primary objective of this study was to demonstrate that Vimovo twice daily (bd) for 12 weeks is non-inferior (NI) to celecoxib 200 mg once daily (qd) in the treatment of the signs and symptoms of osteoarthritis (OA) as measured by mean change from baseline at Week 12 using 3 primary endpoints: Western Ontario and McMaster Universities (WOMAC) OA Index Pain Subscale, WOMAC Function Subscale and Patient Global Assessment (PGA) of OA using a visual analogue scale (VAS). The secondary objectives were to compare efficacy of Vimovo and celecoxib in the time to onset of improvement, to compare the efficacy of Vimovo and celecoxib to each other and to placebo and to compare UGI symptoms in subjects treated with Vimovo and celecoxib.

After the initial screening visit, there was a washout period of 7-14 days during which any chronic analgesic therapy was withdrawn. Subjects were instructed to return to the study site for the Baseline Visit upon experiencing a flare of OA pain. Question 1 of the WOMAC Pain Subscale (VAS), and the PGA-Likert scale were completed and compared to Screening results to assess OA flare. Subjects who met entry criteria including the clinical diagnosis of OA of the knee were randomized in a 2:2:1 ratio to receive either Vimovo bd or celecoxib 200 mg qd or placebo. The most painful knee was selected as the index or study joint.

Allowed and unallowed medications were similar to the pivotal studies. Compliance was assessed by the investigator and/or study personnel at each visit using pill counts and e-diaries. In addition, the importance of study drug compliance was reiterated at each visit.

In this study, celecoxib 200 mg was chosen because its effectiveness has been shown to be similar to that of naproxen 500 mg bd (Bensen 1999).[22] A placebo arm was added to determine the treatment difference between active treatments and placebo in order to support the NI margin of 10 mm chosen *a priori*. The study design and statistical analysis followed that from similar, published studies (Gibofsky 2003, Bingham III, 2007).[23,24]

Study participants (inclusion and exclusion criteria)

The main inclusion criteria were subjects aged >50 years with a 6 month history of OA of knee meeting American College of Rheumatology (ACR) criteria for clinical diagnosis of OA. Subjects were required to have been on a stable dose of NSAIDs, COX-2 inhibitors or other oral analgesic therapy for at least 6 weeks and required to continue treatment for 12 weeks and subjects were required to have an ACR functional class rating of I, II or III.

The main exclusion criteria were:

- Subjects with rheumatoid arthritis, gout/pseudogout, fibromyalgia syndrome, acute joint trauma at the index joint within the 3 months prior to screen with active symptoms
- Previous (in the past 12 months) or anticipated need for surgical or invasive procedure performed on the index joint during the study

[22] Bensen WG, Fiechtner JJ, McMillen JI et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor, a randomized controlled trial. Mayo Clin Proc 1999; 74: 1095-1105.
[23] Gibofsky A, Williams GW, McKenna F, Fort JG. Comparing the efficacy of cyclooxygenase 2 specific inhibitors in treating osteoarthritis. Arthritis Rheum 2003; 48: 3102-3111.
[24] Bingham III CO, Sebba AI, Rubin BR et al. Efficacy and safety of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies. Rheumatol 2007; 46: 496-507.

- Subjects with intra-articular or intramuscular corticosteroids or intra-articular hyaluronic acid injections within 8 weeks prior to randomization
- Subject was currently taking or anticipated to take warfarin, or lithium
- Pregnant/lactating females
- Hypersensitivity or intolerance to esomeprazole (or other PPIs), any NSAIDs or sulphonamides
- Presence of uncontrolled acute or chronic medical illness
- Coagulation disorders including use of anticoagulants
- Severe cardiovascular or psychiatric illness
- Intake of prohibited concomitant medications
- Clinically significant laboratory abnormalities
- History of malignancy, treated or untreated, within the past 5 years, with the exception of successfully treated basal cell or squamous cell carcinoma of the skin

Efficacy endpoints and statistical considerations

Procedures to enhance subject compliance and ease of use in completing the Patient Reported Outcomes (PRO) questionnaires were followed throughout the study. Subjects were provided with a quiet space in the clinic where they could complete the questionnaires independently so that the responses reflected the subject's perceptions and not those of family, spouses, or study staff. The questionnaires were completed prior to other examinations to minimize the transmission of information to the subject that might influence answers provided. All assessments were completed in the morning, prior to the morning dose of study medication.

The 3 co-primary efficacy endpoints were assessed at Week 12 using a 100 mm visual analog scale (VAS) and included the WOMAC Pain Subscale, the WOMAC Function Subscale and the PGA. For each of these primary efficacy endpoints the null hypothesis was that Vimovo is inferior to celecoxib. In order to test the hypothesis of inferiority, the LSM changes from baseline were calculated using analysis of covariance (ANCOVA) with baseline score as covariate and treatment as the factor. Treatment differences between the 2 active groups were calculated as Vimovo minus celecoxib and 2-sided 95% confidence intervals (CIs) were calculated for the differences in the LSM changes between celecoxib and Vimovo (Vimovo minus celecoxib). A negative treatment difference in WOMAC endpoints favours Vimovo. A positive treatment difference in the PGA-VAS endpoint favours Vimovo. The NI of Vimovo compared to celecoxib was established if the upper bound of the 2-sided 95% CI was less than or equal to a NI margin of +10 mm for the Pain and Function domains, and if the lower bound of the 2-sided 95% CI was greater than or equal to a NI margin of -10 mm for PGA-VAS. The sample size and power calculations were made under the assumption that non-inferiority would be tested with the expectation that the difference between Vimovo and celecoxib would be 2 mm VAS in favour of celecoxib. However, details regarding basis for the NI margins were not provided in the study report.

As secondary objective, the LS estimates of the mean changes from baseline and pairwise differences from placebo (Vimovo minus placebo, celecoxib minus placebo) were determined in order to support the use of the NI margin of 10 mm chosen *a priori*. In addition, as part of the secondary endpoints, Vimovo and celecoxib treatments were compared to placebo treatment for change from baseline to Week 12 in WOMAC pain and function domains, and PGA-VAS. Another key secondary endpoint was the mean change from baseline in the modified Severity of Dyspepsia Assessment (the abdominal pain/discomfort subscale of the SODA PRO instrument, administered daily) (mSODA) average daily pain intensity converted total score at Week 12.

Tolerability was assessed by tabulation of the following measures:

- proportion of subjects discontinued due to any AE,
- proportion of subjects with any pre-specified NSAID associated UGI AEs
- proportion of subjects discontinued due to any pre-specified NSAID associated UGI AEs.

Other efficacy endpoints included the following:

- Time (in days) to first report of good or excellent response on Days 1-7 as measured by the PGA – Likert scale
- Mean change from Baseline in Total WOMAC score at Weeks 6 and 12
- Mean change from Baseline in WOMAC Pain, Stiffness and Function scores at Week 6
- Mean change from Baseline in PGA – VAS at Week 6
- Percent of days with heartburn resolution at Weeks 6 and 12
- Proportion of subjects who took rescue paracetamol (for OA pain) or supplemental antacid or any rescue medication during active treatment
- Percent of days in study that rescue medication was used
- Amount (number of tablets) of rescue medication taken
- Time to first rescue paracetamol for OA knee pain
- Mean change from Baseline in MDHAQ RAPID-3 (Rheumatology Assessment of Patient Index Data)
- An overall score for the MDHAQ score and Function, Pain and Global scores at Weeks 6 and 12
- Mean change from Baseline in APS-POQ total score on Days 1-7
- Mean change from Baseline in daily WOMAC Pain score on Days 1-7.

All efficacy and tolerability analyses were performed based on the ITT population (all randomized subjects who received at least 1 dose of study drug and had no ulcer detected by endoscopy at the screening visit). In addition, analyses of the primary efficacy endpoint and was performed using the PP population (all subjects in the ITT population who did not violate the protocol in any major way that would have impacted the evaluation of efficacy and had at least 70% overall treatment compliance) as a supportive analysis.

Clinical response and safety variables assessed in this study are commonly used in clinical trials of NSAIDs and PPIs. The WOMAC and PGA-VAS have been validated for OA of the knee.

Results of non-inferiority study PN400-307

Patient disposition, baseline patient characteristics, treatment compliance

Of the 619 randomised patients, 612 were included in the ITT efficacy analysis (Vimovo=246, celecoxib=242, placebo=124). Approximately 84% of subjects in each treatment group completed the study. Adverse events were the most frequent reason for discontinuation (6.8% overall), with similar proportions in each treatment group (Table 8).

Table 8: PN400-307 subject accountability and disposition

	PN 400 bid N=248	Celecoxib 200 qd N=247	Placebo N=124	Total N=619
	n (%)	n (%)	n (%)	n (%)
Treated (Safety Population)	247 (99.6)	243 (98.4)	124 (100)	614 (99.2)
Intent-to-Treat Population	246 (99.2)	242 (98.0)	124 (100)	612 (98.9)
Per-Protocol Population	232 (93.5)	219 (88.7)	113 (91.1)	564 (91.1)
Completed Study	208 (83.9)	208 (84.2)	105 (84.7)	521 (84.2)
Prematurely Discontinued	40 (16.1)	39 (15.8)	19 (15.3)	98 (15.8)
Adverse Event	19 (7.7)[1]	16 (6.5)	7 (5.6)	42 (6.8)
Withdrew Consent	9 (3.6)	13 (5.3)	7 (5.6)	29 (4.7)
Lost to Follow-up	0	2 (0.8)	0	2 (0.3)
Other	12 (4.8)	8 (3.2)	5 (4.0)	25 (4.0)

Source: Table 14.1.1 [1]One more than reported in Table 14.3.2.3 due to data collection discrepancy between the reason for discontinuation and the adverse event data.

The PP population excluded 16 subjects (6%) from the Vimovo group, 28 (11%) subjects from the celecoxib treatment group and 11 subjects (9%) from the placebo group; non-compliance was the major protocol violation across all treatment groups.
The majority of the patients were female (64%), White (80%), non-smokers (85%) with mean age of 62 years. Slightly more than half of each treatment group was classified as ACR functional Class II. Stiffness and/or crepitus were present in >75% of each treatment group. The mean baseline pain value for WOMAC Question 1 was approximately 78- 80 mm across treatment groups. More than 99% of subjects met all 3 criteria for OA flare at randomization. Approximately 23% of subjects were using LDA at randomization. The baseline demographics and disease characteristics were generally comparable among the 3 treatment groups although there were slight differences in age, gender and smoking status. Ibuprofen was the usual pain medication taken for OA pain prior to randomization (34% of the Vimovo treatment group, 34% of the celecoxib group, and 44% of the placebo group). Naproxen, paracetamol and celecoxib were taken previously by 28%, 22% and 16% of all subjects respectively. All subjects had medical comorbid conditions (hypertension, musculoskeletal and endocrine/ metabolic most common) and use of antihypertensive drugs was similar across treatment groups. The majority of subjects (> 90%) in all 3 treatment groups had ≥ 70% treatment compliance from baseline to Week 6 and baseline to last dose. Compliance with study drug dosing was balanced across the 3 treatment groups.

Overall, the patient population in this study was representative of the patients with OA of the knee who were likely to use Vimovo.

Primary efficacy results

Non-inferiority (NI) of Vimovo compared to celecoxib was established, since the upper bound of the 2-sided 95% CI for treatment difference was ≤ 10 mm for WOMAC Pain (LSM of Vimovo-celecoxib=-0.22, 95% CI: -4.76, 4.32) and Function (LSM diff=-0.09, 95% CI: -4.57, 4.38) domains, and the lower bound of the 95% CI was ≥ -10mm for the PGA-VAS (LSM diff=-0.47, 95% CI: -5, 4.14) (Tables 9, 10, 11).

Table 9: PN400-307 NI analysis of WOMAC pain at Week 12 (ITT population with LOCF)

	PN 400 bid N=246	Celecoxib 200 qd N=242	PN 400 bid minus Celecoxib 200 qd
Baseline			
N	226	221	
Mean (SD)	71.9 (17.1)	68.3 (17.7)	
Week 12			
N	226	221	
Mean (SD)	28.5 (25.6)	27.1 (24.2)	
Week 12 Change from Baseline			
N	226	221	
Mean (SD)	-43.4 (26.8)	-41.1 (26.2)	-2.24
ANCOVA			
LS Mean	-41.99	-41.77	-0.22
95% Confidence Interval			(-4.76, 4.32)

Source: Table 14.2.1
ANCOVA = Analysis of Covariance; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; WOMAC = Western Ontario and McMaster Osteoarthritis Index
Note: a negative change from Baseline indicates improvement

Table 10: PN400-307 NI analysis of WOMAC function at week 12 (ITT population with LOCF)

	PN 400 bid N=246	Celecoxib 200 qd N=242	PN 400 bid minus Celecoxib 200 qd
Baseline			
N	226	221	
Mean (SD)	68. 7 (19.8)	66.0 (19.9)	
Week 12			
N	226	221	
Mean (SD)	31.2 (25.6)	30.1 (24.6)	
Week 12 Change from Baseline			
N	226	221	
Mean (SD)	-37.5 (27.1)	-36.0 (26.4)	-1.56
ANCOVA			
LS Mean	-36.38	-36.29	-0.09
95% Confidence Interval			(-4.57, 4.38)

Source: Table 14.2.1
ANCOVA = Analysis of Covariance; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; WOMAC = Western Ontario and McMaster Osteoarthritis Index
Note: a negative change from Baseline indicates improvement

Table 11: PN400-307 NI analysis of PGA-VAS at Week 12 (ITT population with LOCF)

	PN 400 bid N=246	Celecoxib 200 qd N=242	PN 400 bid minus Celecoxib 200 qd
Baseline			
N	242	230	
Mean (SD)	32.3 (22.3)	31.8 (20.5)	
Week 12			
N	242	230	
Mean (SD)	53.8 (26.0)	54.1 (24.7)	
Week 12 Change from Baseline			
N	242	230	
Mean (SD)	21.5 (33.4)	22.4 (28.7)	-0.92
ANCOVA			
LS Mean	21.17	21.64	-0.47
95% Confidence Interval			(-5.08, 4.14)

Source: Table 14.2.1
ANCOVA = Analysis of Covariance; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; PGA = patient global assessment; VAS = visual analog scale
Note: a positive change from Baseline indicates improvement

The non-inferiority of Vimovo to celecoxib 200 mg qd was also confirmed in the PP population analysis.

Secondary efficacy results

Both Vimovo and celecoxib showed statistically significantly ($p<0.03$) greater improvement in WOMAC- pain and function domains as well as PGA-VAS compared with placebo. The differences between either Vimovo or celecoxib and placebo were similar. These data demonstrate observed NI margins for both WOMAC domains, and PGA-VAS of about 6-8 mm relative to the a priori NI margin of 10 mm.

At Week 12, the LSM change from baseline in the mSODA average daily abdominal pain score showed improvement with all 3 treatments (LSM change was -3.79 with Vimovo, -4.57 with celecoxib, and -3.73 with placebo) with no significant differences between groups; similar changes were seen at Week 6.

During Days 1-7, slightly greater proportion of patients treated with Vimovo (55%) and celecoxib (51%) were responders (report of good or excellent on PGA-Likert scale) compared with placebo (44%). The median time to good or excellent response was 6.0 days with both Vimovo and celecoxib while majority of placebo subjects did not experience good or excellent response during the first 7 days of treatment (median time to good or excellent response > 7 days). However, none of the treatment comparisons showed significant differences in time to good or excellent response.

The change from baseline to Week 6 and Week 12 was similar for Vimovo and celecoxib (both significantly better than placebo) for the WOMAC total score, WOMAC stiffness and average daily pain scores. Furthermore, both the active treatments were associated with improvements in the MDHAQ scores for RAPID-3, physical function, pain, and patient global scores at Week 6 and Week 12; the APS-POQ questionnaire analysis also indicated better pain control with active treatments over placebo by Day 2 or Day 3 and similar pain control with Vimovo and celecoxib treatment from Day 1. Pain interference with general

activities, walking and enjoyment of life, interference with mood and relations, sleep and work also showed similar results.

Subjects in the Vimovo treatment group consistently had a significantly greater percentage of days with no heartburn compared to celecoxib and placebo (78.4%, 71.5% and 66.1% in the Vimovo, celecoxib and placebo groups, respectively) (the difference between celecoxib and placebo was not significant). Although there was no significant difference between treatment groups in percentage of subjects who used at least one dose of paracetamol for OA knee pain (73%, 72% and 80%, respectively), subjects in the Vimovo and celecoxib groups took a lower mean total number of tablets than placebo subjects (52, 51 and 69 tablets, respectively). A significantly smaller percentage of subjects in the Vimovo treatment group (43%) reported antacid use for dyspepsia than in the celecoxib group (55%). Forty nine percent of subjects on placebo used at least one dose of antacid which was not significantly different from Vimovo or celecoxib. For those who used antacid, the mean total number of antacid tablets taken was significantly lower in the Vimovo group compared with celecoxib (24, 32 and 32 tablets in the Vimovo, celecoxib and placebo groups, respectively).

The proportion of subjects reporting pre-specified NSAID associated UGI adverse events, including duodenal ulcers was similar across treatment groups (16.6%, 16.9% and 19.4% in Vimovo, celecoxib and placebo groups, respectively). The proportion of subjects that withdrew from the study due to any AE (7.3%, 6.6% and 5.6%, respectively) or due to pre-specified NSAID associated UGI AEs (1.2%, 1.6% and 2.4%, respectively) was also similar in all 3 treatment groups.

Results of non-inferiority study PN400-309

Patient disposition, baseline patient characteristics, treatment compliance

Of the 610 randomised patients, 607 were included in the ITT efficacy analysis (Vimovo=244, celecoxib=241, placebo= 122). Approximately 83% of subjects treated with Vimovo completed the study, while 76% of the celecoxib group and 79% of the placebo group completed. Withdrawal of consent was the most frequent reason for discontinuation (7%, 10% and 12%, respectively).

The PP population excluded 20 subjects (8%) from the Vimovo group, 33 subjects (13%) from the celecoxib treatment group and 15 subjects (12%) from the placebo group; non-compliance was the major protocol violation across all treatment groups.

A majority of the patients were female (64%), White (80%), non-smokers (83-90%) with mean age of 62 years (all except one subject were aged >60 years with 33% >65 years). A larger proportion of the celecoxib population was classified as ACR Functional Class III (30%, compared to 19% of the Vimovo group and 25% of the placebo group) indicating that patients in the celecoxib group had more severe OA. All subjects had a diagnosis of OA of the knee. Stiffness and/or crepitus were present in > 84% of each treatment group. The mean baseline pain for WOMAC question 1 was approximately 76-80 mm across treatment groups. More than 99% of subjects met all 3 criteria for OA flare at randomization and 18-28% of subjects were using LDA at randomization. The baseline demographics and disease characteristics were generally comparable among the 3 treatment groups although there were slight differences in age, gender and smoking status. Ibuprofen was the usual pain medication taken for OA pain prior to randomization (34% of the Vimovo treatment group, 34% of the celecoxib group, and 44% of the placebo group). Naproxen, paracetamol and celecoxib were taken previously by 28%, 22% and 16% of all subjects respectively. All subjects had medical co-morbid conditions (hypertension, musculoskeletal and endocrine/ metabolic most common) and use of antihypertensive drugs was similar across treatment groups. The majority of subjects (>

90%) in all 3 treatment groups had ≥ 70% compliance from baseline to Week 6 and baseline to last dose. Compliance with study drug dosing was balanced across the 3 treatment groups.

Primary efficacy results

Non-inferiority (NI) of Vimovo compared to celecoxib was established, since the upper bound of the 2-sided 95% CI for the treatment difference was ≤10mm for WOMAC Pain (LSM of Vimovo-celecoxib=-1.30, 95% CI: -5.94, 3.34) and Function (LSM diff=-2.11, 95% CI: -6.82, 2.60) domains, and the lower bound of the 95% CI was ≥ -10mm for the PGA-VAS (LSM diff=3.45, 95% CI: -1.41, 8.31) (Tables 12, 13 and 14). The non-inferiority of Vimovo to celecoxib 200 mg once daily was also confirmed in the PP population analysis.

Table 12: PN400-309 NI analysis of WOMAC pain at Week 12 (ITT population with LOCF)

	PN 400 bid N=241	Celecoxib 200 qd N=244	PN 400 bid minus Celecoxib 200 qd
Baseline			
N	213	220	
Mean (SD)	69.6 (18.2)	71.3 (16.6)	
Week 12			
N	213	220	
Mean (SD)	25.6 (26.2)	27.6 (25.3)	
Week 12 Change from Baseline			
N	213	220	
Mean (SD)	-44.1 (27.5)	-43.6 (25.2)	-0.42
ANCOVA			
LS Mean	-44.24	-42.94	-1.30
95% Confidence Interval			(-5.94, 3.34)

Source: Table 14.2.1
ANCOVA = Analysis of Covariance; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; WOMAC = Western Ontario and McMaster Osteoarthritis Index
Note: a negative change from Baseline indicates improvement

Table 13: PN400-309 NI analysis of WOMAC function at Week 12 (ITT population with LOCF)

	PN 400 bid N=241	Celecoxib 200 qd N=244	PN 400 bid minus Celecoxib 200 qd
Baseline			
N	213	220	
Mean (SD)	66.7 (20.3)	68.7 (18.5)	
Week 12			
N	213	220	
Mean	28.0 (26.5)	31.0 (25.7)	
Week 12 Change from Baseline			
N	213	220	
Mean (SD)	-38.7 (27.2)	-37.7 (27.5)	-0.96
ANCOVA			
LS Mean	-38.90	-36.79	-2.11
95% Confidence Interval			(-6.82, 2.60)

Source: Table 14.2.1
ANCOVA = Analysis of Covariance; LOCF = last observation carried forward; LS = least squares; WOMAC = Western Ontario and McMaster Osteoarthritis Index
Note: a negative change from Baseline indicates improvement

Table 14: PN400-309 NI analysis of PGA-VAS at Week 12 (ITT population with LOCF)

	PN 400 bid N=241	Celecoxib 200 qd N=244	PN 400 bid minus Celecoxib 200 qd
Baseline			
N	235	234	
Mean	32.2 (23.4)	29.6 (20.4)	
Week 12			
N	235	234	
Mean	59.9 (27.7)	56.1 (25.8)	
Week 12 Change from Baseline			
N	235	234	
Mean	27.7 (34.8)	26.4 (30.3)	1.25
ANCOVA			
LS Mean	29.03	25.58	3.45
95% Confidence Interval			(-1.41, 8.31)

Source: Table 14.2.1
ANCOVA = Analysis of Covariance; LOCF = last observation carried forward; LS = least squares; PGA = patient global assessment; VAS = visual analog scale
Note: a positive change from Baseline indicates improvement

Secondary efficacy results

Only Vimovo (not celecoxib) showed statistically significantly ($p<0.05$) greater improvement in WOMAC- pain and function domains as well as PGA-VAS compared with placebo.

At Week 12, the LSM change from baseline in the mSODA average daily abdominal pain score showed improvement with all 3 treatments (LSM change was -4 with Vimovo, -3.4 with celecoxib and -4.3 with placebo) with no significant differences between groups; similar changes were seen at Week 6.

During Days 1-7, the proportion of patients who were responders (report of good or excellent on PGA-Likert scale) was similar in the Vimovo (51%), celecoxib (47%) and placebo (48%) groups. The median time to good or excellent response was 6.0 days with Vimovo and 7 days with celecoxib and placebo.

The change from baseline to Week 6 and Week 12 for the WOMAC total score, WOMAC stiffness and average daily pain scores was significantly better than placebo for Vimovo while celecoxib did not show any significant improvement over placebo. Furthermore, only Vimovo was associated with improvements in the MDHAQ scores for RAPID-3, pain, and patient global scores at Week 6 and Week 12; the APS-POQ questionnaire analysis also indicated better pain control with active treatments over placebo by Day 3 and similar pain control with Vimovo and celecoxib treatment from Day 1. Pain interference with general activities, walking and enjoyment of life, Interference with mood and relations, sleep and work also showed similar results.

Subjects in the Vimovo treatment group consistently had a significantly greater percentage of days with no heartburn compared to celecoxib and placebo (74%, 66% and 66%, respectively). There were no significant differences between active treatment groups in percentage of subjects who used paracetamol (77%, 72% and 85% in Vimovo, celecoxib and placebo groups, respectively) but the mean number of tablets were also lesser in the Vimovo and celecoxib groups compared with placebo (50, 55 and 68 tablets, respectively). The percentage of subjects who used antacids was similar in all 3 treatment groups (50%, 53% and 53% in Vimovo, celecoxib and placebo groups, respectively), although the mean

number of tablets consumed were lesser in the Vimovo group (28, 35 and 39, respectively).

Supportive studies

PN400-303 was a 6 month, randomized, double blind, parallel group, controlled, multicentre study to evaluate the incidence of gastric ulcers with Vimovo versus diclofenac/misoprostol (Arthrotec) in subjects who were at high risk for developing NSAID associated ulcers. Although the study was supposed to enrol 200 subjects, only 20 subjects were treated and the study was terminated (due to low enrolment and after consultation with the FDA); none of the 20 subjects had completed 6 months of treatment and hence no relevant results are available from this Phase III study.

An open label, multicentre, 12 month study PN400-304 evaluated the long term safety of Vimovo in 239 patients at high risk of NSAID associated ulcers. The study was conducted at 58 centres in USA from 7 October 2007 to 16 March 2009. The inclusion and exclusion criteria were similar to those in the pivotal Phase III studies PN400-301 and PN400-302. All subjects were instructed to take two Vimovo tablets a day; 1 in the morning and 1 in the afternoon/evening, each tablet was to be taken 30-60 min before a meal. Compliance was assessed by the investigator and/or study personnel at each visit using tablet counts and information provided by the subject. The importance of study drug compliance was reiterated to the subject at each visit and by telephone every month. Efficacy was not evaluated in this open label study.

A majority of the patients were female (70%), White (88%), non-smokers (87%) with mean age of 62 years (only 8 subjects were <50years old). NSAIDs were previously used by 79% of all subjects for treating OA, 9% for treating rheumatoid arthritis and 1% for treating ankylosing spondylitis. Most of the "other" indications for NSAID use were back pain, chronic back pain, low back pain, or other back conditions (in 28 of the 52 subjects). Approximately 59% of all subjects had a history of UGI disorder. Approximately 59% of all subjects had a history of cardiovascular disorder, and 31% were using LDA. Baseline characteristics of 12 month completers were similar to those of the overall safety population. The majority of subjects (98% of the overall safety population and 100% of 12 month completers) had ≥ 70% overall compliance.

Overall, 82% of the patients required rescue treatment with paracetamol (mean tablet intake was 118 tablets; 67% of the patients required treatment with antacids (mean tablet intake 12). There were 45 subjects (19%) in the overall safety population and 22 (16%) in the 12-month completer population with at least 1 of the pre-specified NSAID associated UGI AEs. Dyspepsia was the most frequent AE, occurring in 8% of the overall safety population and 6% of 12 month completers.

Persistence of efficacy and/ or tolerance effects

While no direct measurements of efficacy were made in the open label, 12 month safety study (PN400-304), several safety endpoints support the improved tolerability findings of the controlled Phase III studies presented above are sustained beyond 6 months. Compliance with Vimovo was greater than 95% in patients who completed the study, and more than 97% of the patients had >70% compliance. Patients in the study used more than 58 doses per month on average. There was no evidence of loss of effect of Vimovo in the reduction of the occurrence of respecified UGI AEs. Discontinuations due to UGI disorders occurred primarily in the first 6 months of therapy with Vimovo. There was no evidence of loss of analgesic effect over the period of the adequate and well controlled studies PN400-307 and PN400-309 (12 weeks) and withdrawals as a whole or due to lack of efficacy in PN400-304 were not time related.

Clinical studies in special populations

Efficacy in patients using LDA

In study PN400-301, of the LDA users, 89% in Vimovo and 78% in delayed release (DR) naproxen treatment groups took 81 mg; it is important to note that aspirin dose of 325 mg was used by more subjects in the naproxen group (20%) compared with the Vimovo group (8%). In the Vimovo group, subjects taking LDA had a lower rate of gastric and/or duodenal ulcers at each study period than subjects not using low dose aspirin (1.9% vs 5.5%, respectively, by 6 months), while in the naproxen group gastroduodenal ulcer rates were similar regardless of LDA use (28% in both groups).

In study PN400-302, of the LDA users, 80% in Vimovo and 77% in DR Naproxen treatment groups took 81 mg. An aspirin dose of 325 mg was used by 17% Vimovo and 20% DR Naproxen subjects. In the Vimovo group, subjects taking LDA had a lower rate of gastric and/or duodenal ulcers at each study period than subjects not using low dose aspirin (7% vs 9%, respectively, by 6 months), while in the naproxen group gastroduodenal ulcer rates were higher among LDA users compared non-users (37% vs 25% at 6 months).

The above results from the pivotal studies suggest that the benefit of Vimovo was maintained with concomitant use of LDA.

Effect of age and ulcer history on efficacy of Vimovo

In pivotal studies PN400-301 and PN400-302, the effect of baseline covariates on the primary efficacy endpoint was analysed using a conditional logistic regression model. The model included treatment as main effect, use of LDA (Yes/No) and the effect of baseline risk factors (age and ulcer history within the previous 5 years).

Both age and use of LDA increased the GU incidence rate in EC naproxen users, but had no effect on the incidence rate of GUs in patients taking Vimovo. In the Vimovo group, the proportion of patients with a GU was lower in the ≥60 year age group than in the <60 year age group (2.8% vs 8.3%). Conversely, in the EC naproxen group, the incidence rate of GUs was higher in patients older than 60 years than in younger patients (26.3% vs 21.2%). Although the sample size of patients ≥70 years was small (55 patients taking Vimovo and 67 patients taking EC naproxen) the incidence of GU was significantly lower in the Vimovo group compared with placebo (0% vs 22.4%).

The number of patients who entered either study with a history of ulcer (GU or DU) within the previous 5 years was very small (N=69); therefore, no substantive analyses could be made of the effect of prior ulcer on the efficacy of Vimovo. Of the patients assigned to Vimovo who had a history of GU or DU, 0% and 16.7% in studies PN400-301 and PN400-302, respectively developed a GU. In contrast, in the EC naproxen group, 61.5% (8/13) and 39.1% (9/23) of patients with such a history developed a GU in PN400-301 and PN400-302, respectively.

The most significant gastroprotective effect (in terms of cumulative proportions of patients with GU at 6 months) of Vimovo over naproxen was evident in patients who had history of ulcer and used LDA (0% vs 60% n Vimovo and naproxen groups, respectively).

Effect of gender, race and smoking

The observed incidence of GUs in the combined data at 1, 3 and 6 months was not different between female and male patients or between White and non-White patients. However, Asian and other races were not represented in significant numbers. In the combined studies, the proportion of patients who smoked was about 16% (N=133). In smokers, the cumulative GU rates at 6 months were similar in the Vimovo group and EC naproxen group (16.2% vs 16.7%). However, in the subgroup of non-smokers, cumulative 6 month GU

rates were significantly lower in the Vimovo group compared with the EC naproxen group (3.6% vs 24.9%). It does appear that the gastroprotective effect of Vimovo was not clearly evident in smokers, although the small sample size, combined with the fact that randomisation to study treatment was not stratified by smoking status, makes it difficult to draw any conclusions from these data.

Subgroup analysis in non-inferiority supportive studies

In the combined analyses of studies PN400-307 and PN400-309, non-inferiority between Vimovo (500/20 mg bd) and celecoxib 200 mg od was demonstrated in the age groups <65 years and >65 to 70 years. NI could not be demonstrated in the age group >75 years (n=81) or in the Hispanics/ Latinos (n=67) due to the small numbers in these subgroups. With regard to the effects of smoking, although there was a trend towards reduced effect of Vimovo in smokers compared to non-smokers, interpretation of this data was confounded by the small number of smokers in the combined analysis (N=68 for Vimovo, N=75 for celecoxib) combined with the fact that randomisation to study treatment was not stratified by smoking status.

Analysis performed across trials (pooled analysis and metaanalysis)

Pooled efficacy results from pivotal, 6 month studies PN400-301 and PN400-302

In the combined analysis, fewer patients who were randomised to Vimovo had GUs than did patients randomised to EC naproxen at 1 month (1.6% and 11.5%, respectively), 3 months (3.3% and 18.5%, respectively) and 6 months (5.6% and 23.7%, respectively) (Table 15).

Table 15: Proportion of patients developing GI throughout 6 months estimated from survival analysis (combined analysis)

	PN 400 (N=428)[a]	EC naproxen (N=426)[a]
Proportion of patients with gastric ulcer (95% confidence Interval)[b]		
0 – 1 month	1.6% (0.8%-3.4%)	11.5% (8.8%-14.9%)
0 – 3 months	3.5% (2.1%-5.9%)	20.2% (16.5%-24.6%)
0 – 6 months	6.6% (4.5%-9.8%)	28.3% (23.8%-33.4%)
Observed gastric ulcer through 6 months, n (%)		
No	404 (94.4%)	325 (76.3%)
Yes	24 (5.6%)	101 (23.7%)
95% confidence interval	(3.6%-8.2%)	(19.7%-28.0%)

[a] Intent-to-treat population.
[b] Patients who did not have gastric ulcer were censored at the 6-month endoscopic assessment, or at the last assessment date.
EC Enteric coated; GU Gastric ulcer; N Number of patients in treatment group; n Number of patients in category.

A sensitivity analysis (ITT population) estimated GU rates by broadening the definition of a GU to include DU or a discontinuation due to a UGI AE. This analysis yielded estimated GU rates of 7.3% (95% CI: 4.3% to 11.6%) in the patients who took Vimovo and 35.2% (95% CI: 28.8% to 42%) in those who took EC naproxen (p<0.001) in study PN400-301. The same sensitivity analysis applied to study PN400-302 gave estimated GU rates of 11.9% (95% CI: 7.9% to 17.1%) in the patients who took Vimovo and 36.2% (95% CI: 29.7% to 43.1%) in those who took EC naproxen (p<0.001).

In the combined analysis, patients treated with EC naproxen had a 5.4% incidence of DUs throughout 6 months, compared to only 0.7% of those taking Vimovo. Most DUs occurred in the first 3 months of treatment. Differences were significant at 1, 3 and 6 months (p< 0.001). The analysis of time to DU occurrence also indicated that DUs occurred significantly sooner and in more patients (p<0.001) in the EC naproxen group than in the Vimovo group.

In the combined analysis, a significantly lower proportion of patients (p<0.001) who took Vimovo had pre-specified NSAID associated UGI AEs or DUs by 6 months than did those who took EC naproxen) (53.3% vs 70.4%, p<0.001) (Table 16). The largest differences were observed in the reduction of erosive gastritis, duodenitis, erosive duodenitis, oesophagitis, and erosive oesophagitis in patients who took Vimovo compared to those who took EC naproxen. Patient reported events of upper abdominal pain in the Vimovo group were approximately one half of those in EC naproxen group. Furthermore, fewer patients who were treated with Vimovo discontinued from the studies due to pre-specified NSAID associated UGI AEs and/or DUs compared with patients who took EC naproxen (4.0% vs 12.0%, p<0.001).

Table 16: Proportions of patients with any 3 specified NSAIDs Associated UGI AE and/or DU (combined analysis)

	PN400-301		PN400-302		Combined studies	
	PN 400 (N=218) n (%)	EC naproxen (N=216) n (%)	PN 400 (N=210) n (%)	EC naproxen (N=210) n (%)	PN 400 (N=428) n (%)	EC naproxen (N=426) n (%)
Any UGI AE and/or DU[a]						
No	104 (47.7)	67 (31.0)	96 (45.7)	59 (28.1)	200 (46.7)	126 (29.6)
Yes	114 (52.3)	149 (69.0)	114 (54.3)	151 (71.9)	228 (53.3)	300 (70.4)
95% CI	(45.4 - 59.1)	(62.4 - 75.1)	(47.3 - 61.2)	(65.3 - 77.9)	(48.4 - 58.1)	(65.8 - 74.7)

[a] p<0.001 between the groups in each of the studies and in the combined studies.

Note: p-value is from Cochran-Mantel-Haenszel test stratified by low-dose aspirin use at randomisation, as reported on the concomitant medications case report form page.

AE Adverse event; CI Confidence interval; DU Duodenal ulcer; EC Enteric coated; ITT Intent-to-treat; N Number of patients in treatment group; n Number of patients in category; NSAID Non-steroidal anti-inflammatory drug; UGI Upper gastrointestinal.

Heartburn resolution was observed in significantly greater proportion of patients in the Vimovo group (63.7%, 71.0% and 76.1% at 1, 3 and 6 months, respectively) compared with the EC naproxen group (44.0%, 46.3% and 53.8%, respectively) (p<0.001 at all time points). The effect of treatment with Vimovo on the resolution of heartburn by treatment group was not affected by the severity of heartburn symptoms at baseline. Significantly more patients who took Vimovo (44.3%) reported improvement in upper abdominal pain or discomfort than did those who took EC naproxen (31.1%; p<0.001) and those patients who took Vimovo reported their improvement to have a higher grade of importance. In addition, significantly more patients treated with EC naproxen reported worsening upper abdominal pain or discomfort (20.3%) compared to patients treated with Vimovo (8.8%, p<0.001).

Improvement in dyspepsia symptoms demonstrated by SODA scores for both pain/non-pain symptoms and for satisfaction improved in those patients who took Vimovo compared to those who took EC naproxen at 1, 3 and 6 months in PN400-301 and PN400-302.

Pooled efficacy results from supportive, 3 month non-inferiority studies PN400-307 and PN400 -309.

In the primary analyses based on the ITT population, Vimovo was non-inferior to celecoxib (200 mg od) in both PN400-307 and PN400-309 with regard to changes from baseline to Week 12 in WOMAC Pain, WOMAC Function and PGA-VAS scores. The upper limits of the 95% CIs for the WOMAC Pain and Function scores were <10 and the lower limit of the 95% CI for the PGA-VAS was >-10, indicating that the pre-specified NI margin of 10 mm was met for each endpoint (Table 17).

Table 17: LSM changes in WOMAC pain, function and PGA-VAS from baseline to 12 weeks (combined analysis)

	PN 400	Celecoxib	PN 400 minus celecoxib (95% CI)
WOMAC pain	-43.1	-42.3	-0.8 (-4.0, 2.5)[a]
WOMAC function	-37.6	-36.6	-1.0 (-4.3, 2.2)[a]
PGA-VAS	25.0	23.6	1.4 (-1.9, 4.8)[b]

[a] A negative difference favours PN 400.
[b] A positive difference favours PN 400.
CI Confidence interval; ITT Intent-to-treat population; LS Least squares; PGA-VAS Patient Global Assessment on a Visual Analogue Scale; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.
Source: Module 5.3.5.3, Table E2.4.

In both studies Vimovo was significantly better than placebo for changes in both WOMAC domains (pain and function) and PGA-VAS. However, celecoxib was significantly better than placebo for all 3 co-primary endpoints only in study PN400-307 but not in study PN400-309.

In general, changes in mSODA score were similar for Vimovo, celecoxib, and placebo. All 3 treatment groups in both studies showed reductions in mSODA average daily pain score from baseline to Week 12, and the differences between groups were not significant. The combined analysis of time to first response of PGA-Likert scale “good” to “excellent” response during Days 1 to 7 demonstrated no difference between Vimovo, celecoxib, and placebo.

Patients in the Vimovo treatment group consistently had a significantly greater percentage of days with no heartburn (LSM= 76.4%), compared to celecoxib (68.8%) and placebo (66.2%). No significant difference was observed between celecoxib and placebo.

Improvement in the pain component of OA of the knee within the first week of treatment was similar between the active medications, Vimovo and celecoxib, when analysed using changes in the APS-POQ scores and the WOMAC pain scores on the first 7 days of treatment. WOMAC pain scores in PN400-307 and PN400-309 show that both Vimovo and celecoxib provided significant pain relief compared to placebo within 24 to 48 h after treatment initiation.

Analyses of MDHAQ RAPID-3, Physical Function, Pain and Patient Global scores from patients in both studies demonstrated similarity in changes in scores between baseline, 6 and 12 weeks whether they were treated with Vimovo or celecoxib. These analyses also demonstrated consistently greater changes in the Vimovo and celecoxib groups than in the placebo groups with respect to RAPID-3 physical functions, pain and patient global scores.

By 12 weeks, the proportion of patients who met the Outcome Measures in Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria for response to treatment were similar in the Vimovo and celecoxib treatment groups

(75.9% and 75.0%, respectively) but were higher than in the placebo group (64.8%). The comparison of Vimovo vs placebo was significant at Week 6 and Week 12, as was the comparison of celecoxib vs placebo at Week 12.

In both studies, discontinuation rates were generally similar in Vimovo, celecoxib and placebo groups although discontinuations due to pre-specified NSAID associated UGI AEs were slightly lower in the Vimovo treatment group.

Evaluator's overall comments on clinical efficacy

The efficacy of both components of Vimovo (EC naproxen/ IR esomeprazole 500 mg/ 20 mg) was evaluated in 5 Phase III studies involving 1166 patients with OA, RA and/or AS who were at risk of developing NSAID associated gastric/duodenal ulcer. The main risk factors for UGI ulcers in NSAID users are age 50 years and older (Hernandez-Diaz 2000, Boers 2007), a history of UGI ulcer or bleeding, and concomitant aspirin use (Laine 2006).[25,26,27] A majority of the patients included in the Vimovo studies were >50 years old (mean age of 62 years), almost 25% were taking concomitant LDA and about 6-11% had history of gastric/duodenal ulcer in past 5 years. Hence, the patients evaluated in the Vimovo studies were representative of the target patient population for Vimovo. The pivotal studies comply with TGA-adopted EU guidelines on fixed combination medicinal products in which one product counteracts "an adverse reaction produced by another one" that is a serious and commonly occurring adverse reaction.[28] In Vimovo, esomeprazole is combined with an EC naproxen core to reduce the risk of GUs and DUs associated with naproxen use.

The efficacy of the esomeprazole component of Vimovo in reducing the occurrence of GUs, DUs, and other NSAID associated UGI events was evaluated in 2 pivotal Phase III, 6 month studies (PN400-301 and PN400-302) involving 854 patients with chronic inflammatory arthritis (OA, RA, AS or any other medical condition) that required daily use of NSAID; EC-naproxen was used as the active control drug in these studies. Efficacy of naproxen for symptomatic relief of OA, RA and AS was not specifically evaluated in these pivotal studies. The studies were well designed and conducted with minimal protocol violations. The efficacy, safety and tolerability variables assessed in the pivotal studies are commonly used in clinical trials of PPIs and NSAIDs. A majority of the patients in the pivotal trials were females, White, non-smokers with diagnoses of OA and mean age of 62 years; approximately 23% were using concomitant LDA. Overall, the patients in the pivotal studies were representative of the target patient population requiring symptomatic relief in treatment of OA, RA and AS and at risk of developing NSAID associated GUs and/or DUs.

Studies PN400-301 and PN400-302 demonstrated individually and when combined that the use of Vimovo results in a significantly lower proportion of patients with NSAID associated GUs or DUs over 6 months of treatment. The effect was consistent through the 6 months of treatment. This was supported by significant improvements in heartburn, severity of dyspepsia and fewer discontinuations due to AEs.

[25] Hernández-Díaz S, Garcia Rodríguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation. Arch Intern Med 2000; 160: 2093-9.

[26] Boers M, Tangelder MJD, van Ingen H, Fort JG, Goldstein JL. The rate of NSAID-induced endoscopic ulcers increases linearly but not exponentially with age: a pooled analysis of 12 randomised trials. Ann Rheum Dis 2007; 66: 417-8.

[27] Laine L. GI risk and risk factors of NSAIDs. J Cardiovasc Pharmacol 2006; 47: S60-6.

[28] EMEA, Committee for Medicinal Products for Human Use (CHMP), 13 October 2005. Note for Guidance of Fixed Combination Medicinal Products, CPMP/EWP/240/95.

The efficacy of Vimovo in the management of the signs and symptoms of OA was based on known efficacy of naproxen for the proposed indications and the bioequivalence of Vimovo to currently marketed formulations of EC naproxen. Additional evidence of similar analgesic effects was provided in patients with OA of the knee in 2 non-inferiority studies (PN400-307 and PN400-309).

In these NI studies, 12 weeks treatment with Vimovo was not inferior to celecoxib (200 mg qd) with regard to WOMAC pain and function changes and PGA-VAS. Both studies met the pre-specified NI margin, showing Vimovo to be similar to celecoxib in the treatment of the signs and symptoms of OA of the knee as assessed by all 3 co-primary variables in the ITT and the PP analysis. With respect to comparisons of Vimovo with placebo, both studies gave similar results. In Study PN400-307, both Vimovo and celecoxib were significantly different from placebo. In Study PN400-309, while the treatment differences seen were numerically similar to those seen in PN400-307 and treatment responses were at least as large as those seen in published studies, the Vimovo vs placebo comparison reached statistical significance but the celecoxib vs placebo comparison did not. Both active treatments showed similar responses in a variety of secondary endpoints associated with the measurement of pain response, confirming that Vimovo was not inferior to celecoxib in this regard. The proportion of Vimovo subjects who discontinued from the study due to any AE or due to any pre-specified NSAID associated UGI AE was similar to celecoxib. Furthermore, Vimovo treatment resulted in a significantly greater percentage of heartburn-free days than celecoxib and significantly less rescue antacid use than celecoxib.

The efficacy of Vimovo compared to EC naproxen alone in terms of reducing risk of gastric ulcers was shown in subgroups of patients aged >60 years, using concomitant LDA and those with history of gastric ulcer. The most significant gastroprotective effect (in terms of cumulative proportions of patients with GU at 6 months) of Vimovo over naproxen was evident in patients who had history of ulcer and used LDA (0% vs 60% in Vimovo and naproxen groups, respectively). Age and gender did not appear to have any significant effect on the efficacy of Vimovo. The number of non-Whites was too small to enable interpretation of effect of race on the efficacy of Vimovo. It does appear that the gastroprotective effect of Vimovo was not clearly evident in smokers, although the small sample size, combined with the fact that randomisation to study treatment was not stratified by smoking status, makes it difficult to draw any conclusions from these data.

Safety

Introduction

The Primary Safety Population (PSP) from the 6 month pivotal studies PN400-301 and PN400-302 provided the safety profile for the studies that were used to generate the primary efficacy endpoints in support of approval of Vimovo; the PSP included 428 and 426 patients treated with Vimovo and EC Naproxen, respectively. All patients in this pool had protocol required endoscopies to assess the primary endpoint of gastric ulcer; the PSP also allows the assessment of effects of Vimovo versus naproxen on the oesophageal, gastric and duodenal mucosal surfaces. The primary endpoint of gastric ulcers and the secondary endpoint of duodenal ulcers were assessed as a treatment emergent adverse event (TEAE) in this safety summary.

The Supportive Safety Population (SSP) included patients from 3 month studies PN400-307 and PN400-309 (490, 488 and 246 patients treated with Vimovo, celecoxib and placebo, respectively). These 3 month studies were designed to assess the signs and symptoms of osteoarthritis as the primary endpoint, and used adverse events, laboratory evaluations, vital signs and physical examinations to assess safety. The SSP differs from

the PSP in the requirement for OA flare (prior to randomisation), in the duration of treatment and that endoscopies were done only if clinically indicated.

The Long term study Safety Population (LSP) included the 239 patients with a history of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis or other medical conditions expected to require daily NSAID therapy for at least 12 months in the open label one year study PN400-304; this included 135 patients that completed 12 months of treatment with Vimovo (defined as a minimum of 348 days of treatment) and formed the Twelve Month Population (TMP). The Six Month Population (SMP) included patients from studies PN400-301, PN400-302 and PN400-304 who completed 6 months of treatment (defined as at least 168 days of treatment) with Vimovo or EC naproxen. The LSP and SMP pools allowed the examination of the effects of time on the safety profile of Vimovo.

Studies PN400-301, PN400-302, PN400-307, PN400-309, and PN400-304 were combined as the Expanded Safety Population (ESP) to provide the largest pool of 1157 patients who took Vimovo (Table 18).

Table 18: Pooled populations for safety comparisons

Named integrated pools and populations						
	PSP	**SSP**	**ESP**	**OAP[a]**	**SMP**	**LSP[b]**
Description	PN 400 vs. EC naproxen, Protocol required endoscopies	PN 400 vs. celecoxib and placebo, endoscopy done only if clinically indicated	Largest pool of patients who took PN 400	Patients in the ESP with osteoarthritis	Includes patients who completed 6 months treatment with PN 400 or EC naproxen	Includes 135 patients who completed 12 months treatment with PN 400 and make up the TMP
Studies	PN400-301 PN400-302	PN400-307 PN400-309	PN400-301 PN400-302 PN400-307 PN400-309 PN400-304	PN400-301 PN400-302 PN400-307 PN400-309 PN400-304	PN400-301 PN400-302 PN400-304	PN400-304
Total number of subjects exposed (patient years)						
Treatment						
PN 400	428 (174.8)	490 (104.8)	1157 (456.8)	951[a] (346.5)	491 (319.8)	239[b] (177.2)
EC Naproxen	426 (142.2)	--	--	--	220 (109.4)	--
Celecoxib	--	488 (101.4)	--	--	--	--
Placebo	--	246 (51.6)	--	--	--	--

Source: Module 5.3.5.3 Table S2.1, Table S3.1, Table S4.1, Table S5.1, Table S6.1, and Module 5.3.5.2, Study PN400-304, Table 14.1.1
[a]This number represents the number of patients with OA in the ESP
[b]This is the number of patients who started the trial. There were 135 subjects who completed the trial and make up the TMP.
PSP Primary safety population; SSP Supportive safety population; ESP Expanded safety population; OAP Osteoarthritis population; SMP 6-month population; LSP Long-term safety population, TMP Twelve month population.

Study PN400-303 was the only study designed and conducted to evaluate patients at high risk (defined as having a documented history of a serious upper gastrointestinal event such as perforation, obstruction or bleeding) with NSAID use. This study was discontinued after 20 patients were enrolled because of difficulty in enrolling the pre-specified study population.

This population was not included in any of the TEAE or laboratory pools but was included in the exposure, serious adverse events (SAEs) and discontinuations.

As part of the Vimovo development program, an independent gastrointestinal adjudication committee (GI-IAC) was chartered. The GI-IAC was charged with the blinded review and adjudication of clinically significant GI adverse events (all serious GI AEs and all other symptomatic GI AEs) that occurred in the course of the Phase III Vimovo development program.

In addition, a separate, independent Cardiovascular (CV) Endpoint Committee was chartered to assess cardiovascular SAEs and other AEs. The primary charge of the CV Endpoint Committee was to assess all serious CV events and any deaths reported by investigators during the course of the Vimovo development program using the Anti-platelet Trialist Collaborative (APTC) defined endpoints and other non-APTC major adverse cardiovascular events (MACE). The APTC endpoints include cardiovascular deaths (including sudden death or death attributable to cardiac causes), nonfatal myocardial infarction and nonfatal stroke; the MACE endpoints include unstable angina, coronary and cerebral revascularisation, transient attacks, venous and/or peripheral arterial vascular thrombotic events (for example, deep venous thrombosis, pulmonary embolism, arterial occlusive disease), congestive heart failure, atrial and ventricular arrhythmias (without evidence of acute ischemia), syncope from a cardiovascular aetiology.

Patient exposure

Overall, 2337 subjects treated in 6 Phase III studies and 317 normal healthy volunteer (NHV) subjects in 8 Phase I studies. A total of 1385 subjects received Vimovo in the clinical development program including 219 normal healthy volunteers and 1166 patients. Another 54 patients received a lower than proposed dose of naproxen/esomeprazole 325 mg/20 mg in Phase I studies PN400-105 and PN200-015. Overall, 579 patients received naproxen (153 in Phase I studies and 426 in Phase III studies), 488 received celecoxib (200 mg qd), 246 received placebo and only 11 patients received Arthrotec (diclofenac/ misoprostol). Of the 1166 patients exposed to Vimovo, 491 were exposed for at least 6 months and 135 were exposed for 12 months. More than 360 doses were taken by 264 subjects and more than 180 doses were taken by 561 subjects. The average number of doses of Vimovo taken over 12 months was 695.6 ± 43.7 and over 6 months was 348.9 ± 27.5 (Table 19).

Table 19: Number of Vimovo subjects treated by exposure in all clinical studies

Duration of study drug exposure (days)							
Total doses taken	1	2 to 14	15 to 30	31 to 90	91 to 181	>180	Total
1	115	1	0	0	0	0	116
2 to 28	21	104	8	9	1	0	143
29 to 60	0	1	48	10	1	0	60
61 to 180	0	1	6	461	34	1	503
181 to 360	0	0	0	13	185	99	297
>360	0	0	0	0	12	252	264
Total	136	107	62	493	233	352	1383

Source: Module 5.3.5.3, Table S1.1 updated with additional exposure data from Module 5.3.1.2, Study PN400-108, Listing 12.2.5

The demographics and baseline disease characteristics of patients in the various Phase III safety populations were generally similar. A majority of the patients were female (66%), White (80-90%), with mean age of 60 years; 23-30% were taking low dose aspirin and 56% of patients had history of some CV disease. The various safety populations showed differences in terms of UGI history (52%, 69%, 34% and 59% in the ESP, PSP, SSP and TMP, respectively).

Overall, the safety of Vimovo was evaluated in an adequate number of patients who were representative of the target patient population.

Adverse events

AEs in healthy volunteers (Phase I studies):

Pooling of the Normal Healthy Volunteer (NHV) studies (Phase I studies) was not performed due to the variable designs and contexts of the studies. All NHV studies except PN400-101 were crossover designs, therefore, the pooling of adverse events or lab changes would be difficult to interpret. Eight Vimovo Phase I studies in healthy volunteers enrolled a total of approximately 335 subjects of whom 219 received Vimovo at least once. Reporting of adverse events was consistent across study treatments and studies. The related events were predominantly in the *Gastrointestinal Disorders* System Organ Class (SOC) comprising abdominal pain, nausea, diarrhoea and occasionally dyspepsia, oesophageal ulcer and constipation. Other events typical of Phase I studies included headache, fatigue and dry mouth and isolated reports of dizziness, eye pruritus and pharyngeal pain. The majority of the TEAEs seen in these studies were mild in severity, a few were of moderate severity and none were reported as severe.

AEs in the PSP (Primary safety population)

Overall, a lower proportion of patients who took Vimovo (78.3%) reported TEAEs than those who took EC naproxen (87.6%). The majority of TEAEs occurred in the SOC of *Gastrointestinal Disorders* with reduced rates in patients who took Vimovo compared to EC naproxen especially reductions in gastric and duodenal ulcers, and less injury to the upper GI tract seen at endoscopy. Additionally, lower rates of dyspepsia, heartburn and upper abdominal pain were seen with Vimovo compared to EC naproxen. The incidence of diarrhoea and gastritis was slightly higher in patients who took Vimovo compared to EC naproxen. The only other non-GI AEs more common in the Vimovo group were headaches and respiratory infections (Table 20).

Table 20: TEAEs occurring at ≥2% in the PSP

Preferred terms	PN 400 n (%) N=428	EC Naproxen n (%) N=426
Subjects with any Adverse Event	335 (78.3)	373 (87.6)
Gastritis erosive	83 (19.4%)	162 (38.0%)
Dyspepsia	77 (18.0%)	114 (26.8%)
Gastritis	73 (17.1%)	60 (14.1%)
Diarrhoea	26 (6.1%)	22 (5.2%)
Abdominal pain upper	24 (5.6%)	37 (8.7%)
Gastric ulcer	24 (5.6%)	101 (23.7%)
Nausea	22 (5.1%)	21 (4.9%)
Upper respiratory tract infection	21 (4.9%)	16 (3.8%)
Hiatus hernia	18 (4.2%)	25 (5.9%)
Abdominal distension	16 (3.7%)	16 (3.8%)
Flatulence	16 (3.7%)	13 (3.1%)
Oesophagitis	15 (3.5%)	32 (7.5%)
Constipation	11 (2.6%)	12 (2.8%)
Headache	11 (2.6%)	6 (1.4%)
Abdominal pain	10 (2.3%)	7 (1.6%)
Bronchitis	10 (2.3%)	8 (1.9%)
Cough	10 (2.3%)	11 (2.6%)
Urinary tract infection	10 (2.3%)	6 (1.4%)
Abdominal pain lower	9 (2.1%)	11 (2.6%)
Dysgeusia	9 (2.1%)	6 (1.4%)
Erosive duodenitis	9 (2.1%)	50 (11.7%)
Sinusitis	8 (1.9%)	9 (2.1%)
Duodenitis	6 (1.4%)	31 (7.3%)
Arthralgia	5 (1.2%)	10 (2.3%)
Gastritis hemorrhagic	5 (1.2%)	9 (2.1%)
Gastroesophageal reflux disease	4 (0.9%)	15 (3.5%)
Nasopharyngitis	4 (0.9%)	10 (2.3%)
Duodenal ulcer	3 (0.7%)	23 (5.4%)
Erosive oesophagitis	2 (0.5%)	24 (5.6%)

Source: Module 5.3.5.3, Table S2.4.
N Total number of patients; n Number of patients; PSP Primary safety population.

There were a higher proportion of patients in the EC naproxen group than in the Vimovo group with TEAEs that were considered by the investigator to be related to study treatment (75.8% vs 53.5%). This difference was primarily due to reports of TEAEs in the

SOC of *Gastrointestinal Disorders*. The preferred term gastritis was the only related TEAE more frequently reported in patients taking Vimovo (15.0%) than in patients taking EC naproxen (12.2%).The only related TEAE in the SOC of *Cardiac Disorders* was a single case of angina in a subject from the EC naproxen group.

The incidence of severe TEAEs and of moderate and severe TEAEs was higher in the EC naproxen group (13.4% and 53.3% reported moderate and severe AEs, respectively) compared with the Vimovo group (9.1% and 39.9%, respectively). Similarly, the incidence of severe GI TEAEs was higher in the EC naproxen group compared with Vimovo (9.6% vs 6.1%) with similar results for the combined moderate/severe GI AEs (40.1% vs 23.6%). There were no major differences in the severity of the TEAEs between treatment groups for other TEAEs or SOCs in the PSP.

Patients who took Vimovo had no increases in rates of TEAEs from SOCs other than *Gastrointestinal Disorders* compared to EC naproxen except headaches and upper respiratory tract infections (URTIs). Cardiac disorders were generally balanced between Vimovo and EC naproxen (1.6% vs 1.4%) and occurred in patients with prior history and risk factors with rates that were consistent with other studies in these populations. Of the 284 patients who entered the PSP with no prior cardiovascular medical history, none reported any cardiovascular TEAEs.

AEs in the SSP (Supportive Safety Population)

The incidence of any TEAEs was similar in the Vimovo, celecoxib and placebo groups (53.3%, 49.6% and 51.2%, respectively). Dyspepsia was reported by slightly lesser proportion of patients treated with Vimovo (8.4%) compared with celecoxib (12.2%) and placebo (10.7%). However, patients assigned to Vimovo had more diarrhoea, constipation, dizziness and peripheral oedema than patients in the other treatment groups. Patients assigned to placebo reported more headache than those in the other treatment groups (Table 21).

Table 21: TEAEs occurring at ≥2% in the SSP

Preferred Terms	PN 400 n (%) N=490	Celecoxib n (%) N=488	Placebo n (%) N=246
Dyspepsia	41 (8.4%)	52 (10.7%)	30 (12.2%)
Diarrhoea	27 (5.5%)	14 (2.9%)	9 (3.7%)
Abdominal pain upper	20 (4.1%)	21 (4.3%)	8 (3.3%)
Constipation	17 (3.5%)	10 (2.0%)	3 (1.2%)
Nausea	17 (3.5%)	15 (3.1%)	9 (3.7%)
Dizziness	15 (3.1%)	4 (0.8%)	5 (2.0%)
Peripheral Oedema	15 (3.1%)	6 (1.2%)	3 (1.2%)
Headache	13 (2.7%)	18 (3.7%)	13 (5.3%)
Upper respiratory tract infection	8 (1.6%)	6 (1.2%)	5 (2.0%)
Arthralgia	7 (1.4%)	14 (2.9%)	4 (1.6%)
Cough	7 (1.4%)	3 (0.6%)	7 (2.8%)
Nasopharyngitis	7 (1.4%)	7 (1.4%)	5 (2.0%)
Back pain	6 (1.2%)	14 (2.9%)	5 (2.0%)
Sinusitis	5 (1.0%)	6 (1.2%)	6 (2.4%)
Gastroenteritis viral	3 (0.6%)	1 (0.2%)	5 (2.0%)
Pyrexia	1 (0.2%)	2 (0.4%)	5 (2.0%)

Source: Module 5.3.5.3, Table S3.4.
N Total number of patients; n Number of patients; SSP Supportive safety population; TEAE Treatment emergent adverse event.

Treatment related AEs were reported in 24.1% of patients taking Vimovo, 22.5% of patients taking celecoxib and 24.0% of patients taking placebo. The overall rate of related TEAEs in the SOC of *Gastrointestinal Disorders* was 17.9% and was balanced between the 3 groups. Dyspepsia was reported as related by 6.9% of patients taking Vimovo, 9.0% of patients taking celecoxib and 11.4% of patients taking placebo. All other preferred terms were generally balanced between treatment groups.

The overall safety of Vimovo was similar to celecoxib over 3 months. Compared with celecoxib, patients treated with Vimovo showed lower incidence of dyspepsia but had higher incidence of diarrhoea and constipation; incidence of abdominal pain and nausea were similar in the celecoxib and Vimovo groups. Patients who took Vimovo had no relevant increases in rates of TEAEs from other SOCs compared to celecoxib except peripheral oedema (3.1%, 1.2% and 1.2% in Vimovo, celecoxib and placebo groups, respectively). The incidence of *Cardiac Disorders* was slightly higher in the Vimovo group (1.2%) compared with the celecoxib group (0.2%) but the cardiac AEs in the Vimovo group occurred primarily in patients with a history of cardiovascular disease.

AEs in the ESP (Extended Safety Population)

Two of the preferred terms reported at ≥ 2% frequency in the Vimovo treatment group were not spontaneously reported terms. The preferred terms 'erosive gastritis' and 'gastric ulcer' were only reported from patients in the PSP. Dyspepsia was reported in 11.8% of patients in the ESP. URTI was the most common TEAE reported that was not from the SOC of *Gastrointestinal Disorders* (Table 22).

Table 22: TEAEs occurring at ≥2% in the PSP, SSP, ESP and LSP

Preferred terms	PN 400 ESP N=1157	PN 400 PSP N=428	PN 400 SSP N=490	PN 400 LSP N=239
Subjects with any TEAE	771 (66.6%)	335 (78.3%)	261 (53.3%)	175 (73.2%)
Gastritis erosive	83 (7.2%)	83 (19.4%)	0 (0.0%)	0 (0.0%)
Dyspepsia	137 (11.8%)	77 (18.0%)	41 (8.4%)	19 (7.9%)
Gastritis	75 (6.5%)	73 (17.1%)	1 (0.2%)	1 (0.4%)
Diarrhoea	64 (5.5%)	26 (6.1%)	27 (5.5%)	11 (4.6%)
Abdominal pain upper	51 (4.4%)	24 (5.6%)	20 (4.1%)	7 (2.9%)
Gastric ulcer	24 (2.1%)	24 (5.6%)	0 (0.0%)	0 (0.0%)
Nausea	51 (4.4%)	22 (5.1%)	17 (3.5%)	12 (5.0%)
Upper respiratory tract infection	43 (3.7%)	21 (4.9%)	8 (1.6%)	14 (5.9%)
Hiatus hernia	19 (1.6%)	18 (4.2%)	0 (0.0%)	1 (0.4%)
Abdominal distension	27 (2.3%)	16 (3.7%)	5 (1.0%)	6 (2.5%)
Flatulence	24 (2.1%)	16 (3.7%)	3 (0.6%)	5 (2.1%)
Oesophagitis	16 (1.4%)	15 (3.5%)	0 (0.0%)	1 (0.4%)
Constipation	42 (3.6%)	11 (2.6%)	17 (3.5%)	14 (5.9%)
Oedema peripheral	30 (2.6%)	4 (0.9%)	15 (3.1%)	11 (4.6%)
Headache	30 (2.6%)	11 (2.6%)	13 (2.7%)	6 (2.5%)
Abdominal pain	18 (1.6%)	10 (2.3%)	7 (1.4%)	1 (0.4%)
Bronchitis	21 (1.8%)	10 (2.3%)	2 (0.4%)	9 (3.8%)
Cough	23 (2.0%)	10 (2.3%)	7 (1.4%)	6 (2.5%)
Urinary tract infection	24 (2.1%)	10 (2.3%)	8 (1.6%)	6 (2.5%)
Dizziness	24 (2.1%)	4 (0.9%)	15 (3.1%)	5 (2.1%)
Abdominal pain lower	24 (2.1%)	9 (2.1%)	4 (0.8%)	11 (4.6%)
Dysgeusia	11 (1.0%)	9 (2.1%)	1 (0.2%)	1 (0.4%)
Erosive duodenitis	9 (0.8%)	9 (2.1%)	0 (0.0%)	0 (0.0%)
Sinusitis	20 (1.7%)	8 (1.9%)	5 (1.0%)	7 (2.9%)
Arthralgia	23 (2.0%)	5 (1.2%)	7 (1.4%)	11 (4.6%)
Vomiting	17 (1.5%)	4 (0.9%)	8 (1.6%)	5 (2.1%)
Influenza	12 (1.0%)	4 (0.9%)	3 (0.6%)	5 (2.1%)
Hypertension	19 (1.6%)	5 (1.2%)	5 (1.0%)	9 (3.8%)

Source: Module 5.3.5.3, Table S4.4, Table S4.3, Table S2.3, Table S3.3; Module 5.3.5.2, Study PN400-304, Table 14.3.1.1.

ESP Expanded safety population; LSP Long-term safety population; N Total number of patients; PSP Primary safety population; SSP Supportive safety population; TEAE Treatment emergent adverse event.

AEs in the TMP and LSP (Twelve Month and Long Term Safety Population)

Patients who entered study PN400-304 comprised the Long-term Safety Population (LSP), and those that completed 12 months were the Twelve Month Population (TMP). Overall rates of TEAEs were marginally higher in the LSP (73.2%) than in the TMP (70.4%) and this difference was due to a higher proportion of patients in the LSP reporting TEAEs in the SOC of *Gastrointestinal Disorders* (35.6%) than patients in the TMP (30.4%). There was

a higher incidence of dyspepsia and constipation in the LSP (7.9% and 5.9%, respectively) than in the TMP (5.9% and 3.7%, respectively), otherwise the preferred terms in this SOC were generally balanced. A higher proportion of patients in the LSP (5.8%) reported any preferred term of 'oedema' compared to those patients in the TMP (2.9%). Similar percentages of patients in the LSP and TMP reported TEAEs in the SOC of *Investigations* for creatinine/creatinine clearance (1.2% and 0.7%, respectively), haematocrit/haemoglobin (2.5% and 2.9%, respectively) or liver function abnormalities (0.8% and 0.0%, respectively). TEAEs reported as mild, moderate and severe by patients in the LSP were 23.8%, 40.2% and 9.2%, respectively and reported by patients in the TMP were 29.6%, 36.3% and 4.4%, respectively. The incidence of treatment related AEs was 28% and 23.7% in the LSP and TMP, respectively and that of related GI TEAEs were 18.8% and 17%, respectively. The incidence of treatment related oedema was 2.5% and 1.4%, respectively and that of hypertension was 1.7% and 2.1%, respectively. There was one report of treatment related acute renal failure in one subject in the LSP.

Treatment emergent selected cardiovascular events excluding hypertension were related in 2.5% of the LSP and 0.7% of the TMP. When hypertension was combined with cardiac events, the rates were 6.3% and 5.2%. No preferred term other than hypertension occurred in more than 1% of the populations. The incidence of treatment related CV AEs was 2.5% and 0.7% in the LSP and TMP, respectively.

Overall safety results in the LSP and TMP suggested that continued exposure to Vimovo over 12 months did not increase the rates or severity of the TEAEs relative to those seen on shorter term exposure.

Deaths and serious AEs

There were no deaths reported in any of the studies in this application.

There were no SAEs reported in the Phase I studies.

There were 58 treatment emergent SAEs reported by 53 patients in the 6 Phase III studies. Overall, the frequency of treatment emergent SAEs was similar between Vimovo (2.7%) and EC naproxen (3.1%). The frequency of SAEs was 1.6% in the celecoxib group and 0.4% in the placebo group. There was one SAE in the placebo group and none were reported with Arthrotec (in study PN400-303).

When adjusted for exposure, the rate of SAEs was similar in the Vimovo, EC naproxen and celecoxib groups (6.8, 9.1 and 7.9 SAEs per 100 patient years, respectively). The most common SAEs by SOC were in *Cardiac Disorders*. The frequency of *Cardiac Disorders* was 0.5%, 0.5% and 0.2% in the Vimovo, EC naproxen and celecoxib groups, respectively; the rate of cardiac SAEs was 1.3, 1.4 and 1 per 100 patient years, respectively. There were 4 reports of atrial fibrillation/flutter in Vimovo patients, 3 of which were SAEs. One subject entered the study with irregular rhythm that was later confirmed to be atrial fibrillation and a second subject developed atrial fibrillation approximately 3 weeks after stopping the study drug. There were 2 cases of atrial fibrillation that occurred while the patients were taking Vimovo. However, none of the events were considered to be related to the study drug by the principal investigator. The second most common SAEs were in the *Infections and Infestations* SOC with similar incidence in all treatment groups.

Laboratory findings, vital signs

There were no consistent or clinically significant changes in clinical laboratory results from the individual studies in normal healthy volunteers.

Haematology

Scattered changes in haematological and blood chemistry parameters appeared to be unrelated to treatment with Vimovo or comparators. Changes in haemoglobin values were generally modest and were consistent between the active comparators with no evidence to suggest increased haemoglobin loss with Vimovo cross studies of 12 weeks to 12 months in duration.

Liver function tests

In the PSP, shifts from low or normal to high in alanine transaminase (ALT) occurred more frequently in the Vimovo group compared with EC naproxen (4.6% vs 1.7%). Similarly, shifts from low or normal to high in aspartate transaminase (AST) occurred in 4.8% and 2.7% of patients taking Vimovo or EC naproxen, respectively. Alkaline phosphatase shifted from low or normal to high in similar proportion of patients in the Vimovo and DC naproxen groups (1.4% vs 1.2%). Only 1 subject in the Vimovo treatment group shifted bilirubin from low or normal to high.

In the ESP, although, the number of patients with abnormal liver function tests was slightly greater in Vimovo group, the overall occurrence rates were less than 1% and comparable between the treatment groups. Group mean, median and maximum shifts in ALT and AST, and in bilirubin, were similar and consistent between the active treatment groups. Small but clinically significant elevations in transaminases were noted in patients in all treatment groups. Similar proportions of patients in all treatment groups had elevations of transaminases to greater than three times (3x) the upper limit of normal (ULN). Two patients who took Vimovo had elevations of transaminases to greater than 5x ULN. One of these subjects had elevations greater than 20 fold. Subsequent lab testing for this subject showed increases in bilirubin and alkaline phosphatase even after significant reductions in transaminases. Most of the cases of increased ALT and AST occurred within 30 to 90 days of the use of the study drug.

Renal function tests

In the PSP, creatinine shifted from low or normal to high in 6.7% in the Vimovo treatment group and 4.4% of the EC naproxen treatment group, and blood urea nitrogen (BUN) shifted from low or normal to high in 21.2% and 16.5% of the Vimovo and EC naproxen treatment groups, respectively. In the SSP, after 12 weeks of treatment, creatinine shifted from low or normal to high in 9.4%, 8.3% and 6.6% of the Vimovo, celecoxib and placebo patients, respectively; BUN shifted from low or normal to high in 20.8%, 12.1% and 5.4%, respectively.

Creatinine shifted from low or normal to high in 11.3% and 11.9% of the LSP and the TMP, respectively, and BUN shifted from low or normal to high in 29.0% and 33.3% of the respective populations.

Creatinine shifted from low or normal to high in 8.8% in the ESP and BUN shifted from low or normal to high in 22.6% using normal ranges. When expanded ranges are applied, the shifts were 1.9% for creatinine and 0.7% for BUN.

An analysis of creatinine increases of ≥ 0.5 mg/dL, chosen as a measure of potentially significant renal function change, based on both incidence and exposure by events per 100 patient years showed that the rates of increases in creatinine are small and similar between the treatment groups.

In the TMP, 12 patients had clinically significant chemistry abnormalities, including 6 with elevated levels of BUN and/or creatinine, 3 with hyperglycaemia, 2 with AST and ALT increases and 1 with elevated potassium.

In the Phase III studies (the PSP, SSP, ESP, LMP and TMP), no substantive in- or between-group changes occurred in haematological or blood chemistry analyses between baseline and study visits with the exception of some changes in hepatic and renal function parameters. Most of these changes reflect the AEs already known to be associated with the individual components of Vimovo (naproxen and esomeprazole).

Vital signs were collected at each visit from all subjects in the trials. Vital signs were analysed using mean change from baseline. There were no clinically relevant changes in vital signs in the PSP, SSP, ESP and LSP. Most patients in both Vimovo and naproxen groups maintained systolic and diastolic blood pressures within 10 mmHg of baseline throughout the study. Majority of patients with changes in blood pressure occurred as a single event and resolved without treatment.

Safety in special populations

Effects of intrinsic factors on safety of Vimovo

The safety of Vimovo appears to be related to the individual components, thus the effects of intrinsic factors are also related to those components.

No substantive differences in the PSP or SSP were noted in the safety of Vimovo or its components that can be directly related to gender or race/ethnicity of the patients although interpretation was confounded by relatively low rates of enrolment of non-White populations into the clinical trials.

Adverse events known to be associated with age, including events from the SOC of *Cardiac Disorders*, were relatively balanced between the treatment groups but did increase with age. While some events in *Gastrointestinal Disorders* (notably, reports of GU from the PSP) increased with age in the EC naproxen treatment group, they did not increase with age in the Vimovo treatment group.

No important differences in the PSP or SSP were noted in the safety of Vimovo or its components that can be directly related to race and ethnicity and naproxen carries a warning, common to all NSAIDs, of the potential for increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke and cautions use in patients with cardiovascular disease or risk factors for cardiovascular disease. In the current studies, cardiovascular disorders, including hypertension, were generally balanced between Vimovo, EC naproxen and celecoxib, occurred primarily in patients with prior history and known risk factors, and occurred at rates consistent with other studies in these populations. Accordingly, current NSAID warnings to the product information) for Vimovo are adequate.

Effects of extrinsic factors on safety

Smoking

The effects of smoking on adverse events were not examined in the safety analysis. However, for the subgroup of smokers in PN400-301, GU rates at 6 months were numerically greater for Vimovo compared with EC naproxen, although the number of patients in the subgroup was small (N=59) In contrast, in PN400-302, the GU rates in the subgroup of smokers (N=74) were similar for the 2 treatments.

Although there does appear to be a trend suggesting that the gastroprotective effect of Vimovo may not be effective in smokers, the small sample size combined with the fact that randomisation to study treatment was not stratified by smoking status, makes it difficult to draw any conclusions from these data.

Safety related to drug drug interactions and other interactions

Drug interaction studies were not been conducted with Vimovo. There were no studies of ethanol interactions with Vimovo.

The concomitant use of LDA did not appear to worsen the rate of adverse events in patients who took Vimovo. In the PSP, there were no major differences in overall TEAEs between patients who took and those that did not take LDA. The incidence of *Gastrointestinal Disorders* reported in patients taking Vimovo was similar in those taking or not taking concomitant LDA (65.7% vs 62.9%) with similar results in patients on naproxen (81.4% vs 79.9%). Similar numbers of GI Disorders were reported by patients. The incidence and distribution of the TEAEs in the SOC of *Gastrointestinal Disorders* were similar with the exception of fewer GU (3.0%) in patients on Vimovo who took LDA than those who did not (6.4%); however, patients who took EC naproxen and LDA reported more GU (28.4%) compared with those who did not take LDA (22.2%).

There were no substantive differences in duodenal ulcer, erosive gastritis, or oesophagitis in those who took LDA compared to those who did not in either the Vimovo or the EC naproxen groups. Patients with a history of UGI disorders made up the majority of the general study population, therefore, the TEAEs seen in this analysis approximated that of the general population

Discontinuations due to AEs

A single subject withdrew from the Phase I study PN400-101 due to a TEAE from the SOC of *Skin and Subcutaneous Tissue Disorders*.

The incidence of discontinuations due to AEs was higher in patients treated with EC naproxen (40.6%) and Arthrotec[29] (45.5%) compared to Vimovo (12.2%), celecoxib (7.8%) and placebo (4.9%). However, it should be noted that discontinuations for celecoxib and placebo are likely underrepresented relative to Vimovo and EC naproxen since scheduled endoscopies in the total safety population were not included in studies PN400-307, PN400-309 or PN400-303. More patients discontinued from the EC naproxen group (40.6%) than from Vimovo (12.2%) and celecoxib (7.8%).

This difference was due to discontinuations from the SOC of *Gastrointestinal Disorders* including gastric ulcer, duodenal ulcer, and dyspepsia. More patients assigned to Vimovo withdrew due to TEAEs from the SOC of *Investigations* than did celecoxib or naproxen or placebo although no pattern or grouping inside of any preferred term was detected; in the Vimovo group, reasons for discontinuation were increased blood pressure (3), decreased haemoglobin (3), increased blood creatinine (1), increased BUN (1), abnormal liver function test (LFT) (1) and increased transaminases (1).

More patients also withdrew from the SOC of *General Disorders and Administration and Site Conditions* in the Vimovo treatment group and the celecoxib treatment group than from the other groups; however, peripheral oedema led to withdrawal of study treatment in four Vimovo patients compared to none in the other treatment groups.

Withdrawal from clinical studies due to TEAEs from the SOC of *Cardiac Disorders* occurred in 0.4% and 0.5% of patients assigned to Vimovo and EC naproxen, respectively. The TEAE of hypertension, using the combined preferred terms of 'hypertension' and 'blood pressure increase', lead to the withdrawal of 4 patients assigned to Vimovo, 2 patients assigned to EC naproxen, 3 patients assigned to the celecoxib treatment group, and 1 subject assigned to placebo.

[29] Arthrotec was only used in 11 patients in study PN400-303 which was terminated early.

Withdrawals due to TEAEs did not proportionally increase with age in the Vimovo group, while withdrawals did increase with age in the EC naproxen group.

The open label study PN400-304 enrolled 239 patients, of which 135 completed ≥ 348 days of treatment and comprised the TMP. There were 45 discontinuations due to treatment emergent adverse events (TEAEs), 39 in the first 180 days of the study and 6 during the remainder of the study. More patients withdrew due to TEAEs from the SOC of *Gastrointestinal Disorders* (19) than any other SOC and all of these withdrawals occurred in the first 180 days of the study. Discontinuations due to dyspepsia (6) were the most common cause and occurred in the first 90 days of the study. No trends to increased frequency of discontinuation could be determined by time of onset of the TEAE. Oedema leading to discontinuation occurred only in days 30 to 90, and there was a single discontinuation due to coronary artery disease in the same period.

Evaluator's overall comments on clinical safety

The safety of Vimovo was evaluated in an adequate number of patients; 1166 patients were treated with proposed dose of Vimovo in Phase III studies including 491 patients treated for 6 months and 125 patients treated for 12 months.

Vimovo reduces the risk of gastric ulcers and duodenal ulcers compared to EC naproxen. Vimovo provides a demonstrably improved UGI safety profile compared to EC naproxen, irrespective of patient age and concomitant use of low dose aspirin.

GI AEs were the most common following treatment with Vimovo although incidence of dyspepsia, GU/ DU and other GI AEs was significantly lesser in patients treated with Vimovo compared with naproxen alone. However, the incidence of diarrhoea, constipation, dizziness and peripheral oedema was slightly higher with Vimovo.

There were no deaths in any of the Vimovo clinical studies. The incidence of SAEs was similar in the Vimovo, naproxen, celecoxib and placebo treatment groups. The incidence of discontinuations due to AEs was significantly higher in patients treated with EC Naproxen compared to Vimovo mainly due to a higher incidence of GI AEs. Withdrawals due to peripheral oedema were more common in Vimovo treated patients, although overall incidence was low (0.3%).

The overall safety of Vimovo is favourable compared with EC naproxen over 6 months of treatment and similar to celecoxib over 3 months of treatment.

Vimovo is well tolerated in use up to 1 year and presents no new safety concerns compared to safety data in short term studies.

Overall, the safety profile of the individual components of Vimovo, that is, naproxen and esomeprazole are well established and no new safety concerns were identified following evaluation of the combination (Vimovo) in an adequate number of patients representative of the target patient population.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Efficacy

Although the sponsor suggests a reduction in total daily dosage in certain patient populations at risk of increased exposure to naproxen (such as moderate renal/ hepatic impairment or those with CV risk factors), the only option available is to reduce it to once daily dosing instead of twice daily dosing as it recommended in the same section that the tablet cannot be split and needs to be swallowed whole. However, giving just one dose

may not provide sustained symptomatic relief for the patients. The sponsor had applied for approval of two dose strengths in the USA (500/20 mg and 375/20 mg) and has also received approval for both dosages. Would the sponsor clarify why a submission for approval of two dose strengths was not made in Australia? Furthermore the sponsor needs to provide information on how the dose adjustment can be made in patients requiring reduced dose of naproxen without compromising on symptomatic relief for the patients?

Clinical Summary and Conclusions

Clinical Aspects

Clinical pharmacology

Vimovo consists of an immediate release esomeprazole magnesium layer and an enteric coated naproxen core. As a result, esomeprazole is released first in the stomach, prior to the dissolution of naproxen in the small intestine. The enteric coating prevents naproxen release at pH levels below 5.5. The PK profiles of naproxen and esomeprazole in Vimovo are consistent with the sequential delivery design of the tablet: esomeprazole is released rapidly, followed by delayed release of naproxen. Esomeprazole AUCs observed with Vimovo at steady state are greater than those reported with EC esomeprazole 20 mg qd but lower than those reported with EC esomeprazole 40 mg qd. The effect of food on the bioavailability of naproxen and esomeprazole in Vimovo suggests that Vimovo should be taken at least 30 min prior to meals.

The clinical pharmacology of naproxen and esomeprazole has been well characterised in the original marketing applications for EC Naprosyn and Nexium, respectively, and in the scientific literature. In clinical practice, these drugs have been used extensively in combination as separate tablets/capsules, and esomeprazole has been studied and approved for the treatment and prophylaxis of NSAID induced GI damage.

Based on naproxen exposures, Vimovo is bioequivalent to a Vimovo tablet without IR esomeprazole in the film coat. In addition, Vimovo is bioequivalent to commercially available naproxen (Proxen S, Naprosyn E, and EC Naprosyn), supporting the efficacy of Vimovo in the management of the signs and symptoms of OA, RA, and AS.

In Australia, naproxen 500 mg is only available as IR tablets (Naprosyn). This is acceptable as Vimovo contains delayed release naproxen for which rapid onset of action is not essential for the proposed indication. The exposure to naproxen was shown to be similar between the delayed release naproxen in the Vimovo and the IR naproxen 500 mg tablets available in Australia. Therefore, in order to validate the CDP for this submission and as per Australian regulatory requirements, the sponsor conducted a separate bioavailability study to compare bioavailability of the naproxen component of Vimovo with immediate release Naprosyn tablets available in Australia at presumed steady state; this study demonstrated bioequivalence for extent of absorption of naproxen but as expected showed delayed T_{max} for the Vimovo (containing delayed release naproxen) compared to Naprosyn (containing IR naproxen).

There is no evidence of a PK interaction between naproxen and esomeprazole when combined in Vimovo. No new drug interaction studies were conducted with Vimovo but the proposed PI for Vimovo contains appropriate information regarding drug interactions with its components, naproxen and esomeprazole.

Clinical efficacy

The efficacy of the naproxen component of Vimovo was established by showing bioequivalence to commercially available EC naproxen (including EU sourced Proxen S in

Study PN400-108). To further support pain management efficacy, two identical 12 week studies (PN400-307 and PN400-309) demonstrated that Vimovo bd is significantly better than placebo and non-inferior to celecoxib 200 mg qd in patients with OA of the knee, based on the 3 co-primary efficacy measures: WOMAC Osteoarthritis Index Pain and Function Subscales, and Patient Global Assessment Visual Analogue Scale (PGA-VAS).

The efficacy of the esomeprazole component of Vimovo in reducing GU and DU incidence in chronic NSAID users was shown by evidence of significantly lower ulcer incidence through 6 months for Vimovo compared to EC naproxen alone in two identical, well controlled pivotal Phase III studies (PN400-301 and PN400-302). Importantly, the pronounced reductions in rates of GU, DU, and pre-specified NSAID associated UGI AEs in those who took Vimovo were similar in patients who were older or younger than 60 years, did or did not take LDA, and did or did not have a history of ulcer in the past 5 years.

Vimovo, compared with EC naproxen, was significantly effective in reducing the occurrence of GUs, DUs, and other NSAID associated UGI AEs. This was evident after just one month of treatment and the efficacy was maintained over 6 months. Vimovo also showed significant improvements in dyspepsia symptoms and heartburn resolution.

Efficacy endpoints used were standard for the proposed indication and efficacy was demonstrated in a population which was representative of the target patient population for Vimovo.

While no direct measurements of efficacy were made in the open label, 12 month safety study (PN400-304), several safety endpoints support the assertion that tolerability findings of the controlled Phase III studies presented above are sustained beyond 6 months. Mean compliance with Vimovo (based on pill counts) was greater than 95% in the overall safety population, and more than 97% of the patients (100% of the 12-month completers) had at least 70% compliance. Patients in the study used more than 58 doses per month on average. There was no evidence of loss of effect of Vimovo in the reduction of NSAID associated UGI AEs. Patients treated for up to 12 months with Vimovo have rates of pre-specified UGI AEs similar to those observed in patients treated for up to 6 months. Discontinuations due to UGI disorders occurred primarily in the first 6 months of treatment with Vimovo.

Clinical safety

The safety of Vimovo was evaluated in an adequate number of patients; 1166 patients were treated with proposed dose of Vimovo in Phase III studies including 491 patients treated for 6 months and 125 patients treated for 12 months. GI AEs were the most common following treatment with Vimovo although incidence of dyspepsia, GU/ DU and other GI AEs was significantly lesser in patients treated with Vimovo compared with naproxen alone. However, the incidence of diarrhoea, constipation, dizziness and peripheral oedema was slightly higher with Vimovo. There were no deaths in any of the Vimovo clinical studies. The incidence of SAEs was similar in the Vimovo, naproxen, celecoxib and placebo treatment groups. The incidence of discontinuations due to AEs was significantly higher in patients treated with EC Naproxen compared to Vimovo mainly due to a higher incidence of GI AEs. Withdrawals due to peripheral oedema were more common in Vimovo treated patients, although overall incidence was low (0.3%).

Although Vimovo contains an IR form of esomeprazole, in contrast to the EC Nexium formulation, esomeprazole exposures following bd administration of Vimovo were well within the range that has been extensively studied and shown to be safe and well tolerated using Nexium at doses up to 240 mg/day.

The overall safety of Vimovo was favourable compared to EC naproxen over 6 months of treatment and similar to celecoxib over 3 months of treatment. Vimovo provides a demonstrably improved UGI safety profile compared to EC naproxen, irrespective of patient age and concomitant use of low dose aspirin. Vimovo was well tolerated in use up to one year and presented no new safety concerns compared to the active, marketed agents.

Overall, the safety profile of the individual components of Vimovo, that is, naproxen and esomeprazole are well established and no new safety concerns were identified following evaluation of the combination (Vimovo) in an adequate number of patients representative of the target patient population.

Benefit risk assessment

Benefits

Vimovo was designed as a multilayer, sequential delivery tablet formulation combining an immediate release esomeprazole magnesium layer and a delayed release (DR) naproxen core. As a result, esomeprazole is deployed prior to the dissolution of the NSAID. The DR layer prevents naproxen release at pH levels below 5, providing protection against possible local gastric toxicity of naproxen.

Vimovo is intended to be dosed bd for symptomatic relief in the treatment of OA, RA, and AS in patients at risk for developing NSAID associated GUs and/or DUs who require 500 mg of naproxen bd to manage their pain symptoms. The combination of esomeprazole and naproxen requires twice daily dosing because of the naproxen component.

Naproxen 500 mg bd is the most commonly prescribed dosing regimen in the EU (that is, in France, Italy, Spain, United Kingdom, and Germany, not including hospital scripts; IMS Health). Approximately 75% of total naproxen use is at the 500 mg bd dose or at the 250 mg bd dose of naproxen. Phase I studies have demonstrated bioequivalence between naproxen in Vimovo and commercially available naproxen preparations (including the immediate release preparation in Australia). Because the risk of NSAID associated ulcers and GI bleeding is dose dependent, the benefit of gastroprotection is likely greatest with a naproxen dose of 500 mg bd compared with lower dose regimens.

Phase III studies in the Vimovo clinical program have demonstrated that Vimovo bd is non-inferior to celecoxib 200 mg qd in the management of pain associated with OA of the knee.

With respect to the esomeprazole component of Vimovo, IR esomeprazole 20 mg dosed bd in Vimovo has been demonstrated to be pharmacodynamically and clinically efficacious, well tolerated and safe. The 20 mg esomeprazole dose in Vimovo was chosen as optimal based on Phase I pharmacodynamic studies comparing 10 mg, 20 mg and 30 mg doses of esomeprazole in Vimovo, with respect to intragastric acid control and reduction of naproxen associated gastroduodenal injury. Although Vimovo contains an IR form of esomeprazole, in contrast to the EC Nexium formulation, esomeprazole exposures following bd administration of Vimovo are well within the range that has been extensively studied and shown to be safe and well tolerated using Nexium.

The gastroprotective efficacy of the esomeprazole component is based on two identical, pivotal Phase III studies which showed that the esomeprazole component of Vimovo dosed bd is effective in reducing the risk of NSAID associated GI side effects, including GUs, DUs, dyspepsia, and UGI AEs, in patients at increased risk of developing ulcers based on age, ulcer history or LDA use.

The safety profile of Vimovo is based on the well documented profiles of the individual components, the demonstrated lack of PK interaction between them, and the safety data from the Vimovo development programme. The risks associated with administration of the individual components of Vimovo, that is, naproxen and esomeprazole are well established and no new safety concerns were identified during the Vimovo clinical development program.

Noncompliance has been recognized as a specific risk in several patient populations, including the elderly, who are at increased risk of NSAID induced gastropathy (Abraham et al 2005, Goldstein et al 2006).[30,31] A published survey of 300,000 US veterans showed that adherence to PPI co-therapy in NSAID users "at risk of gastroduodenal ulcers" was low (27%), and that the likelihood of adherence is further decreased if NSAIDs are prescribed for 90 days or more (Abraham et al 2005, Abraham et al 2008).[30,32] Non-adherence to gastroprotective co-therapy strategies increases the chance of a UGI event by 2.5- to 4-fold (Goldstein et al 2006) and a link between noncompliance and increased risk for UGI bleeding has been demonstrated (Van Soest et al 2007).[31,33] Vimovo would be expected to improve treatment compliance and offer simplicity of use as the single tablet would provide symptomatic relief and offer gastroprotection against naproxen associated UGI-AEs. Mean compliance with Vimovo (based on pill counts) was greater than 95% in the overall safety population and more than 97% of the patients (100% of the 12-month completers) had at least 70% compliance.

Risks

In 2006, the Committee for Medicinal Products for Human Use (CHMP) of the EU issued guidance on the use of non-selective NSAIDs. The TGA also issued guidance on the use of non-selective NSAIDs. This guidance recommends that doctors continue to prescribe, and patients continue to use, the lowest effective dose of NSAIDs for the shortest possible duration to control symptoms. It further advises doctors to base their choice of NSAID on the patient's underlying conditions and the safety profiles of the medicines.

Vimovo is mainly intended for use in patients requiring a higher dose of naproxen. However, as already advised in the proposed PI, in certain special populations at risk of increased exposure to naproxen (mild/moderate renal/ hepatic impairment or cardiovascular risk factors), the dose should be reduced. Prescription of a reduced dose of naproxen (such as the 375/20 mg dose approved in USA) is not an option for Australia as this submission is only for the 500/20 mg dose. Vimovo is likely to have benefit only in patients requiring one gram of naproxen daily.

Esomeprazole is approved for long term use at a daily dose of only 20 mg od while the daily dose of esomeprazole in Vimovo is 40 mg. Esomeprazole 40 mg is only approved for treatment of GORD up to 4 weeks. Hence, the long term safety of using esomeprazole 40 mg has not been adequately established.

[30] Abraham NS, El-Serag HB, Johnson ML et al. National adherence to evidence-based guidelines for the prescription of non-steroidal anti-inflammatory drugs. Gastroenterology 2005; 129: 1171-8.

[31] Goldstein JL, Howard KB, Walton SM, McLaughlin TP, Kruzikas DT. Impact of adherence to concomitant gastroprotective therapy on nonsteroidal-related gastroduodenal ulcer complications. Clin Gastroenterol Hepatol 2006; 4: 1337-45.

[32] Abraham NS, Hartman C, Castillo D, Richardson P, Smalley W. Effectiveness of National provider prescription of PPI gastroprotection among elderly NSAID users. Am J Gastroenterol 2008; 103: 323-32.

[33] Van Soest et al. Adherence to gastroprotection and the risk of NSAID-related upper gastrointestinal ulcers and haemorrhage. Aliment Pharmacol Ther 2007; 26: 265-75.

Balance

While NSAIDs remain a key therapy for pain, it is well accepted that there is a substantial risk of UGI ulcerations and ulcer complications, such as bleedings and perforations, with chronic NSAID therapy. The cumulative incidence of gastroduodenal ulcers with conventional NSAID use has been reported to be as high as 25-30% at 3 months and 45% at 6 months, while that of placebo is 3-7% (Bias 2004, Laine 1999, Hawkey 2000, Hawkey 2003, Simon 1999).[19,20,21,20,21] At any given time, the incidence of UGI ulcers in NSAID users has been estimated to be as high as 30% (Laine 1996).[34] The main risk factors for UGI ulcers in NSAID users are age 50 years and older (Hernandez-Diaz 2000, Boers 2007), a history of UGI ulcer or bleeding, and concomitant aspirin use (Laine 1996).[25,26,34] A majority of the patients included in the Vimovo studies were >50 years old (mean age of 62 years) and almost 25% were taking concomitant LDA and thus were representative of the target patient population for Vimovo.

It has been shown that once-daily administration of an enteric coated PPI significantly reduces the development of NSAID associated ulcers. However, a published survey of 300,000 veterans showed that adherence to these recommendations in NSAID users "at risk" was low (27%). The study also reported that the likelihood of adherence is further decreased if NSAIDs are prescribed for 90 days or more (Abraham 2005 and 2008; Goldstein et al 2006).[30,31,32]

Efficacy of Vimovo has been shown in 1166 patients representative of a target patient population requiring treatment with NSAIDs and who are at risk of developing NSAID associated gastric/duodenal ulcers. Vimovo (500/20 mg twice daily) was effective in reducing incidence of gastroduodenal ulcers in subgroups of patients aged >60 years, taking concomitant LDA and with a history of gastric ulcer. The most significant gastroprotective effect (in terms of cumulative proportion of patient with GU at 6 months) of Vimovo compared to EC-naproxen alone was evident in patients who used LDA and had a history of gastric ulcer (0% vs 60%). However, Vimovo (500/20 mg bd) is an effective therapeutic strategy only in patients who require a daily dose of 1 g naproxen. If a daily dose of 1 g naproxen is not considered appropriate, then alternative therapeutic strategy needs to be used.

Treatment compliance in the overall safety population was 97% and in the 12 month open label study, almost 95% of the patients were treatment compliant. Furthermore, neither active component of Vimovo is expected to interfere with the efficacy of the other component or to lead to new safety concerns. On the contrary, use of Vimovo should help to optimise co-therapy compliance and ensure that patients who require naproxen therapy receive, with each dose of naproxen, a dose of esomeprazole that provides prophylaxis against UGI injury.

Conclusions

The benefit risk profile for Vimovo (Vimovo) containing EC naproxen/esomeprazole 500 mg/20 mg is favourable for the symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, in patients at risk for developing NSAID associated gastric and/ or duodenal ulcers. However, the wording of the proposed indication needs to be more specific as follows:

Vimovo is a combination product that contains naproxen and esomeprazole. It is indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of

[34] Laine L. Nonsteroidal anti-inflammatory drug gastropathy. Gastrointest Endosc Clin N Am 1996; 6: 489-504.

developing NSAID associated gastric ulcers. Vimovo is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen-containing products. Controlled studies do not extend beyond 6 months.

V. Pharmacovigilance Findings

Risk Management Plan

The Office of Product Review concluded that a Risk Management Plan (RMP) evaluation was not required for the fixed dose combination product Vimovo unless there was a specific issue of concern identified by the Delegate.

Safety specification

A Risk Management Plan (RMP) edition 1 dated August 2009 was included in the submission and the clinical evaluator reviewed the safety specification. It was noted that a majority of the identified risks are similar to those of the individual components of Vimovo, that is, naproxen and esomeprazole. However, newly identified safety concerns included osteoporotic fractures associated with prolonged use of PPIs (esomeprazole) and potential interaction of naproxen with clopidogrel. The summary of ongoing safety concerns for both components in Vimovo is shown in Table 23.

Table 23: Ongoing safety concerns for Vimovo

Important identified risks	Aseptic meningitis, Agranulocytosis, Aplastic and haemolytic anaemia, Hypersensitivity reactions, Depression, Hypertension, Heart failure and pulmonary oedema, MI, Asthma, Bronchospasm, Serious GI AEs including bleeding, ulceration, obstruction and perforation of the stomach or intestines, Hepatitis, Hepatic failure, Hepatic encephalopathy, EM, SJS/TEN, Renal failure, Renal papillary necrosis and other renal injury, Nephritis interstitial
Important potential risks	Thrombotic stroke, Renal failure/acute renal failure, Blindness/Blindness transient, Rhabdomyolysis, Hypomagnesaemia
Newly identified safety concerns	Osteoporotic fractures including hip fracture. Potential interaction with clopidogrel
Important missing information	Pregnant and lactating women, Patients with renal impairment
Identified and potential interactions	Warfarin or other coumarine derivates, NSAID preparations and ASA, Other platelet aggregation inhibitors, SSRIs, Antihypertensives, Diuretics, Methotrexate, Lithium, Cyclosporin, Corticosteroids, Phenytoin, Atazanavir, Nelfinavir

The clinical evaluator noted that results of a recent cohort study (with a nested control analysis) (Garcia Rodriguez et al, 2009) identified another safety concern showing that newly diagnosed community acquired pneumonia (CAP) was significantly associated with current use of PPIs (RR=1.16, 95% CI: 1.03- 1.31) but not of H_2 receptor antagonists (H_2RAs) (RR=0.98, 95% CI: 0.80-1.20) with no clear duration response with either PPIs or H_2RAs.[35] The occurrence of CAP appeared to be related to users of PPIs treated for dyspepsia or peptic ulcer suggesting that the small risk observed might be linked to the

[35] García Rodríguez LA, Ruigómez A, Wallander M-A, Johansson, S. Acid-suppressive drugs and community-acquired pneumonia. Epidemiology 2009; 20: 800-806.

background risk of patients with this underlying indication rather than a direct effect of the drug. The risk of CAP will only be followed within the framework of the routine pharmacovigilance process and no specific action to evaluate this risk is planned.[36] No other new safety concerns were identified for Vimovo.

Pharmacovigilance Activities

The newly identified safety concerns were being addressed with the pharmacovigilance activities outlined in Table 24.

Table 24: Pharmacovigilance activities for newly identified safety concerns

Actions	Milestones/calendar time	Study status
Osteoporotic fractures		
A meeting with external experts in the field was held on 7 March 2009. AstraZeneca is currently considering and evaluating the outcome of this meeting together with new data presented at the Digestive Disease Week (DDW) in June 2009. The global product team will decide on actions at a meeting during autumn 2009.	Q3 2009	Ongoing
Potential interaction with Clopidogrel		
A pharmacoepidemiological study of the potential interaction between clopidogrel and PPIs and the risk of acute MI, coronary heart disease death, and UGIB.	Q4 2010	Study protocol finalized. To be initiated Q3 2009.
In addition, AstraZeneca plans to conduct a PK/PD study. A study design concept is currently under preparation.	Q3 2009	Planned

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator recommended approval of the submission with respect to chemistry and quality control. With respect to bioavailability, the evaluator commented that:

[36] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- It was accepted that the combination and monotherapy enteric coated naproxen tablets used in the Phase III clinical efficacy studies were bioequivalent to each other with respect to naproxen response and that the combination formulation proposed for registration will be bioequivalent with respect to both naproxen and esomeprazole to the combination formulation used in the Phase III clinical efficacy studies.
- It was accepted that the naproxen response from the proposed tablet was bioequivalent to that from the naproxen immediate release tablets registered in Australia. There was however, an expected delay in T_{max}.
- The esomeprazole response from the proposed tablet will be only approximately 50% that from the esomeprazole enteric coated tablets registered in Australia. The sponsor states that this is not clinically relevant as bioequivalence is not expected or required.
- It was accepted that there were no pharmacokinetic interactions between naproxen and esomeprazole.

Nonclinical

No nonclinical studies with Vimovo or the combination of naproxen and esomeprazole were submitted. Thus the safety assessment of the proposed fixed combination will rely on clinical data.

Oral esomeprazole administration to rats and dogs resulted in increased pH of gastric fluid (values up to 8.4 and 7.7, respectively), which may result in degradation of the pH sensitive coating of the naproxen component of Vimovo tablets in the stomach, rather than the small intestine, which has potential implications for local GI tract toxicity. The *in vitro* degradation profile of esomeprazole in gastric fluid from rats, dogs and humans at lower pH values (but not the maximum observed pH values) was characterised; the relationship of the *in vitro* degradation profile to that anticipated *in vivo* is unknown. Thus, it is unclear whether previous toxicity studies with esomeprazole adequately addressed the safety of degradation products anticipated clinically.

The sponsor was requested to respond to both these concerns: that of the potential for local GI tract toxicity as a result of release of naproxen in the stomach and that of the uncertainty of the relationship of the in vitro and in vivo degradation profiles of esomeprazole.

The nonclinical evaluator noted that both active substances have been approved and on the market for many years and there are extensive nonclinical and clinical data available for the individual components. Thus there are no nonclinical objections to the registration of Vimovo, provided that the clinical data adequately demonstrate the safety and efficacy of the combination product, particularly with respect to the potential for local GI tract toxicity as a result of release of naproxen in the stomach.

Clinical

Pharmacokinetics

Three formulations were used in the Phase I studies, an initial Phase I formulation, the Phase III formulation and the proposed commercial formulation. Only minor film coating formulation changes were made in each case. No formulation changes were made to the naproxen core. Bioequivalence was established between the Phase III formulation, the proposed formulation for marketing and commercial formulations of naproxen (Proxen S, the German product; Naprosyn E, the Canadian product and EC Naprosyn, the US product).

Based on naproxen exposures, Vimovo was found to be bioequivalent to a similar tablet without the IR esomeprazole in the film coat, that is, containing only enteric coated naproxen. In addition, Vimovo was found to be bioequivalent to commercially available

naproxen (Proxen S, Naprosyn E and EC Naprosyn). In Australia, none of the enteric coated naproxen formulations is available and only the immediate release (IR) Naprosyn is approved. Thus in Study D1120C00035, because a non-delayed release comparator was used, PK parameters were studied at steady state, rather than after a single dose. This is appropriate for a product which is intended for use in chronic pain. Study D1120C00035 was a Phase I, single centre, two treatment, two period, two sequence, randomized crossover steady state BE study which compared the steady state pharmacokinetics of naproxen in two tablet formulations given twice daily (Vimovo tablets containing 500 mg of enteric coated naproxen plus 20 mg of IR esomeprazole versus Naprosyn containing 500 mg IR naproxen). The two formulations were demonstrated to be bioequivalent with respect to the rate/extent of absorption of naproxen in terms of the ratio of geometric means for C_{ssmax}, C_{min}, C_{ssavg} and AUC_{0-t}. There was a statistically significant difference in C_{ssmin}, although this was not considered clinically relevant given that the C_{min} was observed immediately after the dose and not before the next dose (as in the case of the IR naproxen). Also the failure was only with regard to the upper limit of the acceptance interval at 1.261 (just above the generally accepted upper limit of 1.25). As expected, the T_{max} was significantly greater with Vimovo (containing delayed release naproxen) compared to Naprosyn (containing the immediate release naproxen). The corresponding median values of T_{max} were 3.52 and 1.53 h, respectively.

The PK profiles of naproxen and esomeprazole in Vimovo were consistent with the sequential delivery design of the tablet, namely that esomeprazole is released rapidly, followed by delayed release of naproxen.

Esomeprazole AUCs observed with Vimovo at steady state are greater than those reported with EC esomeprazole monotherapy 20 mg once daily but lower than those reported with EC esomeprazole monotherapy 40 mg once daily.

The effect of food on the bioavailability of naproxen and esomeprazole in Vimovo suggests that Vimovo should be taken at least 30 min prior to meals. According to the clinical evaluator, the Phase I, open label, randomized, four way crossover study (PN400-103) evaluated the effect of food on the bioavailability of naproxen and esomeprazole from the proposed Vimovo tablet. This study identified that the rate and extent of bioavailability of each of naproxen or esomeprazole was essentially unaffected when a Vimovo tablet was administered 30 or 60 min before a high fat meal. This dosing instruction was used in the Phase III pivotal clinical trials evaluating the efficacy and safety of Vimovo tablets and was consistent with the dosing instruction in the proposed PI.

There was no evidence of a PK interaction between the two components when combined in Vimovo. No new drug-drug interaction studies were conducted with Vimovo. However, as noted by the clinical evaluator, drug interactions between the individual monotherapies and other medicines are already well characterised.

The sponsor was requested to display in some sort of summary form, whether by flow chart or tabulation, the logical chain establishing bioequivalence between the Vimovo products used in the Phase I clinical trials and the Phase III clinical trials and the actual product proposed for marketing. In this same chain of evidence establishing bioequivalence, the sponsor was requested to indicate which particular Vimovo product was used at which point or in which study.

Pharmacodynamics

In Study PN400-101, the percentage of subjects with a Grade 3 or Grade 4 Lanza score was significantly greater ($p < 0.01$) with EC naproxen than with any of the Vimovo treatments (naproxen 500 mg with esomeprazole 10, 20 and 30 mg) with the hint of a possible dose related response according to esomeprazole dose.

In Study PN400-104, administration of Vimovo containing 20 or 30 mg esomeprazole resulted in a higher percentage time with intragastric pH > 4.0 compared to Vimovo/E10 (the latter also having the highest variability in this response) after 9 days of twice daily dosing. Based on pH control and low inter-subject variability, Vimovo/E20 was selected for studies in subjects at risk for NSAID associated gastric ulcers.

Efficacy

There were five Phase III studies conducted to demonstrate efficacy of Vimovo for the proposed indication. These included 2 pivotal, 6 month, active controlled studies (PN400-301 and PN400-302) which compared gastric ulcer occurrence in patients who took Vimovo twice daily with those who took EC naproxen 500 mg twice daily. Two non-inferiority, 3 month, Phase III supportive studies (PN400-307 and PN400-309) were designed to show that Vimovo is similar to Celebrex (celecoxib), a widely used COX-2 inhibitor, in the treatment of signs and symptoms of OA of the knee. The 12 month, open label study (PN400-304) was conducted to evaluate long term safety of Vimovo but also to provide supportive efficacy data in terms of upper gastrointestinal tolerability.

Pivotal Studies comparing Vimovo with EC-Naproxen alone: PN400-301 and PN400-302

These were identical, 6 month, randomized, double blind, parallel group, active controlled, multicentre, outpatient studies conducted concurrently in the USA. The pivotal studies included patients who had chronic inflammatory arthritis that would require daily use of NSAIDs for at least 6 months and were considered to be at risk of GI toxicity from the chronic use of NSAIDs.

The primary efficacy endpoint was the incidence of gastric ulcers at any time throughout the 6 months of treatment, with the results stratified by the concomitant use of low dose aspirin (LDA) (≤ 325 mg daily). Key secondary efficacy/tolerability endpoints included the proportion of subjects with pre-specified NSAID associated upper GI AEs or duodenal ulcers, the proportion of subjects discontinuing from the study due to pre-specified NSAID associated upper GI AEs or due to duodenal ulcers and the proportion of subjects developing duodenal ulcers throughout the 6 months of study treatment. All efficacy and tolerability analyses were performed based on the ITT population.

Results of pivotal study PN400-301

The cumulative observed incidence of gastric ulcers throughout 1, 3 and 6 months was significantly lower with Vimovo treatment than with naproxen ($p < 0.001$ at all time points) (Table 3). These results were supported by similar results in the PP population.

The secondary efficacy results were all supportive of the primary efficacy results. In the Vimovo group, subjects taking LDA had a lower rate of gastric and/or duodenal ulcers at each study period compared with subjects not using LDA (1.9% vs 5.5%, respectively, at 6 months), while in the naproxen only group, gastroduodenal ulcer rates were similar regardless of LDA use (28% in both groups).

Results of pivotal study PN400-302

The cumulative observed incidence of gastric ulcers throughout the 1, 3 and 6 months was significantly lower with Vimovo treatment than with naproxen ($p < 0.001$ at all time points) (Table 6). These results were supported by similar results in the PP population.

The secondary efficacy results were all supportive of the primary efficacy results. In the Vimovo group, subjects taking LDA had a lower rate of gastric and/or duodenal ulcers at each study period compared with subjects not using LDA (7% vs 9%, respectively, at 6

months), while in the naproxen only group, gastroduodenal ulcer rates were higher among LDA users compared with non-users (37% vs 25% at 6 months).

Effect of age and ulcer history on efficacy of Vimovo from pivotal studies PN400-301 and PN400-302

In these two studies, the effect of baseline covariates (age and ulcer history within the previous 5 years) was analysed using a conditional logistic regression model. Both age and use of LDA increased the gastric ulcer incidence rate in EC naproxen users but had no effect on the incidence rate of gastric ulcers in patients taking Vimovo. The most significant gastroprotective effect of Vimovo over naproxen (as measured by the cumulative proportions of patients with gastric ulcers at 6 months) was evident in patients who had a history of ulcer and used LDA (0% vs 60% in the Vimovo and naproxen groups, respectively).

Pooled efficacy results from the pivotal, 6 month studies PN400-301 and PN400-302

In the combined analysis, fewer patients who were randomized to Vimovo had gastric ulcers than did patients randomized to EC naproxen at 1 month (1.6% and 11.5%, respectively), 3 months (3.3% and 18.5%, respectively) and 6 months (5.6% and 23.7%, respectively).

In the combined analysis, patients treated with EC naproxen had a 5.4% incidence of duodenal ulcers throughout 6 months, compared to only 0.7% of those taking Vimovo.

In the combined analysis, a significantly lower proportion of patients ($p < 0.001$) who took Vimovo had pre-specified NSAID associated upper gastrointestinal AEs or duodenal ulcers by 6 months than did those who took EC naproxen (53.3% vs 70.4%, $p < 0.001$).

Pivotal non-inferiority studies comparing Vimovo with celecoxib: Studies PN400-307 and PN400-309

Studies PN400-307 and PN400-309 were identical, 6 month, randomized, double blind, placebo and active controlled, parallel group, multicentre, outpatient studies conducted concurrently at sites in the USA. In these studies, celecoxib 200 mg once daily was chosen because its efficacy had been shown to be similar to that of naproxen 500 mg bd. A placebo arm was added to determine the treatment difference between active treatments and placebo in order to support the non-inferiority margin chosen *a priori*.

The 3 co-primary efficacy endpoints were assessed at Week 12 using a 100 mm visual analog scale (VAS) and included the WOMAC Pain Subscale, the WOMAC Function Subscale and the Patient Global Assessment (PGA). For each of these, the null hypothesis was that Vimovo was inferior to celecoxib. Treatment differences between the 2 active groups were calculated as Vimovo minus celecoxib and 2-sided 95% CIs were also calculated for the differences in the least squares mean changes. A negative treatment difference in the WOMAC endpoints favoured Vimovo while a positive treatment difference in the PGA-VAS favoured Vimovo. The non-inferiority of Vimovo compared to celecoxib was established if the upper bound of the 2-sided 95% CI was less than or equal to +10 mm (on a scale of 0-100 mm) for the Pain and Function domains and if the lower bound of the 95% CI was greater than or equal to -10 mm (on a scale of 0-100 mm) for PGA-VAS. There were a number of secondary objectives including the comparisons with placebo.

Results of the non-inferiority study PN400-307

Of the 619 randomized patients, 612 were included in the ITT efficacy analysis (246 Vimovo, 242 celecoxib and 124 placebo). Non-inferiority of Vimovo compared to celecoxib was established since the upper bound of the 2-sided 95% CI for treatment difference was ≤ 10 mm for WOMAC Pain (LS Mean of Vimovo – celecoxib = -0.22, 95% CI

[-4.76, 4.32] and Function (LS Mean difference = -0.09, 95% CI [-4.57, 4.38] domains. For the PGA-VAS, the lower bound of the 95% CI was ≥ - 10 mm (LS Mean difference = - 0.47, 95% CI [-5, 4.14] (Tables 9, 10, 110). The non-inferiority of Vimovo to celecoxib 200 mg once daily was also confirmed in the PP population.

Both Vimovo and celecoxib showed statistically significantly ($p < 0.03$) greater improvement in WOMAC pain and function domains as well as PGA-VAS compared with placebo. The differences between both active and placebo were similar. These data demonstrated non-inferiority margins for both WOMAC domains and PGA-VAS of about 6-8 mm compared to the *a priori* margin of 10 mm. The other secondary efficacy results were generally supportive of the primary outcomes. Of note, subjects in the Vimovo treatment group consistently had a significantly greater percentage of days with no heartburn compared to celecoxib and placebo (78.4%, 71.5% and 66.1% in the Vimovo, celecoxib and placebo groups, respectively).

Results of the non-inferiority study PN400-309

Non-inferiority of Vimovo compared to celecoxib was established since the upper bound of the 2-sided 95% CI for treatment difference was ≤ 10 mm for WOMAC Pain (LS Mean of Vimovo – celecoxib = -1.30, 95% CI [-5.94, 3.34] and Function (LS Mean difference = -2.11, 95% CI [-6.82, 2.60] domains. For the PGA-VAS, the lower bound of the 95% CI was ≥ - 10 mm (LS Mean difference = 3.45, 95% CI [-1.41, 8.31] (Tables 12, 13, 14). The non-inferiority of Vimovo to celecoxib 200 mg once daily was also confirmed in the PP population.

Only Vimovo (not celecoxib) showed statistically significantly ($p < 0.05$) greater improvement in WOMAC pain and function domains as well as PGA-VAS compared with placebo. This may be reflective of the more severe OA in the celecoxib group but the placebo group appeared to have subjects with slightly more severe OA than the Vimovo group (by ACR Functional Class), yet Vimovo performed better than placebo. Again, these data demonstrated non-inferiority margins for both WOMAC domains and PGA-VAS of about 6-8 mm compared to the *a priori* margin of 10 mm. The other secondary efficacy results were somewhat supportive of the primary outcomes. Of note subjects in the Vimovo treatment group consistently had a significantly greater percentage of days with no heartburn compared to celecoxib and placebo (74%, 66% and 66% in the Vimovo, celecoxib and placebo groups, respectively).

Pooled efficacy results from the supportive, 3 month non-inferiority studies PN400-307 and PN400-309

These were generally supportive of the results of the individual studies.

Supportive Studies

Open label study PN400-304

An open label, multicentre, 12 month study PN400-304 evaluated the long term safety of Vimovo in 239 patients at high risk of NSAID associated ulcers. While no direct measurements of efficacy were performed in PN400-304, several safety endpoints supported the improved tolerability findings of the controlled Phase III evaluated above and demonstrated maintenance of effect beyond 6 months. Compliance with Vimovo was greater than 95% in patients who completed the study and more than 97% of the patients had > 70% compliance. There was no loss of effect of Vimovo in the reduction of the occurrence of pre-specified upper gastrointestinal AEs.

Safety

The Primary Safety Population (PSP) from the 6 month pivotal studies PN400-301 and PN400-302 included 428 and 426 patients treated with Vimovo and EC Naproxen, respectively. All patients in this pool had protocol required endoscopies to assess the primary endpoint of gastric ulcer.

The Supportive Safety Population (SSP) included patients from the 3 month studies PN400-307 and PN400-309 with 490, 488 and 246 patients treated with Vimovo, celecoxib and placebo, respectively. The Long term Safety Population (LSP) included 239 patients with a history of OA, RA, ankylosing spondylitis or other medical conditions expected to require daily NSAID therapy for at least 12 months in the open label one year study PN400-304. This included 135 patients who completed 12 months of treatment with Vimovo and these 135 patients formed the Twelve Month Population (TMP).

All the above studies were combined to form the Expanded Safety Population (ESP) to provide the largest pool of 1157 patients who took Vimovo.

A total of 1385 subjects received Vimovo in the clinical development program including 219 healthy volunteers and 1166 patients.

In the PSP overall, a lower proportion of patients who took Vimovo (78.3%) reported TEAEs compared with those who took EC naproxen (87.6%). The majority of TEAEs occurred in the SOC of *Gastrointestinal Disorders* with reduced rates in patients who took Vimovo compared to EC naproxen, especially reductions in gastric and duodenal ulcers and less injury to the upper GI tract seen at endoscopy. Additionally, lower rates of dyspepsia, heartburn and upper abdominal pain were seen with Vimovo compared to EC naproxen. The incidence of diarrhoea and gastritis was slightly higher in patients who took Vimovo compared to EC naproxen. The only other non-GI AEs more common in the Vimovo group were headaches and respiratory infections.

In the PSP, there were a higher proportion of patients in the EC naproxen group than in the Vimovo group with TEAEs that were considered by the investigator to be related to study treatment (75.8% vs 53.5%). This difference was primarily due to reports of TEAEs in *Gastrointestinal Disorders*. The preferred term gastritis was the only related TEAE more frequently reported in patients taking Vimovo (15.0%) than in patients taking EC naproxen (12.2%). The only related TEAE in the SOC of *Cardiac Disorders* was a single case of angina in a subject from the EC naproxen group.

In the SSP, the incidence of any TEAEs was similar in the Vimovo, celecoxib and placebo groups (53.3%, 49.6% and 51.2%, respectively). Dyspepsia was reported by slightly lesser proportion of patients treated with Vimovo (8.4%) compared with celecoxib (12.2%) and placebo (10.7%). However, patients assigned to Vimovo had more diarrhoea, constipation, dizziness and peripheral oedema than patients in the other treatment groups. Patients assigned to placebo reported more headache than those in the other treatment groups.

In the SSP, treatment related AEs were reported in 24.1% of patients taking Vimovo, 22.5% of patients taking celecoxib and 24.0% of patients taking placebo. The overall rate of related TEAEs in *Gastrointestinal Disorders* was 17.9% and was balanced between the 3 groups. Dyspepsia was reported as related by 6.9% of patients taking Vimovo, 9.0% of patients taking celecoxib, and 11.4% of patients taking placebo. All other preferred terms were generally balanced between treatment groups.

The overall safety of Vimovo was favourable compared with EC naproxen over 6 months of treatment and similar to that of celecoxib over 3 months of treatment.

Overall safety results in the LSP and the TMP suggested that continued exposure to Vimovo over 12 months did not increase the rates or the severity of TEAEs relative to those seen with shorter term exposure.

There were no deaths reported in any of the studies in this application. There were no SAEs reported in the Phase I studies. There were 58 treatment emergent SAEs (TESAEs) reported by 53 patients in the 6 Phase III studies. Overall, the frequencies of TESAEs were similar between Vimovo (2.7%) and EC naproxen (3.1%). The frequencies of SAEs were 1.6% in the celecoxib group and 0.4% in the placebo group. There was 1 SAE in the placebo group and none was reported with Arthrotec (in study PN400-303). When adjusted for exposure, the rates of SAEs were similar in the Vimovo, EC naproxen and celecoxib groups (6.8, 9.1 and 7.9 SAEs per 100 patient-years, respectively). The most common SAEs by SOC were in *Cardiac Disorders*. The frequencies of cardiac disorders were 0.5%, 0.5% and 0.2% in the Vimovo, EC naproxen and celecoxib groups, respectively; the rates of cardiac SAEs were 1.3, 1.4 and 1 per 100 patient years, respectively. There were 2 cases of atrial fibrillation that occurred while the patients were taking Vimovo but neither event was considered to be related to the study drug.

Adverse events known to be associated with age, including events from *Cardiac Disorders*, were relatively balanced between the treatment groups but did increase with age. While some events in *Gastrointestinal Disorders* (notably, reports of GU from the PSP) increased with age in the EC naproxen treatment group, they did not increase with age in the Vimovo treatment group.

The concomitant use of LDA did not appear to worsen the rate of adverse events in patients who took Vimovo. There were no substantive differences in the rates of duodenal ulcer, erosive gastritis or oesophagitis in those who took LDA compared to those who did not in either the Vimovo or the EC naproxen groups.

The incidence of discontinuations due to AEs was significantly higher in patients treated with EC naproxen compared to Vimovo mainly because of a higher incidence of gastrointestinal AEs. Peripheral oedema led to the withdrawal of study treatment in 4 Vimovo patients (0.3%) compared with none in the other treatment groups. Withdrawals from clinical studies due to TEAEs from *Cardiac Disorders* occurred in 0.4% and 0.5% of patients assigned to Vimovo and to EC naproxen, respectively. The TEAE of hypertension led to the withdrawal of 4 patients assigned to Vimovo, 2 patients assigned to EC naproxen, 3 patients assigned to celecoxib and 1 subject assigned to placebo. Withdrawals due to TEAEs did not proportionally increase with age in the Vimovo group while withdrawals did increase with age in the EC naproxen group.

Risk Management Plan

A Risk Management Plan (RMP) edition 1 dated August 2009 indicated that the majority of the identified risks are similar to those of the individual components of Vimovo, that is, naproxen and esomeprazole. However, newly identified safety concerns included osteoporotic fractures associated with prolonged use of PPIs (esomeprazole) and potential interaction of naproxen with clopidogrel.

The results of a recent cohort study (with a nested control analysis) (Garcia Rodriguez et al, 2009) identified another safety concern showing that newly diagnosed community acquired pneumonia (CAP) was significantly associated with current use of PPIs (RR=1.16, 95% CI: 1.03- 1.31) but not of H2 receptor antagonists (H2RAs) (RR=0.98, 95% CI: 0.80-1.20) with no clear duration response with either PPIs or H2RAs.[35] The occurrence of CAP appeared to be related to users of PPIs treated for dyspepsia or peptic ulcer suggesting that the small risk observed might be linked to the background risk of patients with this underlying indication rather than a direct effect of the drug. The risk of CAP will only be

followed within the framework of the routine pharmacovigilance process and no specific action to evaluate this risk is planned. No other new safety concerns were identified for Vimovo by the clinical evaluator.

The Office of Product Review concluded that a Risk Management Plan evaluation was not required for the fixed dose combination product Vimovo unless there was a specific issue of concern identified by the Delegate. *The Delegate asked for specific comment from the sponsor with regard to the issues of osteoporotic fractures and community acquired pneumonia.*

Clinical Evaluation and List of Questions

The clinical evaluator recommended approval. The evaluator recommended that the proposed indication should be clearly worded to convey that Vimovo is only to be used in patients who require both the components and that it should be specified that Vimovo is not recommended for initial treatment of acute pain and that controlled studies of the product do not extend beyond 6 months. That is, the evaluator recommended implementation of many elements of the US approved indication. The evaluator also asked a number of questions of the sponsor and they all deal with the issue of how a prescriber can initiate dosage reduction if required. Bearing in mind that NSAIDs in general are to be used for the shortest possible time at the lowest possible dose and that there is only one dosage strength (500 mg/20 mg) available and further that there no data supporting once daily use of this strength, the options for dosage reduction are unclear. Also esomeprazole as monotherapy is approved only for long term use at a daily dose of 20 mg once daily, half the effective daily dose recommended for the fixed dose combination. *The sponsor needs very clearly to articulate its position on this issue.*

As noted earlier, two dosage strengths, 500 mg/20 mg and 375 mg/20 mg are registered in the USA. The clinical evaluator asked the sponsor to clarify why a submission for approval of the two dosage strengths had not been made in Australia and to provide information on how the dosage adjustment can be made in patients requiring reduced dose of naproxen without compromising on symptomatic relief for patients. *The sponsor was also asked to clarify its position on the issue that, while esomeprazole as a monotherapy is approved for long term use at a daily dose of only 20 mg once daily, the daily dose of esomeprazole in Vimovo is 40 mg and further, how it would manage this apparent conflict in the PI for Vimovo.*

With regard to the issue of the availability of the two dosage strengths, the sponsor indicated that an analysis it undertook of Australian prescribing patterns led it to conclude that the 500 mg/200 mg strength would be far more frequently prescribed than the lower strength of 375 mg/20 mg. This was demonstrated by data from the BEACH report[37] which the sponsor included in its response. Insofar as the justification for only wishing to register the higher dosage strength is concerned, the sponsor's arguments were acceptable. This is largely because there are alternative dosage strategies available, utilising available monotherapies, which would allow a practitioner to prescribe the necessary amount of naproxen for the shortest time possible at the lowest dose possible. If it were not for the existence of these alternative dosing regimens, the Delegate indicated it would be difficult to agree with the sponsor. The sponsor goes on to state that there are prominent statements already proposed in the PI regarding the lack of suitability of Vimovo for patients requiring a different naproxen dose. However, it was the view of the Delegate, these do not go far enough and further statements are required.

[37] Bettering the Evaluation and Care of Health (BEACH) NSAIDs: January 2008-December 2008 (12 month data), 2009, University of Sydney School of Public Health.

The sponsor was also asked for comment on the issue that esomeprazole is approved as a monotherapy for long term use at a daily dose of only 20 mg once daily while the daily dose of esomeprazole in Vimovo is 40 mg.

The sponsor replied that available PK and PD data on Vimovo indicate that esomeprazole exposure following twice daily administration of Vimovo is greater than that reported for Nexium (enteric coated esomeprazole) 20 mg once daily but lower than that reported for Nexium 40 mg once daily, while the acid inhibition achieved with Vimovo twice daily is similar to that achieved with Nexium 40 mg once daily. The sponsor also presented a summary of the comparative C_{max} and AUC data of Vimovo twice daily and Nexium 20 mg once daily. The Delegate agreed that, given the magnitude of the differences in C_{max} and AUC between Vimovo twice daily and Nexium 20 mg once daily, it is not likely that there is a clinically relevant difference between these two regimens with regard to the potential for drug-drug interactions. The Delegate agreed that provided that there are prominent statements in the PI that there is only a maximum of 6 months of controlled clinical trial use of Vimovo.

Initial Risk Benefit Analysis

Delegate Considerations

Efficacy

The gastroprotective efficacy of the esomeprazole component has been conclusively demonstrated in 2 identical, pivotal Phase III studies [PN400-301 and PN400-302] which showed reduced rates of NSAID associated GI side effects including gastric ulcers, duodenal ulcers, dyspepsia and upper GI AEs in patients at increased risk of developing ulcers based on age, ulcer history and LDA use with the use of Vimovo 500 mg/20 mg bd compared with the use of EC Naprosyn 500 mg bd.

Phase III studies in the Vimovo clinical development programme [PN400-307 and PN400-309] demonstrated that Vimovo 500 mg/20 mg twice daily is non-inferior to celecoxib 200 mg once daily in the management of pain associated with OA of the knee.

While the gastroprotective efficacy of Vimovo has been demonstrated in comparison with enteric coated naproxen, only about 6-7% of patients in PN400-301 [15 patients in Vimovo arm and 13 in EC naproxen arm] and about 9-11% of patients in PN400-302 [18 patients in Vimovo arm and 23 in EC naproxen arm] had had an ulcer within the previous 5 years, that is an ulcer report whether formally documented or not. The Delegate was of the opinion that this is not a sufficiently large number of subjects to enable the complete removal of the present Contraindications in the Naprosyn PI relating to ulcer history when they are transferred to the proposed PI for Vimovo.

Safety and RMP

The safety profile of Vimovo is based on the well documented profiles of the individual components, the demonstrated lack of PK interaction between them and the safety data from the Vimovo development program. The risks associated with administration of the individual components of Vimovo are well established and no new safety concerns were identified during the Vimovo clinical development program.

In a wide ranging review of NSAID use conducted by the TGA in 2007, several recommendations were made. The most important of these, implemented in the PI documents of all NSAIDs, was that doctors should continue to prescribe and patients continue to use the lowest effective dose NSAID for the shortest possible duration to control symptoms. The proposed PI must be consistent with all of the recommendations of that review.

As noted by the clinical evaluator, Vimovo is mainly intended for use in patients requiring a higher dose of naproxen. It can only be intended for those patients for whom a total daily dose of naproxen 1000 mg is needed and is appropriate. The sponsor has proposed statements in the PI regarding the lack of suitability of Vimovo for patients requiring a different naproxen dose, specifically in the Precautions section (*General, Hepatic Insufficiency & Renal Impairment* headings) and in the Dosage and Administration section (*Patients with renal impairment and Patients with hepatic impairment*). Prescription of a reduced dose of naproxen with Vimovo (such as the 375 mg/20 mg dose approved in USA) is not an option for Australia as this present submission is only for the 500 mg/20 mg dose. As noted by the clinical evaluator, it is clear that Vimovo 500 mg/20 mg is an effective therapeutic strategy only in patients who require a daily dose of 1000 mg naproxen. If a daily dose of 1000 mg is not considered appropriate, then alternative therapeutic strategies need to be used and necessarily these involve the return to monotherapies. Vimovo tablets cannot be broken or split. Vimovo tablets have only been studied when taken twice daily. Taking them once daily is not an option because 24 h symptom control will not be available to the patient. The availability of these alternative treatment strategies do not only apply to patients with renal or hepatic impairment. The issue applies to anyone for whom and for whatever reason, a dose of 1000 mg total daily naproxen is inappropriate. It is quite simple and that is why there needs to be a number of specific directions in the PI regarding the situation where a dose of 1000 mg total daily naproxen is inappropriate. Further, these specific directions must be very clearly articulated, transparent and not able to be missed by the reader. There is already a statement to this effect in the Precautions section. This needs to be repeated in the Dosage and Administration section where it also needs to be reinforced with a statement that alternative dosing strategies can only be achieved with the use of single component therapies, that is the taking of naproxen on its own plus esomeprazole on its own. The Delegate regarded the issue to be of such importance that it must be made part of the Indications. Clearly, it was also an issue of concern in the EU and the Delegate requested that the sponsor add the following wording to the indication, "*and where treatment with lower doses of naproxen or of other NSAIDs is not considered sufficient*". *The Delegate requested specific advice on this issue from the ACPM.*

The Delegate agreed with the clinical evaluator that there elements of the wording of the US approved indication of Vimovo which touch on other important issues. The first of these is that Vimovo is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen containing products. This is a most important precaution to be placed in the PI and so it should be placed in the Precautions section. This will further promote the appropriate use of this fixed dose combination product. The second of the issues is that controlled studies of the efficacy and safety of Vimovo do not extend beyond 6 months. This statement should be prominently displayed in the first paragraph of the Clinical Trials section of the PI which should also include a general preamble to that section. The Delegate was of the opinion that such a statement will mitigate to some extent the concerns about the prolonged use of esomeprazole. *The Delegate requested specific advice on this issue from the ACPM*. *The sponsor was requested to provide the most up-to-date information on the newly identified safety concerns of osteoporotic fractures in association with prolonged use of PPIs and of community acquired pneumonia in association with the use of PPIs, including the rates of these risks and the strengths of the findings.* The Delegate was unable to find any comment about these issues in the PI for the monotherapy Nexium and directed the following questions to the sponsor.

Are there any amendments planned or pending to the latter PI with regard to these concerns?

What particular pharmacovigilance monitoring or risk minimisation strategies does the sponsor have or intend to put in place with regard to these concerns?

Indication

As noted already by the Delegate, Vimovo is only intended for those patients for whom a total daily dose of naproxen 1000 mg is needed and is appropriate. Therefore the delegate requested the indication be amended to the following:

Vimovo is indicated for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, in patients at risk of developing gastric and/or duodenal ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs) and where treatment with lower doses of naproxen or of other NSAIDs is not considered sufficient.

Summary

Vimovo has been demonstrated to be non-inferior to celecoxib 200 mg once daily in the management of pain associated with OA of the knee and to offer significantly greater gastroprotective effect than EC naproxen.

There were two issues of most concern to the Delegate. The first of these was that the proposed PI for Vimovo 500 mg/20 mg must unambiguously and as effectively as possible highlight the fact that it is only an effective therapeutic strategy in patients who require a total daily dose of 1000 mg naproxen and for whom that dose is both appropriate and tolerable. The second concerns the implied long term use of esomeprazole in this product. As noted, controlled clinical studies of only 6 months are available. There is supportive evidence in a sufficient number of patients for 12 months to satisfy the appropriate guideline. However, the sponsor has been asked a number of questions concerning the association of both osteoporotic fractures and of community-acquired pneumonia with the use of proton pump inhibitors. These must be addressed before this application can be approved.

The Delegate proposed to approve the submission conditional upon full implementation of requested amendments to the PI (not discussed in detail in this AusPAR), including the revised indication which follows:

Vimovo is indicated for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, in patients at risk of developing gastric ulcers and/or duodenal ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs) and where treatment with lower doses of naproxen or of other NSAIDs is not considered sufficient.

The sponsor should address the issues shown in italics in this section in its Pre-ACPM response.

Response from Sponsor

The sponsor noted that the Delegate proposed approval of the following indication:

Vimovo is indicated for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, in patients at risk of developing gastric and/or duodenal ulcers associated with nonsteroidal anti-inflammatory drugs (NSAIDs) and where treatment with lower doses of naproxen or <u>lower doses</u> of other NSAIDs is not considered sufficient.

The sponsor agreed with the Delegate that this is a suitable indication, except that the second "lower doses" (indicated by underlining above) was proposed to clarify that a patient could be prescribed Vimovo without first having to trial maximum doses of other NSAIDs.

The sponsor also addressed the questions directed by the Delegate.

The potential for local GI tract toxicity as a result of release of naproxen in the stomach and that of the uncertainty of the relationship of the* in vitro *and* in vivo *degradation profiles of esomeprazole.

The sponsor noted the nonclinical evaluator's conclusion that:

"Both active substances have been approved and on the market for many years and there are extensive nonclinical and clinical data available for the individual components. Thus, there are no nonclinical objections to the registration of Vimovo, provided the clinical data adequately demonstrate the safety and efficacy of the combination product, particularly with respect to the potential for local GI tract toxicity as a result of release of naproxen in the stomach."

The clinical evaluator and Delegate have both concluded that the clinical data adequately address the safety and efficacy of Vimovo. Furthermore, naproxen is currently supplied in Australia in an IR product (Naprosyn) and thus a product directly releasing naproxen into the stomach is already registered and therefore accepted as safe.

The sponsor also noted the nonclinical evaluator's comments in relation to the 2 issues as follows:

"Oral esomeprazole administration to rats and dogs resulted in increased pH of gastric fluid (values up to 8.4 and 7.7, respectively), which may result in degradation of the pH sensitive coating of the naproxen component of Vimovo tablets in the stomach, rather than the small intestine, which has potential implications for local GI tract toxicity. The *in vitro* degradation profile of esomeprazole in gastric fluid from rats, dogs and humans at lower pH values (but not the maximum observed pH values) was characterised; the relationship of the *in vitro* degradation profile to that anticipated *in vivo* is unknown. Thus, it is unclear whether previous toxicity studies with esomeprazole adequately addressed the safety of degradation products anticipated clinically."

The sponsor noted that it is a misconception that the increase in pH in the stomachs of the rats and dogs dosed with a suspension of IR esomeprazole has any direct relevance as to any changes in the stomach of a patient who takes a Vimovo tablet, as the animals received a completely different formulation that was neither Vimovo nor a combination of naproxen and esomeprazole. It must also be taken into account that the rats received 280 mg/kg and the dogs 28 mg/kg IR esomeprazole, compared to 0.4 mg/kg in man (20 mg esomeprazole in a 50 kg person). The objective of the new toxicity studies performed was not to illustrate any changes in pH in the stomach following Vimovo administration and these studies are therefore not relevant in this context. They were instead designed to show that:

i. The pH levels in the stomachs of the rats and dogs in the previous oral omeprazole/esomeprazole toxicity studies resulted in a relevant acid degradation profile of esomeprazole compared to that which occurs in a patient who takes the IR compound.

ii. The relative abundances of the different acid degradation products formed in the stomach are similar in rats, dogs and man.

iii. The degradation profile of IR esomeprazole in the stomach is similar to that of EC esomeprazole once it has entered the small intestine in a human.

For obvious reasons, there are practical limitations when dosing animals with a drug, especially in rodents, and particularly when high and toxicologically relevant doses are required. It might be physically possible to give a limited number of Vimovo tablets to a dog but not a sufficient number to be able to attain the required high dose of 28 mg/kg esomeprazole. In addition, naproxen cannot be given to dogs at toxicological doses; due to

the extremely long half life of this drug in this species, repeated dosing with naproxen is not feasible. Neither is naproxen treatment in rodents relevant, as these animals are also very sensitive to NSAIDs and show toxic symptoms at doses far below clinical exposure. In all the nonclinical studies with either esomeprazole or omeprazole, a suspension of non-EC esomeprazole Mg in buffered hydroxypropyl methyl cellulose (HPMC) or a solution of esomeprazole Na in water or physiological saline has been used. Solutions of esomeprazole Na have an inherently high pH (>10.0) and thus also show several hours of chemical stability at room temperature, but the esomeprazole Mg suspensions in HPMC must be buffered to pH 9.6 in order to attain sufficient chemical stability (8 h at room temperature) to enable dosing of the animals in the toxicity studies.

In these 2 studies to map the pH in the animal stomachs, the pH values at 24 h after dosing (HAD) were considered to be particularly important, as this is the pH range that the non-EC (IR) esomeprazole will encounter directly after the dosing formulation is instilled into the gastric lumen, when the animals in a repeat dose toxicity study are dosed each day. Thus, this is the pH range at which initial acid degradation of the IR esomeprazole will occur. In rats, the inter- and intra-individual variation in the pH values of the gastric fluid noted at this time point was large, but both the mean and range values in the vehicle (which also had a pH of 9.6) and esomeprazole treated rats were very similar. Therefore it was considered that at 24 HAD there was no remaining influence of treatment with either the vehicle and/or esomeprazole. These pH values can thus be regarded as base line values, equivalent to those in untreated animals.

Dogs, like humans, do not have a constant production of gastric acid. This increases for instance following overnight fasting, when the animals are hungry, or when they smell or anticipate the availability of food. This explains the large variation in pH values in the gastric fluid at base line (in the morning, before feeding) noted in this study; about 30 to 40% of the animals showed pH values of the gastric fluid that lay in the range of pH 1 to 2, while the remaining 60 to 70% lay in the range of pH 3 to 7. This corresponds well with knowledge from the literature and previous but unpublished studies that approximately 30% of untreated and fasting dogs will have a gastric pH of about 1 to 2, and the remainder will have a neutral gastric pH. In the dogs, the inter- and intra-individual variation in the pH values of the gastric fluid noted at 24 HAD was large, but both the mean and range values in the vehicle and esomeprazole treated dogs were very similar. Therefore it was considered that, as in rats, there was no remaining influence of treatment with either the vehicle and/or esomeprazole at 24 HAD.

These pH values can thus be regarded as base line values, equivalent to those in untreated animals.

The sponsor noted that the pH changes in the rat and dog stomachs were discussed in detail in the presentation of the relevant toxicology studies and these were summarised.

The difference between the pH changes in the stomach in the animals dosed with IR esomeprazole in the toxicity studies and those in patients in the clinical situation has been confirmed in multiple clinical studies using Vimovo, and it is these studies that should be considered as representative for the clinical use of the naproxen/esomeprazole combination in Vimovo.

Further to the above, the sponsor also noted that the nonclinical evaluator suggested that the issue “may be addressable from clinical data”, and that both the clinical evaluator and the Delegate concluded that the clinical data adequately address the safety and efficacy of Vimovo, as stated at the beginning of the sponsor’s comments

Clinical data indicate that at steady state there are times during the day when the esomeprazole component of Vimovo, dosed twice daily causes intragastric pH to rise

above 5. Thus, the sponsor would not exclude the possibility that small amounts of naproxen may be released in the stomach, albeit significantly less than with non-EC naproxen.

However, NSAID associated gastroduodenal damage can be substantially reduced by elevating intragastric pH above 4.0 (see Yeomans et al 1998) and this is borne out in clinical trials demonstrating an improved upper GI profile for Vimovo versus EC naproxen.[38] In Study PN400-101, Vimovo was associated with a significantly lower proportion of patients with endoscopically detected gastroduodenal injury (Grade 3 or 4 Lanza scores) compared to EC naproxen. In the Phase III program, Vimovo was shown to reduce the occurrence of gastric ulcers, duodenal ulcers, and NSAID-associated upper GI adverse events, including dyspepsia, as compared to EC naproxen. Therefore, the clinical data do not point to an issue related to release of the naproxen component of Vimovo in the stomach.

The sponsor also considered that it was a very important point that naproxen in doses of up to 1000 mg daily is registered and supplied in Australia as an IR product (Naprosyn) and thus extensive postmarketing experience already exists for a product where naproxen is released into the stomach. This alone suggests that any potential for local GI tract toxicity from a probably insignificant release of naproxen in the stomach from Vimovo should not present concern or uncertainty.

The* in vitro *degradation profile of esomeprazole in gastric fluid from rats, dogs and humans at lower pH values (but not the maximum observed pH values) was characterised; the relationship of the* in vitro *degradation profile to that anticipated* in vivo *is unknown. Thus, it is unclear whether previous toxicity studies with esomeprazole adequately addressed the safety of degradation products anticipated clinically.

The sponsor noted that benzimidazole PPIs are unstable in an acidic environment and as such have traditionally been EC to reduce degradation in the acidic environment of the stomach, prior to absorption from the small intestine. If non-EC (IR) esomeprazole is given clinically, some degradation of esomeprazole in the acidic environment of the stomach of the patient is anticipated. Potentially, new degradation products may result compared to when EC esomeprazole is given, and also these may vary in quantity and/or identity at different pH values in the stomach. Even if these acid degradation products are not a result of esomeprazole degradation in the drug product, it was considered appropriate to investigate whether or not they have been qualified in previous toxicity studies using IR esomeprazole.

Structure activity relationship (SAR) analyses and other information on mutagenicity and toxicity studies on the degradation products of esomeprazole originating from previous toxicology/qualification packages for other AstraZeneca projects were included in the application as additional supporting information. In particular, the SAR analyses that were included in the original submission are considered to add relevant information as to the lack of a mutagenic potential for all the identified acid degradation products of esomeprazole.

The information from these studies was presented and discussed in detail in the original submission and was included with the response.

[38] Yeomans ND, Tulassay Z, Juhasz L, Racz I, Howard JM, van Rensburg J, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal anti-inflammatory drugs. N Engl J Med 1998; 338: 719-26.

The sponsor noted that it is not experimentally feasible to study the acid degradation of IR esomeprazole *in situ* in the stomach, in either animals or man. In the changing environment of the stomach it would be impossible to standardise (or even record) such factors as the acidity and volume of stomach content, the rate of dissolution of the IR compound/Vimovo tablet, the food content, gastric motility/emptying, sampling volume etc. A further issue is the instability and inherent variability of the acid degradation process, which would continue during and after sampling and during sample processing. Thus, analysis results obtained would not truly represent the actual situation in the stomach at the time of sampling. It was therefore considered appropriate and justified to instead investigate the acid degradation of esomeprazole under well controlled *in vitro* conditions, enabling direct comparison of the degradation profiles and amounts of degradation products formed in standardised experimental systems using gastric and intestinal fluids.

Therefore, the profile of degradation products formed *in vitro* was investigated in 2 studies in rat, dog, and human gastric fluid at pH 2 and 5, and simulated intestinal fluid at pH 6.5. The profiles were qualitatively similar at all 3 pH values and independent of the source of gastric or simulated intestinal fluid, although there were quantitative differences due to the increased stability of esomeprazole with increasing pH.

While the relationship between the *in vitro* and *in vivo* degradation profiles is, in fact, unknown, based on the sponsor's *in vitro* studies, a foundation was provided for what can be anticipated *in vivo*. The design of the sponsor's *in vitro* studies mimics the *in vivo* situation as far as was reasonably possible. The sponsor did consider sampling of gastric fluid from *in vivo* studies, but discarded any such plans based on that the results from such studies would be inconclusive.

Measurement of absolute amounts of degradation products *in vivo* in rats or dogs in gastric contents would be compromised because, for example, aspiration of gastric fluid after esomeprazole suspension dosing would give highly variable, non-homogeneous samples. Degradation continues after sampling and there is no known procedure to stop degradation during transportation and pending analysis. The dissolution rate of esomeprazole suspension will be variable, depending on non-stirred conditions, pH and chemical degradation. Furthermore, samples will be contaminated with solid esomeprazole suspension that will result in incorrect estimates of the fraction of esomeprazole degraded. For humans, IR esomeprazole will dissolve rapidly, but the samples will nonetheless be non-homogeneous and the degradation would be influenced by gastric pH and gastric emptying variability.

The results in these *in vitro* studies showed that the degradation product profiles of esomeprazole in gastric fluid from humans, rats and dogs and in simulated intestinal fluid were similar, both qualitatively and quantitatively.

Based on these data, it was concluded that humans given IR esomeprazole are exposed to the same degradation products, in similar relative proportions, as animals that were treated orally with the IR compound in previous toxicity studies with esomeprazole. Similar degradation profiles were also observed in simulated intestinal fluid, mimicking the conditions to which EC esomeprazole is exposed after ingestion of a standard EC esomeprazole formulation. In conclusion, the sponsor maintained that these acid degradation products have been adequately assessed and qualified in previous toxicity studies using IR esomeprazole.

Based on *in vitro* studies the sponsor therefore concluded that it is anticipated that humans and animals will be exposed to the same degradation products in similar proportions, regardless of if this is in GI fluid from IR esomeprazole or in the intestine

from EC esomeprazole. Although the absolute fraction of esomeprazole degradation products formed *in vivo* has not been established, it is reasonable to assume that the amounts of degradation products formed in animals in the toxicity studies were higher than those from the IR esomeprazole in humans given Vimovo, based on the significantly higher doses administered to the animals; approximately 0.4 mg/kg in a 50 kg human, whereas rats and dogs were dosed at up to 280 and 28 mg/kg respectively.

The logical chain establishing bioequivalence between the Vimovo products used in the Phase I clinical trials and the Phase III clinical trials and the actual product proposed for marketing. In this same chain of evidence establishing bioequivalence, the sponsor is requested to indicate which particular Vimovo product was used at which point or in which study.

The sponsor provided this information which was complemented by a table to illustrate the formulations used.

The most up-to-date information on the newly identified safety concerns of osteoporotic fractures in association with prolonged use of PPIs and of community acquired pneumonia in association with the use of PPIs, including the rates of these risks and the strengths of the findings. Also, the delegate was unable to find any comment about these issues in the PI for the monotherapy Nexium. Are there any amendments planned or pending to the latter PI with regard to these concerns? What particular pharmacovigilance monitoring or risk minimisation strategies does the sponsor have or intend to put in place with regard to these concerns?

The sponsor noted that available PK and PD data on Vimovo indicate that esomeprazole exposure following bd administration of Vimovo (IR esomeprazole 20 mg) is greater than that reported for Nexium (EC esomeprazole) 20 mg once daily (qd) but lower than that reported for Nexium 40 mg qd, while the level of intragastric acid inhibition achieved with Vimovo bd is similar to that achieved with Nexium 40 mg qd. The safety of Nexium has been very well documented and the safety profiles of Nexium 20 mg qd and Nexium 40 mg qd are similar. In general, no relation to dose or length of treatment has been seen with Nexium at doses up to 40 mg bd.

The Patient Risk Management Plan (RMP) has been updated with respect to the issues of osteoporotic fractures and lower respiratory infections and was included with the response. There were no changes to the Vimovo core data sheet as a result of these updates. Although the FDA imposed bone fracture labelling for Vimovo and for the entire PPI class in 2010, the sponsor's position is that there is insufficient evidence to warrant a warning in the label.

Osteoporosis/Osteoporotic fractures

With regard to the issue of osteoporosis, the sponsor provided an extract from the "Important Identified and Potential Risks" of the second edition RMP which described the formation of an expert panel and the conduct of a pharmacoepidemiological study to estimate the risk of hip fracture with and without concurrent episode of fall and associated with use of PPIs and H_2-receptor antagonists, and to estimate the dose and duration response of PPIs and H_2-receptor antagonists on the risk of hip fracture with and without concurrent episode of fall. It was decided to keep 'osteoporosis/osteoporotic fractures' under close surveillance including a questionnaire for ensuring comprehensive data collection for AE reports during marketed use."

The pharmacoepidemiological study on the association between acid suppressing treatment and the risk of hip fracture and falls in The Health Improvement Network

database (THIN) has been completed and the study report was provided. An excerpt from the Discussion section of the report was provided:

"In conclusion, our population-based cohort study showed a small but statistically significant, increased risk of hip fractures in patients on PPI (OR 1.09, 95%CI, 1.01-1.17). For current users of PPIs on high dose [>esomeprazole 40 mg, omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg and rabeprazole 20 mg, cimetidine 800 mg, famotidine 40 mg, nizatidine 300 mg and ranitidine 300 mg] the OR was 1.31 (95% CI 1.06-1.61). Among users of H_2RAs a small increased risk of hip fractures was found, OR 1.04 (95% CI 0.90-1.19), however not statistically significant. For current users of H_2RAs a statistically significant increased risk was found when taking high daily dose (OR 2.77, 95% CI 1.21-6.37). No evidence was found for an increased risk of hip fractures with duration of use among users of PPIs and H_2RAs. No evidence was found for an increased risk of falls among users of PPIs and H_2RAs s. The marked reduction between the crude estimate of risk and the adjusted one together with the small increased risk of hip fracture for current PPI users after adjustment and lack of duration effect is compatible with minor residual confounding underlying this small observed increased risk."

Thus from the RMP analysis and the above summarised study, the sponsor's position was that changes to the core data sheet are not needed with respect to osteoporotic fractures and consequently there was no proposal to update the Australian Nexium PI. The bone fracture paragraph in the USPI was a result of an FDA PPI class labelling imposition in August 2010. The sponsor noted that PIs for other PPIs in Australia do not have a bone fracture precaution.

Community acquired pneumonia

With regard to community acquired pneumonia (CAP) the sponsor provided an extract from the "Important Identified and Potential Risks" of the second edition RMP as follows:

"The relationship between gastric suppressive therapy and pneumonia is controversial. It has been proposed that use of gastric acid suppressive therapy is associated with an increased risk of community acquired pneumonia, presumably due to reduction of gastric acid secretion resulting in facilitating oral infections (Laheij RJ et al 2004).[39] However, data from two other large epidemiological cohorts, one with a nested case control analysis, but in which the GPRD database in the UK was used, did not show any increased risk for pneumonia in asthma patients treated with PPIs compared to the asthma control group (Ruigómez A et al 2004, Ruigómez A et al 2005).[40,41]"

The sponsor's position concerning CAP as described in the RMP is that no evidence for a link between CAP and the use of esomeprazole has been revealed; however, it is kept under close surveillance for Vimovo and addressed specifically during the routine safety surveillance work and in the Periodic Safety Update Reports (PSURs).

Thus, at this point in time there are no amendments planned for the Australian Nexium PI relating to CAP.

The sponsor also provided supportive comments with respect to advice sought by the Delegate from the ACPM.

[39] Laheij RJH, Sturkenboom MCJM, Hassing R-J, Dieleman J, Stricker BHC, Jansen JBMJ. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA 2004; 292: 1955-1960.

[40] Ruigómez A, García Rodríguez LA, Wallander M-A, Johansson, S, Graffner F, Dent J. Natural history of gastro-oesophageal reflux disease diagnosed in general practice. Aliment Pharmacol Ther 2004; 20: 751-760.

[41] Ruigómez A, García Rodríguez LA, Wallander M-A, Johansson, S, Thomas M, Price D. Gastrooesophageal reflux disease and asthma: a longitudinal study in UK general practice. Chest 2005; 128: 85-93.

Issue of alternative therapeutic regimens when dose of less than 1000 mg of naproxen is required

The sponsor proposed an additional sentence for the Dosage and Administration section of the PI.

Long term use of esomeprazole 20 mg twice daily

The sponsor drew attention to their response provided to the clinical evaluation report in which a summary of comparative C_{max} and AUC data of Vimovo bd and Nexium 20 mg qd was presented. The conclusion from this is that considering the magnitude of difference in both C_{max} and AUC between Vimovo bd and Nexium 20 mg qd, it is not likely that there is a clinically relevant difference between Vimovo bd and Nexium 20 mg qd in potential for drug-drug interaction. The data show that esomeprazole AUC and C_{max} values for Vimovo bd (a total daily dose of 40 mg of IR esomeprazole)are significantly closer to Nexium 20 mg qd (20 mg EC, delayed release esomeprazole) than Nexium 40 mg qd (40 mg EC, delayed release esomeprazole).

Issue of use when patient presents with upper GI symptoms

The sponsor proposed an additional Precaution of the PI.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended rejection of the submission.

In making the recommendation that the overall risk benefit profile for this product was negative, the ACPM considered the following -:

Efficacy: The population at risk of gastrointestinal ulceration was not sufficiently defined to provide a positive risk benefit profile to support the rationale for the new fixed dose combination. While the primary clinical endpoint was endoscopically proven gastrointestinal ulceration, it was not clear whether these were determined to be symptomatic or clinically significant. The ACPM noted that many patients potentially at risk were excluded from the study and that no data were given on the rate of gastrointestinal haemorrhage, perforation or other serious gastrointestinal adverse events.

The proposed indications and dosage regimens did not reflect current recommended best practice guidelines in relation to lowest effective dose or duration of therapy for the separate agents. The ACPM reinforced its view that fixed dose combinations should not be used as first dose therapies and that monotherapy should be initially trialled and established. The ACPM advised that the study was limited to 6 months and therefore the long term use has not been adequately studied or reflected in the Dosage and Administration or Precautions sections of the PI/CMI.

Safety: Pivotal studies did not define the population at risk of NSAID induced GI risks and the benefits conferred by the proposed combination.

The ACPM expressed significant concern that the proposed indications for Vimovo did not align with the current indications for the separate active ingredient products. This will impact on the population utilising the proposed product and therefore its use will be in a population that was not included in the study and hence likely to be exposed to increased safety risks.

Fixed Dose Rationale: The ACPM advised that there is a risk of inappropriate exposure to unnecessarily high doses of both agents which is not consistent with the current recommendations for the individual agents.

In addition, the ACPM expressed significant concerns about the omissions from the PI and CMI but these are outside the scope of this AusPAR.

The ACPM noted the increased fracture rates for proton pump inhibitors generally, and recommended that a statement of this risk be considered for insertion in the PIs of all the drugs in this class.

Further Risk Benefit Analysis

The submission was forwarded a second time to the ACPM for a reconsideration of the issues. The Delegate indicated that the sponsor had sent to the TGA a detailed response to the ACPM recommendation described above.

Delegate's Summary of the Sponsor Response to the ACPM

The definition of the population at risk

The ACPM had resolved that the population at risk of gastrointestinal ulceration was not sufficiently defined. The inclusion criteria required that patients 18 to 49 years of age must have had a documented, uncomplicated gastric ulcer or duodenal ulcer within 5 years of study enrolment. Patients 50 years of age or older were eligible to be randomised regardless of ulcer history. The study population also included smokers, patients taking concomitant low dose aspirin or corticosteroids and patients with comorbid disease. All of these along with age and a history of gastrointestinal ulcerations have been shown to increase the risk of gastrointestinal events associated with NSAID therapy. Thus the study population included patients with one or more known, published risk factors for NSAID associated ulcers. The sponsor acknowledged that patients with a documented history of a complicated upper gastrointestinal event such as bleeding, perforation or obstruction were excluded from the studies presented in the submission. However, as pointed out by the sponsor, the prevalence of patients with a history of prior ulcer complication is very low and, given this, the sponsor did not agree that the implementation of this exclusion criterion would have resulted in "many patients potentially at risk" having been excluded from the study.

The Delegate noted that this argument would appear to have some merit and requested therefore that the sponsor enlarge upon this argument by stating exactly how low is the prevalence of patients with a history of prior ulcer complication and by giving as precise an estimate as possible of the number of "patients potentially at risk" who may have been excluded from the relevant studies.

Clinical relevance of endoscopically detected ulcers

This was an issue discussed at a November 2010 US FDA Advisory Committee meeting and the sponsor presented evidence to support the view that endoscopically detected ulcers are correlated with the occurrence of clinical gastrointestinal events. This evidence was best summed up in the recent review by Moore et al 2009[42] cited by the sponsor. The Delegate summarised the major points of this review:

1. Endoscopic ulcers are clinically important in and of themselves; in practice, they always precipitate a change in patient management.

[42] Moore et al 2009. Evidence for endoscopic ulcers as meaningful surrogate endpoint for clinically significant upper gastrointestinal harm, Clin Gastroenterol Hepatol 2009; 7: 1156-1163.

2. Endoscopic ulcers are prognostic of more serious upper gastrointestinal events as they represent an early step in the biological progression from mucosal injury to ulcer and ulcer complications.
3. There is a substantial body of evidence that risk factors and interventions generally affect the incidence of both endoscopic ulcers and serious upper gastrointestinal events in the same direction and to a comparable extent.

Having considered all the evidence put before it, the US FDA Advisory Committee reached a consensus view that, while imperfect, the relative risk reduction of endoscopically diagnosed gastroduodenal ulcers observed in clinical trials is a clinically meaningful endpoint. The US FDA minutes, with this statement, were provided in the sponsor's pre-ACPM response.

The Delegate indicated that the sponsor should address this issue further.

The second point expounded by Moore is that endoscopic ulcers represent an early step in the biological progression from mucosal injury to ulcer and ulcer complications.

The Delegate asked the sponsor whether there were any data which estimate the likelihood that the earliest sign of mucosal injury identifiable as an ulcer will progress for example to become an larger ulcer and then progress further to an ulcer complication. In the pivotal study PN400-301, the cumulative observed incidence of gastric ulcers (the primary endpoint) at 6 months was 4.1% (9/218) in the fixed dose combination group versus 23.1% (50/216) in the naproxen only group while in the second pivotal study PN400-302, the corresponding values were 7.1% (15/210) versus 24.3% (51/210). These results were highly statistically significant (all p-values < 0.001). *The Delegate requested that the sponsor indicate whether there was any real, qualitative difference in the make-up of the gastric ulcers observed in each treatment group, in terms of severity.*

Ulcer complications in the Vimovo program

In its resolution, the ACPM noted that no data were given on the rate of gastrointestinal haemorrhage, perforation or other serious gastrointestinal adverse events. In reply, the sponsor indicated that complications of NSAID associated upper gastrointestinal adverse events such as bleeding, obstruction and perforation have been estimated to occur in approximately 1% to 4% of chronic NSAID users per year. Thus, given the duration of treatment and the size (approximately 2300 patients) of the population studied in the Vimovo program, a low incidence of upper gastrointestinal complications was expected and there were only 2 events:

1. One serious upper GI event (haematemesis with a source for upper gastrointestinal bleeding not found) among the patients who received Vimovo
2. One event (bleeding DU) among the patients who received naproxen only.

The sponsor was asked to confirm whether or not the second event, namely the bleeding DU, was also serious.

The sponsor demonstrated that the above rate of upper GIT complications was consistent with the corresponding rate from the Nexium NSAID studies conducted by the sponsor. Given the low rates of such complications, it would require much larger, longer studies to demonstrate a statistically significant reduction in these rates. There may also be ethical issues in the conducting of such studies. The Delegate indicated that it would be anticipated that treatment with a concomitant PPI reduces the rates of such serious complications.

The Delegate requested that the sponsor provide data on this issue or discuss the consideration it has given to the sorts of data collection activities which could be undertaken in the postmarketing period to throw light on this matter?

Proposed indications and dosage regimens do not reflect current recommended best practice guidelines

As noted already, the sponsor, in the pre-ACPM response had already agreed to the addition of a rider to the indications to restrict use of Vimovo to those situations where lower doses of naproxen or of other NSAIDs are not considered sufficient. The sponsor had also agreed to the inclusion of a statement in the Dosage and Administration section of the PI reinforcing the use of the lowest possible dose for the shortest possible time. In the response to the ACPM resolution, the sponsor offered to modify the indications, by addition of the following statement:

"After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used. If a total daily dose of 1 g of naproxen is not considered appropriate, alternative therapeutic regimens should be utilised".

The Delegate agreed that such a statement would help considerably in clarifying this issue and asked the ACPM whether it agrees.

With regard to the ACPM's expressed concerns about the "lowest effective dose" (of either the naproxen or the esomeprazole components), the sponsor noted that naproxen as a monotherapy is dosed twice daily and therefore Vimovo with its esomeprazole component must likewise be dosed daily and that use of an immediate release formulation of esomeprazole allows for the sequential release of esomeprazole first, followed by the release of naproxen. The sponsor supplied data which demonstrates that the most common dose of naproxen prescribed by Australian general practitioners (GPs) is a total daily dose of 1000 mg (usually as 500 mg bd). The Delegate had already expressed concern that the lower strength fixed dose combination, 375 mg/20 mg, will not be available in Australia, as it is in the USA.

The sponsor was requested to clarify its position with regard to the availability of the lower dose strength in Australia. The Delegate accepted the argument of the sponsor that 20 mg twice daily esomeprazole is the lowest dose of the immediate release formulation which has been shown to provide effective and consistent gastroprotection.

Fixed dose combinations should not be used as first line therapies

The Delegate agreed with the sponsor that Vimovo meets the criteria for such a product as outlined in the TGA-adopted EU guideline in that one component of the product counteracts an adverse reaction produced by another component.[28] The sponsor referred to evidence from the literature which showed that compliance with chronic treatment regimens is greater with fixed dose combination drugs than it is with the separate monotherapies. The sponsor was uncertain whether the focus of ACPM's concern was to do with dose titration or with sequential prescribing. The Delegate acknowledged that, if a prescriber wishes to commence a patient on a lower total daily of naproxen than 1000 mg, there is now appropriate advice in the PI with regard to the use of monotherapies. The Delegate also accepted that it may not be a rational approach to establish efficacy and safety of the monocomponents separately before co-prescribing, given that the PPI is being recommended specifically to address an assessment of increased gastrointestinal risk by the clinician. However, this is an important issue which was of concern to both the ACPM and the Delegate. There is a justified concern that there will be a certain proportion of patients unnecessarily exposed to the fixed dose combination and therefore to the adverse event profiles of both drugs in the combination. These are the patients who

do not develop gastric and/or duodenal ulcers on exposure to naproxen. However, even in patients deemed at risk, there will be a proportion of them who will not develop gastrointestinal ulceration on exposure to an NSAID.

Does the sponsor have any data which gives an insight into the size of this proportion? Does the sponsor have any suggestions as to how this risk of unnecessary exposure may be mitigated, either through the PI or through postmarketing pharmacovigilance and other activities?

The Delegate noted that all the relevant TGA-adopted EU guidelines indicate that a 6 month study duration is sufficient to assess efficacy and that the sponsor agreed to include a statement about the 6 month length of the studies in various sections of the PI as requested by the Delegate and by the ACPM. The Delegate regarded this response as acceptable. It should also be noted that there was a 12 month open label safety study.

The ACPM expressed concern that, with regard to safety, long term use of the fixed dose combination product had not been adequately studied. However, the two 6 month pivotal studies and the 12 month open label study have provided sufficient exposure to the drug to satisfy the relevant TGA-adopted EU guidelines. As well, the sponsor made the very valid point that there is extensive data on each of the monocomponents and that this extensive body of data is able to inform the safety profile of the fixed dose combination, given the thoroughly investigated PK profiles of the monocomponents when derived from the fixed dose combination.

Proposed indication

The ACPM expressed concern that the proposed indications for Vimovo do not align with the current indications for the separate active ingredients. The sponsor considered that the Vimovo indication is well aligned with the Naprosyn and Nexium indications considering that PPI co-therapy is appropriate for chronic use of naproxen and that the Vimovo clinical trials were designed to demonstrate efficacy of the esomeprazole component only in reducing the risk of NSAID associated ulcers. In order to clarify the role of each active, the sponsor has proposed the following wording of the indication, including a rider proposed earlier:

Vimovo is a fixed dose combination product that contains naproxen and esomeprazole.

Vimovo is indicated for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, in patients at risk of developing gastric and/or duodenal ulcers associated with non-steroidal antiinflammatory drugs (NSAIDs) and where treatment with lower doses of naproxen or lower doses of other NSAIDs is not considered sufficient.

The naproxen component of Vimovo provides the symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. The esomeprazole component of Vimovo provides the prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk.

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used. If a total daily dose of 1 g of naproxen is not considered appropriate, alternative therapeutic regimens should be utilised.

The sponsor responded to concerns of the ACPM in relation to specific precautions within the proposed PI but these are beyond the scope of this AusPAR.

Delegate Considerations

Efficacy

The Delegate asked the sponsor a number of questions which cover a wide range of issues. Perhaps the four most contentious issues are those relating to the definition of the population at risk, the clinical relevance of endoscopically detected ulcers, the question of ulcer complications and how the indications and dosage regimens may, as accurately as possible, reflect the current recommended best practice guidelines. While acknowledging that these are complex issues and that the relevant USA FDA Advisory Committee agreed that the relative risk reduction of endoscopically detected gastroduodenal ulcers is a clinically meaningful endpoint, the Delegate was particularly interested in knowing whether there were any qualitative (or quantitative) differences in the ulcers between the two patient groups and whether there were any reported changes, for example, in severity, in those ulcers over the duration of the studies.

Safety and RMP

As noted by the Delegate, given the low rates of serious complications of NSAID associated upper gastrointestinal adverse events, it would require much larger, longer clinical studies in order to demonstrate a statistically significant reduction in these rates. However, the Delegate asked whether the sponsor is aware of any data which shows that treatment with a concomitant PPI does reduce the rates of serious complications. The sponsor was also been invited to propose data collection activities which could be undertaken in the postmarketing period to demonstrate this effect.

The Delegate has also sought comment by the sponsor on the concern that there will be a certain proportion of patients unnecessarily exposed to the fixed dose combination and therefore to the adverse event profiles of both drugs in the combination, although the Delegate acknowledged the gastroprotective effects of the esomeprazole in relation to the gastrointestinal AE profile of the naproxen component. The sponsor was asked to comment on how this risk of unnecessary exposure may be mitigated, either through the PI or through postmarketing pharmacovigilance or other activities.

The Delegate noted that the sponsor proposes to keep 'osteoporosis/osteoporotic fractures' under close surveillance including a questionnaire for ensuring comprehensive data collection for AE reports during marketed use. The Delegate wished to know precisely how this strategy will be implemented and how it will be different from routine pharmacovigilance activities. The Delegate agreed with the sponsor that, at this stage, the evidence in support of a causal link between osteoporotic fractures and PPIs is not sufficiently robust, at least not without a proper and formal evaluation. The Delegate proposed that the matter be reviewed by the Office of Product Review.

Indication

The Delegate did have one concern about the proposed wording and this is related to the ACPM's concern about first line use. The proposed phrase, "is not considered sufficient" at the end of the first major paragraph is not entirely consistent with the current recommended best practice guidelines and, in the Delegate's view, would be more safely and more simply phrased as "is not sufficient". Generally, it is best to commence, if possible, with a lower dose and proceed, if necessary, to a higher dose. In many cases with patients commencing Vimovo, it will be known from past experience what the required dose of NSAID has to be but in the case of patients naive to NSAIDs, this may not be known and such patients should be commenced on a low dose which is then titrated according to clinical response. Therefore the Delegate proposed the following wording (combined also with some minor editing):

Vimovo, a fixed-dose combination product that contains naproxen and esomeprazole, is indicated for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, in patients at risk of developing gastric and/or duodenal ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs) and where treatment with lower doses of naproxen or lower doses of other NSAIDs is not sufficient.

The naproxen component of Vimovo provides the symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. The esomeprazole component of Vimovo provides the prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk.

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used. If a total daily dose of 1 g of naproxen is not considered appropriate, alternative therapeutic regimens should be utilised.

The sponsor also proposed that it would agree to the addition of wording within the indication which would accurately define the at-risk population in whom an efficacy benefit has been demonstrated. However, the Delegate was mindful that the indication above is already quite long and also noted the sponsor's comments about future shifts in clinical opinion regarding risk factors. In the Delegate's view, a more appropriate location for expanding upon the nature of the risk factors would be in the Clinical Trials section. Here could be detailed the actual risk factors used in patient selection for the studies and being historical fact in relation to those trials, they would not themselves change. The ACPM may also be of the opinion that the second paragraph above is more suitably placed in the Pharmacodynamics section of the PI and that the third is more suitably placed in the Dosage and Administration section of the PI.

Delegate's overall summary

Vimovo has been demonstrated to be non-inferior to celecoxib 200 mg once daily in the management of pain associated with OA of the knee and to offer significantly greater gastroprotective effect than EC naproxen.

The Delegate agreed with the sponsor that Vimovo meets the criteria for such a product, namely that one component of the product counteracts an adverse reaction produced by another component as described in the TGA-adopted EU guideline. There is now appropriate and sufficient advice in the PI with regard to the use of monotherapies where a prescriber wishes to commence a patient on lower total daily dose of naproxen than 1000 mg. It would appear then that the most important issue is proper patient selection. Having decided that one's patient is at risk, it would be appropriate for a prescriber to commence a patient on a combination of an NSAID and a PPI. It is therefore most important that the PI give as much help as possible to the prescriber in the appropriate selection of patients for the fixed dose combination.

The sponsor was invited to expand upon its argument that the implementation of the exclusion criterion of a history of prior ulcer complication would not have resulted in "many patients potentially at risk" having been excluded from the study. While noting the acceptance by the relevant US FDA Advisory Committee of the clinical relevance of endoscopically detected ulcers, the Delegate asked the sponsor to provide more clarity with regard to the actual severity of gastric and/or duodenal ulceration suffered by the patients in the clinical trials.

The Delegate raised a number of safety issues for further comment by the sponsor. These include serious complications of NSAID associated upper gastrointestinal adverse events, the concern that there will be a certain proportion of patients perhaps unnecessarily exposed to the fixed dose combination and the concern of the possible link between PPIs

and osteoporosis/osteoporotic fractures. The sponsor was asked to comment on the role of possible pharmacovigilance or other activities in the postmarketing phase which may shed more light on these matters.

The Delegate proposed to approve the submission conditional upon satisfactory answers to all the questions posed by the Delegate and full implementation of the requested amendments to the PI, including the revised indication which follows:

Vimovo, a fixed-dose combination product that contains naproxen and esomeprazole, is indicated for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, in patients at risk of developing gastric and/or duodenal ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs) and where treatment with lower doses of naproxen or lower doses of other NSAIDs is not sufficient.

The naproxen component of Vimovo provides the symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. The esomeprazole component of Vimovo provides the prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk.

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used. If a total daily dose of 1 g of naproxen is not considered appropriate, alternative therapeutic regimens should be utilised.

Sponsor Response

The sponsor agreed with the proposed indication except that it considered "reduces the risk" would be more appropriate than "provides the prevention" in the second paragraph as no treatment can completely prevent the risk of ulceration. The sponsor also proposed adding the words "When prescribing an NSAID" at the commencement of the last paragraph, as "lowest effective dose" is not meaningful with respect to Vimovo given there is only one strength and one dosage regimen proposed.

The issues highlighted by the Delegate and the sponsor's responses are presented sequentially below.

Registration of the lower strength/lowest dose possible for the shortest possible time

Under the currently proposed indication, Vimovo would be inappropriately prescribed if:

- the risk/benefit ratio is not considered by the physician
- lower doses of naproxen or lower doses of other NSAIDS have not been assessed in agreement with best practice principles for NSAID use
- the patient is not considered at risk of NSAID associated gastric and or duodenal ulceration.

Thus, the sponsor agreed that Vimovo should be prescribed to patients only when lower doses of naproxen or lower doses of other NSAIDs are not sufficient and for the shortest possible duration. The proposed PI makes this clear in a number of locations including the Indications and Dosage and Administration sections.

The possibility of seeking registration for the Vimovo 375/20 strength was extensively considered by the Australian affiliate of the sponsor leading up to the Vimovo submission. The sponsor's decision not to pursue registration of the 375/20 strength was not primarily driven by commercial considerations, as stated by the Delegate. The key considerations underpinning the decision to seek registration of the 500/20 strength alone were clinical and were supported by the analysis of the Australian prescribing patterns contained in the BEACH report.[37] The BEACH analysis indicated that naproxen

1000 mg daily is by far the most commonly prescribed naproxen dose for arthritic conditions, representing approximately 72% of naproxen prescriptions written for these indications.[43] In contrast, naproxen 750 mg daily represents only 15% with the remaining prescriptions being written for other doses, both above 1000 mg and below 750 mg per day. It is well established that the requirement for gastroprotection increases with increasing NSAID dose as reflected in the Australian GESA guideline which lists "high NSAID dose" as a risk factor. Accordingly, a proportion of the 15% of patients currently receiving a daily dose of 750 mg would not be classified as being "at risk" of developing ulcers. Thus the medical need and fixed dose combination rationale for Vimovo is most robust at the 500/20 strength. The reduced need for gastroprotection with a naproxen dose at 750 mg daily increases the need for a clinician to carefully assess GI risk before co-prescribing a PPI, which further erodes the fixed dose combination rationale for the 375/20 strength. Considering that the lower strengths of the mono-components are freely available to prescribers and the proposed Vimovo PI contains appropriate statements regarding dosage, the sponsor was of the opinion that the absence of a 375/20 Vimovo presentation creates no difficulties or disadvantages with regards to patient access or prescriber options. It is important to note that naproxen prescribing patterns reported in the BEACH data are not necessarily reflective of the doses used in other regulated markets and this affects the clinical rationale for the lower strength in these markets, for example, USA and Canada. After considering all of these factors, the sponsor concluded that a submission applying just for the 500/20 strength was appropriate and clinically justifiable.

The issue of unnecessary exposure to a PPI was also raised by the Delegate generally and more specifically as an issue for the sponsor's attention. The sponsor agreed that a patient should not be prescribed gastroprotective therapy if it is not required, however, in considering this issue, it was important to note the high probability that a patient will require gastroprotective therapy (particularly with high NSAID dose). A recent assessment of gastrointestinal and cardiovascular risk in patients with osteoarthritis who require NSAIDs (the LOGICA study, Lanas et al 2010) found that most patients (86.6%) were at increased GI risk and a considerable number (22.3%) were at high GI risk.[44] Secondly, it is important to note that there remains significant underutilisation of gastroprotective therapy, a view supported by clinical practice guidelines (GESA 2008 guidelines). In addition to underutilisation of gastroprotective therapy, studies have also demonstrated that up to 60% of patients are noncompliant with a prescribed NSAID/gastroprotection co-therapy regimen (Sturkenboom et al 2003, Vonkeman et al 2007) and that noncompliance increases the risk of an upper-gastrointestinal (UGI) event by 2.5- to 4-fold (Goldstein et al 2006, Van Soest et al 2007).[31,33,45,46,]

Registration of Vimovo will help to alleviate these problems in Australia in a number of ways:

1. The sponsor will undertake a number of risk minimising activities aimed at increasing awareness and understanding of appropriate NSAID and gastroprotective co-therapy

[43] A figure of 67% is incorrectly quoted by the Delegate. The 67% relates to naproxen for any use, not just arthritic conditions. The figure of 72% accepts 550 mg of naproxen sodium is equivalent to 500 mg naproxen.

[44] Lanas A. A review of the gastrointestinal safety data--a gastroenterologist's perspective. Rheumatology (Oxford). 2010; 49 (Suppl 2): ii3-10.

[45] Sturkenboom M, Burke T, Tangelder M, Dieleman J, Walton S, Goldstein J. Adherence to proton pump inhibitors or H2-receptor antagonists during the use of non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther 2003;18:1137–1147.

[46] Vonkeman H, Fernandes R, van de Laar M. Under-utilization of gastroprotective drugs in patients with NSAID-related ulcers. Int J Clin Pharmacol Ther 2007; 45: 281-288.

and Vimovo in line with clinical practice guidelines and the PI. These activities will assist in increasing appropriate prescribing in this clinical setting in Australia.

2. Vimovo was designed to ensure that patients who require chronic therapy for arthritis (at 1000 mg naproxen daily) and gastroprotective therapy will receive a dose of PPI in conjunction with each dose of NSAID in a consistent and sequential manner that ensures compliance and enables effective prophylaxis against GI injury.

As with any medicine, inappropriate prescribing presents a risk to the patient. Due to the unique benefits associated with Vimovo compared to co-prescription of the monocomponents, that is, improved patient compliance, sequential release of esomeprazole then naproxen and therapy simplification, a physician may be tempted to prescribe Vimovo before assessment of lower doses of naproxen or of other NSAIDs or to patients who don't require gastroprotective therapy according to clinical practice guidelines. However, if the physician does this with full knowledge and understanding of the indication, the restrictions in the PI (for example, not to be used for acute pain or as contraindicated), the risks associated with each active (as per PI) and the clinical practice guidelines, then this is a reflection on prescribing behaviour and not the safety of Vimovo. This argument applies to any medicine, including Australian registered Arthrotec (diclofenac + misoprostol) which has the same fixed dose combination rationale as Vimovo. The prescriber has a responsibility to prescribe appropriately and to maintain their knowledge base in order to do so. However, the sponsor recognised that knowledge gaps and misunderstanding concerning the appropriate use of NSAIDs, gastroprotective co-therapy and Vimovo may exist for a variety of reasons such as variation in clinical practice guidelines and a lack of familiarity with the Vimovo PI. The sponsor therefore committed to a range of measures both to improve understanding and awareness of appropriate prescribing of NSAIDs according to best practice principles, gastroprotective co-therapy and Vimovo in line with clinical practice guidelines and the Vimovo PI and to address more directly the possibility of unnecessary prescribing of Vimovo. These measures are formalised in the Risk Management Plan (RMP) and can be summarised as follows:

1) PBAC restriction. Vimovo will not be subsidised for use in acute pain, soft tissue injuries and arthrosis without an inflammatory component. Within the PBAC submission, the sponsor committed to a series of activities to support appropriate use of Vimovo which are in the RMP addendum.

2) Prescribing support. The sponsor is working with the Medical Director software vendors to develop the tools to support physicians in making an appropriate decision about prescribing Vimovo. This will take the form of prompts at the time of prescribing.

3) Evaluation of prescribing behaviour. In conjunction with an expert steering committee, the sponsor will undertake a clinical audit (ACCOUNT) to try to understand the extent to which guidelines impact on the treatment choices that physicians make with respect to NSAID use. The outcome of this audit will be to highlight gaps between guidelines and current practice in Australia and to develop an educational program which incorporates practical solutions for addressing these.

4) Risk assessment tool. To compliment this educational activity the sponsor will be working with an expert committee to assess the need for a tool to assist clinicians to rapidly assess key GI and CV risk factors, and to develop this if necessary.

5) Control of educational and promotional materials. All Vimovo promotional materials will be reviewed by the sponsor's Medical Department for compliance with the PI and Medicines Australia Code of Conduct Guidelines. Core materials will emphasize correct

use, that is, Vimovo can only be used for arthritic conditions and ankylosing spondylitis, where lower doses are not sufficient and only when gastroprotection is required.

6) Sales representative training. All the sponsor representatives receive training covering, disease state and therapeutics, Medicines Australia Code of Conduct and AEs reporting procedure. Vimovo training will incorporate full coverage of the PI and will emphasize correct use of Vimovo.

7) Educational activities. The sponsor will conduct a number of educational activities including an online medical education program (RACGP 40 point Category 1 CME program) and a series of cross disciplinary meetings to educate GPs on NSAID use, identification and management of risk factors.

The strengthened indication proposed by the Delegate will also minimise risk of unnecessary exposure as it points out the presence and function of esomeprazole and naproxen and places emphasis on the requirement for assessment of lower doses of naproxen and other NSAIDs, risk/benefit assessment and best practice, and the fact that alternative therapeutic regimens should be utilised if 1 g of naproxen is not considered appropriate.

The sponsor also drew attention to the CHARACTERIZE study planned for Europe. During review of the Vimovo Marketing Authorisation Application in the EU (also 500/20 strength only), health authorities in The Netherlands (Reference Member State) and the UK (Concerned Member State) requested that the sponsor assess its real world use of Vimovo given the indication: "where treatment with lower doses of naproxen or of other NSAIDs is not considered sufficient". This resulted in the planning of the CHARACTERIZE study, previously referred to as the EVIDENCE 2 study. CHARACTERIZE is proposed to meet the requirements of these regulatory authorities as a part of the EU RMP. This retrospective study will describe the extent to which various factors influence the decision to prescribe Vimovo in patients with OA, RA or AS at risk for developing NSAID associated gastric and/or duodenal ulcers. This study demonstrates the sponsor's global commitment to appropriate prescribing of Vimovo.

Risk of osteoporosis/osteoporotic fractures

The sponsor re-confirmed that the identified safety concerns associated with 'osteoporosis/osteoporotic fractures' will be kept under close surveillance. Close surveillance of a risk implies intensified data collection from reported events, in this case including a follow up questionnaire to achieve targeted safety information. This process was described by the sponsor.

A risk under close surveillance is also addressed specifically, including cumulative review, in the PSURs. As described in the 1 year PSUR, no medically confirmed case reports of osteoporosis/osteoporotic fractures were received from postmarketing use during this update period. One consumer report was received.

The sponsor reiterated its position that the Vimovo PI should be consistent with that of other PPI products with respect to the risk of osteoporosis/osteoporotic fractures.

Patients potentially at risk

Data on the number of patients excluded from the Vimovo clinical trials due to a history of ulcer complication are not available. Based on the estimate that complications of NSAID-associated UGI AEs such as bleeding, obstruction, and perforation occur in approximately 1% to 4% of chronic NSAID users per year (*Clinical Overview*), if patients with a history of ulcer complications had not been excluded from the Vimovo clinical trials, one might expect that approximately 9 to 34 of the 854 patients in the pivotal trials would have had a

history of ulcer complication during the previous year, and a higher number would have had a history of ulcer complication at some point.

According to the American College of Gastroenterology practice guidelines (Lanza 2009), "The consensus opinion of most experts in the field is that patients with a history of a recent complicated peptic ulcer are at very high risk and should be treated with NSAIDS with extreme caution and in the presence of maximal protective measures".[47] Therefore, these patients were excluded from the pivotal trials for safety reasons, as patients assigned to the EC naproxen arm were taking a high dose NSAID with no gastroprotection (only antacids were allowed as rescue medication).

The sponsor planned to evaluate the safety and efficacy of Vimovo in 200 higher risk patients (that is, patients with a history of a serious GI event such as bleeding, perforation, or obstruction) in a study using Arthrotec as a comparator, but was unable to recruit a sufficient number of patients. The study was stopped following consultation with the United States Food and Drug Administration (FDA), which had requested that the study be performed. The following paragraph excerpted from the Clinical Study Report may be of interest:

> On May 2, 2008 POZEN reached an agreement with the FDA to terminate the study based on difficulty in recruiting subjects. Reasons behind the low enrollment were mostly related to the reluctance of subjects to use an NSAID again, since past NSAID usage was determined a plausible cause for their previous complicated ulcer. A second reason for the low enrollment was related to a relatively low number of subjects having a history of POB. The latter was reflected in the long period open for enrollment (more than 8 months) with 66 active sites being able to randomize only 20 subjects out of a total of 31 candidates with a history of POB. A third reason for the low enrollment was reluctance of subjects to be randomized to ARTHROTEC®, because of its known, unfavorable side effect profile.

The sponsor proposes to state explicitly in the Clinical Trials section of the Vimovo PI the key study inclusion criteria, and that patients with a history of ulcer complication were excluded from the studies.

Clinical relevance of endoscopically detected ulcers

The clinical correlation between endoscopic ulcer and ulcer complication in an individual patient is difficult to assess, as once an ulcer is identified, steps to heal the ulcer (for example, with a PPI) and decrease the offending agent (be it H. pylori or NSAIDs) are introduced. It would not be ethical to observe progression of an uncomplicated to a complicated ulcer without intervention. The Vimovo pivotal trials were aligned with clinical practice in this regard: upon detection of an ulcer and thus meeting the primary endpoint, patients were discontinued and given appropriate treatment. (Patients were treated in the same way in the TGA evaluated clinical trials supporting the Nexium NSAID associated ulcer prevention indication.)

Studies PN400-301 and PN400-302 were not designed to compare the number, diameter, or depth of lesions across treatments. None of these factors has been shown to be correlated with progression to a complicated ulcer. The location of the lesion, especially proximity to a blood vessel, is a more likely determinant of the clinical relevance of the ulcer.

There are, however, data supporting the assertion that gastroprotective agents that have been shown to reduce the risk of endoscopic ulcers (that is, reduce the risk of an ulcer of a certain minimum diameter [usually 3 mm with depth], regardless of symptoms or number/diameter/depth of lesions) also reduce the risk of ulcer complications. These data

[47] Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009; 104: 728-738.

are summarized in the previously submitted Briefing Document for the November 2010 FDA Advisory Committee meeting on the appropriateness of endoscopic ulcers as an endpoint in clinical trials of gastroprotective agents.

Prospective, randomized outcome trials have been performed comparing various NSAIDs (mainly COX-2 selective to non-selective NSAIDs), but not for PPIs in this target population of chronic NSAID users at risk of an ulcer. However, in a study in patients with a history of a GI bleed who were on NSAIDs, EC esomeprazole 20 mg bd or placebo was added to celecoxib 200 mg bd (Chan et al 2007).[48] The primary endpoint was recurrent ulcer bleeding during treatment or within 1 month of the end of treatment. This study demonstrated that, in addition to its efficacy in reducing the risk of NSAID associated ulcers, esomeprazole reduces the risk of a subsequent complication in these at-risk patients over the ensuing year from 8.9% to zero. Of the 12 cases of recurrent UGI bleeding (UGIB), all 12 were diagnosed with peptic ulcers on follow up endoscopy (7 GUs and 5 DUs).

In an earlier study (Chan et al 2001), 400 patients with a history of upper gastrointestinal bleeding (UGIB) and active H pylori infection were studied.[49] These patients had been treated with either NSAIDs or low dose aspirin (LDA) before they presented with GI bleeding and over 90% of them had an endoscopic ulcer at baseline. All patients were initially treated with 8 weeks of omeprazole 20 mg/day until their ulcers/erosions were healed. Subsequently, they were restarted on either LDA or naproxen 500 mg bd, depending on which medication they had been taking prior to their UGIB. Patients were then randomized to either omeprazole 20 mg qd for 6 months or H pylori eradication therapy for 7 days (with bismuth, tetracycline, and metronidazole) followed by placebo for 6 months. Among the group of patients taking NSAIDs, recurrent UGIB from ulcers was 4 times more likely in the H pylori eradication group (18.8%) than in the omeprazole group (4.4%). The authors concluded that omeprazole therapy was superior to H pylori eradication in preventing recurrent bleeding in patients previously diagnosed with ulcer bleeding. These data provide further support for a central role for peptic ulcer as an important cause of UGIB and emphasises the importance of acid suppression in patients at risk for UGIB.

Further on the question of acceptance, the TGA and other health authorities have accepted endoscopically detected ulcers as a primary endpoint in trials designed to support an ulcer prevention indication, leading to the approval for Nexium, and to the approval of Vimovo in many countries.

Ulcer complications

GI bleeding, ulceration, obstruction, and perforation of the stomach or intestines are "identified risks" for the naproxen component of Vimovo as stated in the RMP. Due to the seriousness of these events the sponsor will keep them under close surveillance. An extract from the proposed RMP was provided which described this process in detail.

During post marketed use, altogether 34 adverse events (33 case reports) related to GI bleeding, ulceration, obstruction, or perforation of the stomach and intestines had been received up to 19 July 2011. All 33 case reports were from the United States; 25 were medically confirmed and 8 were consumer reports. Of the 34 events, 21 were serious and 13 were non-serious. The events reported were gastrointestinal haemorrhage (11 events),

[48] Chan FK, Wong VW, Suen BY, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. Lancet 2007; 369: 1621-1626.

[49] Chan F, Chung S, Suen B, et al. Preventing recurrent upper gastrointestinal bleeding in patients with helicobacter pylori infection who are taking low-dose aspirin or naproxen. NEJM 2001; 344: 967-973.

haematochezia (6), rectal haemorrhage (4), gastric ulcer (3), ulcer (2), gastric haemorrhage (2), melaena (2), duodenal ulcer (1), peptic ulcer (1), gastric ulcer haemorrhage (1), and ulcer haemorrhage (1). No adverse events related to GI obstruction or perforation of the stomach or intestines have been reported. In some case reports there were other contributing factors such as alcohol, concomitant medication (for example, warfarin), or underlying diseases.

From market experience, the total worldwide exposure to Vimovo has been estimated by the sponsor to be approximately 35000 patient-years up until 30 June 2011. Taking the exposure into consideration, the overall reporting frequency of ulcer complications is considered low.

Complications of UGI AEs were infrequent in the Vimovo program. Complications of NSAID associated UGI AEs such as bleeding, obstruction, and perforation have been estimated to occur in approximately 1% to 4% of chronic NSAID users per year (*Clinical Overview*). Given the duration of treatment and the size (approximately 2300 patients) of the population studied in the Vimovo program, a low incidence of UGI complications was expected, and in fact there were just 2 events:

- 1 serious UGI event (haematemesis with a negative source for UGI bleeding) was seen among the patients who received Vimovo
- 1 serious GI event (bleeding DU) was seen among patients who received naproxen

For comparison, out of the approximately 1400 patients in the Nexium-NSAID studies SH-NEN-0013 ('PLUTO') and SH-NEN-0014 ('VENUS') 4 patients (all in the NSAID + placebo group) were hospitalized with confirmed UGI bleeding. PLUTO and VENUS were both 6 month, multicentre, randomized, placebo controlled, double blind, parallel group Phase III studies comprising in total 472 patients treated with esomeprazole 40 mg qd, 464 patients treated with esomeprazole 20 mg qd, and 454 patients treated with placebo, in combination with a variety of NSAIDs. They were performed in support of the Nexium indication "Prevention of gastric and duodenal ulcers associated with non-steroidal antiinflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk".

The sponsor and others have considered conducting clinical trials with ulcer complications as an endpoint but there are seemingly insurmountable obstacles to conducting these trials, as described in the previously submitted FDA Advisory Committee Briefing Document. These obstacles were described in detail. Given these obstacles to obtaining clinical trial data on serious NSAID associated GI events, the sponsor will focus on pharmacovigilance activities as described in the RMP.

Risk of this unnecessary exposure

The cumulative incidence of gastroduodenal ulcers with conventional NSAID use has been reported to be as high as 25% to 30% at 3 months and 45% at 6 months, while the corresponding placebo incidence is 3% to 7%. At any given time, the prevalence of UGI ulcers in NSAID users has been estimated to be as high as 30%. As a result of the GI toxicity of NSAIDs, and of the potential for serious complications, several treatment guidelines (GESA 2008, NICE 2008 and Zhang et al 2005), recommend co-therapy with a PPI for patients receiving chronic therapy with NSAIDs.[50]

[50] Zhang W et al 2005. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005; 64: 669-81.

With reference to the Delegate's question on what proportion of "at risk" patients will not develop GI ulceration on exposure to an NSAID, it is difficult to know what proportion of the percentages quoted above would be associated with patients conventionally considered "at risk" and thus be able to derive an estimate of what proportion didn't develop an ulcer. As both the Vimovo and Nexium studies included patients at risk of NSAID associated gastric and/or duodenal ulceration, the placebo arms of these studies are informative with respect to the Delegate's question, but only for a period of 6 months (study duration) and may lead to an underestimate of ulcer incidence in the wider 'at risk' population as patients with a history of complicated ulcer and patients with an endoscopically identified ulcer at screening were excluded from the studies. The sponsor provided a table which indicated that the percentage of patients not developing an ulcer over 6 months of treatment is greatly dependent on the type and number of risk factors. For example, only 44.4 % (100% - 55.6%) of patients aged 50 or more with a history of ulcer did not experience an ulcer during the 6 months, but the proportion is quite different in other groups. Of course, the studies cannot inform us of what will happen after 6 months, but the Vimovo studies do indicate an increase over time in the cumulative proportion of patients developing an ulcer.

The Delegate also asked how "unnecessary exposure" in patients at risk might be mitigated. The sponsor agreed that, as with PPI co-therapy generally, if Vimovo is given to patients who require a chronic NSAID dose equivalent to naproxen 500 mg bd and are at risk of developing peptic ulcers according to known risk factors, a proportion of patients who would not have developed an ulcer, even in the absence of gastroprotection will be exposed to esomeprazole. In this sense, Vimovo may be seen as analogous to drugs used to reduce the risk of cardiovascular events; for example, statins are prescribed to patients at risk of cardiovascular events due to high cholesterol levels even though they may never have experienced a cardiovascular event even in the absence of statin therapy. In both cases, the number of patients at risk is very high, so even a low risk of a (potentially very serious) event represents an important medical concern and steps are taken to further reduce that risk, in accordance with treatment guidelines. In both cases, the medicine is prescribed to "at risk" patients in order to reduce the risk of an event, even though it may never have happened, regardless of treatment. It is therefore most appropriate for the prescriber to make the benefit risk assessment in the full context of the patient's medical history, NSAID dose and duration, and concomitant medications. This assessment, combined with consideration of treatment algorithms in clinical practice guidelines (for example, GESA) define if treatment with a PPI is necessary.

The risk of inappropriate use, that is, in those not at risk according to known risk factors, will be mitigated by appropriate PI text (as per indication), combined with physician education and other risk management activities as previously described.

The sponsor proposed to include in the Clinical Trials section of the Vimovo PI a brief description of the key study entry criteria from the pivotal trials, to inform prescribers about the population in whom the safety and efficacy of Vimovo have been demonstrated. Recognised risk factors for developing NSAID associated GUs and/or DUs include advanced age, history of previous GU and/or DU, history of previous NSAID related upper GI complications (UGICs), combinations of NSAIDs including aspirin and COX-2 inhibitors, concomitant corticosteroids, comorbid disease, and lifestyle factors such as smoking (*Clinical Overview*). Evidence that NSAID associated ulcer risk is increased in patients over 50 years old is available from a review of epidemiological studies (Hernández-Díaz et al 2000), which shows increasing risk with increasing age, and specifically a 1.8-fold greater risk for patients 50 to 59 years old than for patients 25 to 49 years old (95% CI: 1.5-2.1).[25] In addition, in Studies PN400-301 and PN400-302, the GU rate among patients 50 to 59 years old who received naproxen 500 mg bd for 6 months was 21.2%, as compared to

26.3% for those ≥60 years old. These data suggest that there is likely to be substantial risk for developing NSAID associated ulcers in the 50- to 59 year old subpopulation, as well as in older patients.

The combined data from Studies PN400-301 and PN400-302 allowed the expanded examination of the effects of factors known to increase the risk of GU with the use of naproxen. Combinations of these risk factors were also examined.

Thus, significantly lower GU occurrence was consistently observed in the Vimovo group compared with the naproxen group, regardless of patient age, history of ulcer, or concomitant use of LDA. In particular, Vimovo was effective in reducing the risk of endoscopic ulcers in those >60 years of age (the cut-off used in the Nexium NSAID studies) and those with 2 of the risk factors used in the Vimovo program (age >50, use of LDA, or history of an uncomplicated ulcer).

Overall, endoscopic gastric ulcer rates were much lower with the EC naproxen-esomeprazole combination (5.6%) than EC naproxen alone (23.7%: RR = 0.24; 95% CI, 0.16‑1.37; NNT = 5.5). Endoscopic duodenal ulcers were also much less frequent with the combination (0.7%) than with EC naproxen alone (4.2%: RR = 0.17; 95% CI, 0.05‑1.57; number needed to treat [NNT] = 28.6).

It should be noted that Vimovo was also effective in reducing the risk of pre-specified NSAID associated UGI AEs, relative to EC naproxen, and improved dyspepsia symptoms, based on the Severity of Dyspepsia Assessment (SODA), a validated Patient Reported Outcome instrument. The incidence of UGI AEs in the combined studies was 53% on the Vimovo arm and 69% on the EC naproxen arm, suggesting that the vast majority of patients taking naproxen 500 mg bd are at risk of GI AEs.

GI complications are serious, and mortality from GI bleeding is estimated to be 14.4% within 3 months of the event. The number of events occurring in Australia, as indicated by hospital separations for GI events, exceeded 25,000 in 2005-2006, and this has grown to over 30,000 in 2009-2010. Given the increasing average age of the Australian population, this number is likely to continue to increase. There is therefore a need to improve awareness of gastroprotective requirements in at risk populations, together with strategies to improve patient therapy compliance.

Defining patients "at risk" and thus who should be treated with Vimovo.

The Delegate raised the question as to how "patients at risk of developing gastric and/or duodenal ulcers associated with NSAIDs" would be best identified in order to aid the prescriber in deciding if treatment with Vimovo is appropriate. The Delegate noted the sponsor's suggestion that this could be done in the Clinical Trials section of the PI and invited the sponsor to clarify how this might be done. The sponsor also suggested that it may be possible to identify at risk patients in the Indication but with the concern that this may be quickly rendered inaccurate as medical opinion and clinical practice guidelines evolve. The Delegate noted this and concluded that the more appropriate location to expand upon the nature of the risk factors would be in the Clinical Trials section where the actual risk factors used in patient selection for the studies (PN400-301 and PN400-302) could be detailed and being historical fact, they would not change. The sponsor agreed with this approach.

It is also important to note that the intended function of esomeprazole in Vimovo is the same as that already approved for esomeprazole in the Nexium indication for prevention of NSAID associated gastric and/or duodenal ulcers in patients at risk. Furthermore, the pivotal studies in the Vimovo clinical program (PN400-301 and PN400-302) have the same primary endpoint (endoscopically detected ulcers) and very similar inclusion and

exclusion criteria as the corresponding Nexium studies. The only notable difference in inclusion criteria was the demarcation at 60 years of age in the Nexium studies as opposed to 50 years of age in the Vimovo studies. Patients were also excluded from the Nexium studies due to a prior history of a complicated upper gastrointestinal event, but only if it had occurred within 6 months of screening. Patients were discontinued from Nexium and Vimovo studies once an ulcer was detected (meeting primary endpoint). Given the close similarity it would seem appropriate to follow the approach used in the Nexium PI.

This agrees with the Delegate's suggestion. Thus the sponsor proposed a corresponding text for the Vimovo PI in the Clinical Trials section.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the Delegate's revised overview, as well as the sponsor's response to this document, advised that it was satisfied that the gastroprotective efficacy of the fixed dose combination was demonstrated. Therefore in the light of the TGA adopted EMA guideline, the justification provided by the sponsor for a fixed dose combination was considered adequate.

The committee agreed that the wording of the indication proposed by the sponsor and by the Delegate more clearly defines the target population for the fixed dose combination. However, for succinctness and greater clarity, in the committee's opinion, the wording of the indication should be amended to:

Vimovo is indicated for patients with an increased risk of gastrointestinal ulceration, who require NSAID therapy for symptomatic management of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis with an inflammatory component AND in whom lower doses of naproxen or other NSAIDs have proven insufficient.

If a total daily dose of 1 gram naproxen is not required, VIMOVO should NOT be used.

The committee was of the opinion that deficiencies identified with the submission could be adequately addressed by further amendments, including the addition of some precautionary statements to the Product Information (PI) and Consumer Medicines Information (CMI), as well as ensuring that the proposed Risk Management Plan is implemented after review by the TGA.

These further amendments to the PI and CMI are beyond the scope of this AusPAR.

The committee also recommended implementation of the following:

- The Risk Management Plan included in the submission (edition 1 dated August 2009)
- An education program for health professionals which includes accurate targeting of the patient population for Vimovo and the critical importance of cessation of monotherapies prior to commencement of Vimovo
- An enhanced pharmacovigilance program which specifically captures any relevant information concerning adverse events of osteoporotic fractures and community acquired pneumonia

The ACPM advised that the implementation by the sponsor of the recommendations outlined above should be to the satisfaction of the TGA. The implementation of the latter, in addition to the evidence provided with the submission from the sponsor for the registration of the product naproxen and esomeprazole (as magnesium trihydrate) (Vimovo) 500 mg/20 mg, would support the safe and effective use of the product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Vimovo modified release tablets containing naproxen/esomeprazole (as magnesium trihydrate) 500 mg/20 mg.

Vimovo is indicated for patients with an increased risk of gastrointestinal ulceration, who require NSAID therapy for symptomatic management of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis with an inflammatory component AND in whom lower doses of naproxen or other NSAIDS have proven insufficient. If a daily dose of 1 g of naproxen is not required, Vimovo should NOT be used.

Among specific conditions of approval were the following:

- The implementation of the Risk Management Plan identified currently as Version 2, dated 28 October 2010 and updated in the future as may be agreed between the sponsor and the TGA;
- The sponsor, in consultation with the Office of Product Review of the TGA, should design and implement an education program for health professionals with regard to appropriate prescribing of Vimovo.
- The sponsor, in consultation with the Office of Product Review, should design and implement an enhanced pharmacovigilance program which specifically captures any relevant information concerning the adverse events of osteoporotic fractures and community acquired pneumonia or adverse events which may be of special concern to the Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

VIMOVO™

naproxen/esomeprazole

MODIFIED RELEASE TABLETS

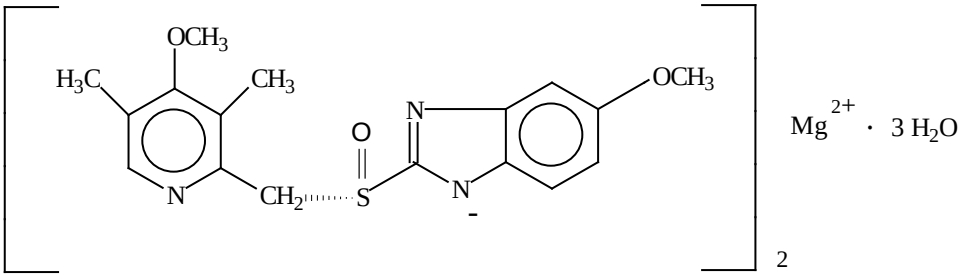
PRODUCT INFORMATION

NAME OF THE MEDICINE

The active ingredients in VIMOVO modified release tablets are naproxen and esomeprazole (as magnesium trihydrate).

Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate.

The chemical structure of esomeprazole magnesium trihydrate is:



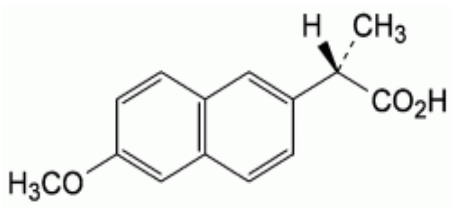
CAS number: 217087-09-7

Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg.3H_2O$

Molecular weight: 767.2 (trihydrate)

Naproxen is a propionic acid derivative related to the arylacetic acid class of drugs. It is unrelated to salicylates and the corticosteroid hormones. The chemical name is (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid. It is an odourless, white to off-white crystalline substance.

The chemical structure of naproxen is:



CAS number: 2224531

Molecular formula: $C_{14}H_{14}O_3$

Molecular weight: 230.3

DESCRIPTION

Each modified-release tablet contains 500 mg naproxen and 20 mg esomeprazole (as magnesium trihydrate). The tablet consists of an inner enteric coated naproxen core and an outer immediate release film coating containing the esomeprazole magnesium. The excipients within the naproxen core are: croscarmellose sodium, magnesium stearate, povidone and colloidal anhydrous silica. The other excipients in the tablet are carnauba wax, glyceryl monostearate 40-55, hypromellose, iron oxide (yellow and black), macrogol 8000, methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30%, methyl hydroxybenzoate E218, polydextrose, polysorbate 80, propyl hydroxybenzoate E216, propylene glycol, titanium dioxide, triethyl citrate and OPACODE WB monogramming ink NS-78-17821 BLACK (proprietary ingredient # 12156).

PHARMACOLOGY

VIMOVO has been developed as a sequential-delivery tablet formulation combining an immediate release esomeprazole magnesium layer and an enteric coated delayed-release naproxen core. As a result, esomeprazole is released in the stomach prior to the dissolution of naproxen in the small intestine. The enteric coating prevents naproxen release at pH levels below 5.5 providing protection against possible local gastric toxicity of naproxen.

Naproxen is a NSAID with anti-inflammatory, analgesic and antipyretic properties. The mechanism of action of the naproxen anion, like that of other NSAIDs, is not completely understood but may be related to cyclo-oxygenase inhibition.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+, K^+-ATPase (the acid pump) and inhibits both basal and stimulated acid secretion. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Effect on gastric acid secretion

After 9 days of dosing twice daily with three VIMOVO combinations, naproxen 500 mg combined with 10 mg, 20 mg or 30 mg esomeprazole, intragastric pH above 4 was maintained for a mean time of 9.8 hours, 17.1 hours and 18.4 hours, respectively, over 24 hours in healthy volunteers. The interindividual variability in time with intragastric pH above 4, expressed as coefficient of variation (CV) was 55%, 18% and 16%, respectively.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Naproxen

At steady state following administration of VIMOVO twice daily, peak plasma concentrations of naproxen are reached within a median time of 3 hours following both the morning and the evening dose. Time to peak plasma concentrations of naproxen is slightly longer on the first day of administration, with median times of 4 hours and 5 hours for the morning and evening dose, respectively.

Bioequivalence between VIMOVO and immediate release naproxen, based on area under the plasma concentration-time curve (AUC) maximum plasma concentration (C_{max}), minimum plasma concentration (C_{low}) and average plasma concentration over the dosing interval (C_{ave}), has been demonstrated.

Naproxen is rapidly and completely absorbed from the gastrointestinal tract with an *in vivo* bioavailability of 95%.

Steady-state levels of naproxen are reached in 4 to 5 days.

Esomeprazole

Following administration of VIMOVO twice daily, esomeprazole is rapidly absorbed with peak plasma concentration reached within a median time of 0.5-0.75 hours following the morning and evening dose on both the first day of administration and at steady state. The peak plasma concentrations of esomeprazole are higher at steady state compared to the first day of dosing of VIMOVO. This is probably partly a result of an increased absorption due to the pharmacodynamic effect of esomeprazole with increased intragastric pH, leading to reduced acid degradation of esomeprazole in the stomach. A decrease of first pass metabolism and systemic clearance of esomeprazole with repeated dosing also contributes to the higher plasma concentrations at steady state (see Metabolism).

Concomitant administration with food

Administration of VIMOVO together with food does not affect the extent of absorption of naproxen but significantly delays the absorption by about 8 hours and decreases peak plasma concentration by about 12%.

Administration of VIMOVO together with food delays the absorption of esomeprazole by about 1 hour and significantly reduces the extent of absorption, resulting in 52% and 75% reductions of area under the plasma concentration versus time curve and peak plasma concentration, respectively.

Administration of VIMOVO 30 minutes before food intake has only minimal or no effect on the extent and time to absorption of naproxen and has no significant effect on the rate or extent of esomeprazole absorption compared to administration under fasted conditions (see DOSAGE AND ADMINISTRATION).

Distribution

Naproxen

Naproxen has a volume of distribution of 0.16 l/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough Css 36.5, 49.2 and 56.4 mg/l with 500, 1000 and 1500 mg daily doses of naproxen, respectively). The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma (see PRECAUTIONS).

Esomeprazole

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Naproxen

Naproxen is extensively metabolized in the liver by the cytochrome P450 system (CYP), primarily CYP2C9 and CYP1A2, to 6–0–desmethyl naproxen. Neither the parent drug nor the metabolites induce metabolizing enzymes. Both naproxen and 6–0–desmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites. Consistent with the half-life of naproxen, the area under the plasma concentration-time curve increases with repeated dosing of VIMOVO twice daily (see Excretion).

Esomeprazole

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The area under the plasma esomeprazole concentration-time curve increases with repeated administration of VIMOVO. This increase is dose-dependent and results

in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is partly due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. An increased absorption of esomeprazole with repeated administration of VIMOVO probably also contributes to the time-and dose-dependency (see Absorption).

Excretion

Naproxen

Following administration of VIMOVO twice daily, the mean elimination half-life for naproxen is approximately 9 hours and 15 hours following the morning and evening dose, respectively, with no change with repeated dosing.

The clearance of naproxen is 0.13 ml/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (<1%), 6-0-desmethyl naproxen (<1%) or their conjugates (66% to 92%). Small amounts, 3% or less of the administered dose, are excreted in the faeces. In patients with renal failure metabolites may accumulate (see Precautions).

Esomeprazole

Following administration of VIMOVO twice daily, the mean elimination half-life for esomeprazole is approximately 1 hour following both the morning and evening dose on day 1, with a slightly longer elimination half-life at steady state (1.2-1.5 hours).

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration.

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

Special Populations

Renal impairment

The pharmacokinetics of VIMOVO have not been determined in patients with renal impairment.

Naproxen: Naproxen pharmacokinetics have not been determined in subjects with renal impairment. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment. VIMOVO is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) (see Precautions).

Esomeprazole: No studies have been performed with esomeprazole in patients with decreased renal function. Since the kidney is responsible for the excretion of

the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Hepatic impairment

The pharmacokinetics of VIMOVO have not been determined in patients with impaired hepatic function.

Naproxen: The pharmacokinetics of naproxen have not been determined in subjects with hepatic impairment. Chronic alcoholic liver disease and probably also other forms of cirrhosis reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. The implication of this finding for the naproxen component of VIMOVO dosing is unknown but it is prudent not to exceed the recommended dose. Patients with severe hepatic insufficiency should not receive VIMOVO (see PRECAUTIONS and CONTRAINDICATIONS).

Esomeprazole: The metabolism of esomeprazole in patients with mild to moderate hepatic impairment may be impaired. The metabolic rate is decreased in patients with severe hepatic impairment resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg daily should not be exceeded in patients with severe hepatic impairment (see Precautions).

Patients with severe hepatic insufficiency should not receive VIMOVO (see Contraindications).

Elderly

There are no specific data on the pharmacokinetics of VIMOVO in patients over age 65.

Naproxen: Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly, however the unbound fraction is <1% of the total naproxen concentration. Unbound trough naproxen concentrations in elderly subjects have been reported to range from 0.12% to 0.19% of total naproxen concentration, compared with 0.05% to 0.075% in younger subjects. The clinical significance of this finding is unclear, although it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some elderly patients.

Esomeprazole: The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years of age).

Poor CYP2C19 metabolisers

Esomeprazole: Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma

concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were about 60% higher.

These findings have no implications for the Dosage and Administration of VIMOVO.

Gender

Esomeprazole: Following a single dose of 40 mg esomeprazole the mean area under the plasma concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the posology of VIMOVO.

CLINICAL TRIALS

The Phase III clinical program to assess the efficacy and safety of VIMOVO consisted of two 6-month randomized, double-blind, active-controlled studies (studies 301 and 302) of VIMOVO (n = 428 in total) vs naproxen (n = 426 in total) to assess gastroprotection, and two 3-month double-blind, active and placebo-controlled, non-inferiority studies (studies 307 and 309) of VIMOVO (n = 490 in total) vs celecoxib (n = 488 in total) and placebo (n = 246) to assess pain control. In studies 301 and 302, The total number of patients who entered either trial with a history of ulcer within the previous 5 years was very small (N=69 [8.1%]); therefore, no substantive analyses could be made of the effect of prior ulcer history on the efficacy of VIMOVO.

Controlled studies assessing the efficacy and safety of VIMOVO do not extend beyond 6 months of treatment.

Studies with VIMOVO – Efficacy in Reducing Ulcers

In two 6-month randomized, double-blind, active-controlled studies (301 and 302), patients (n=854; 33/67 %M/F, 86/12/2 %Caucasian/Black/Other; median age 59 years (range 27 – 90 years)) with chronic inflammatory arthritis requiring daily use of NSAIDs or chronic musculoskeletal conditions requiring ongoing NSAID therapy, and were at risk of GI toxicity from daily NSAID use, were randomized to either VIMOVO 500/20 mg twice daily or EC-naproxen 500 mg twice daily. Approximately 24% of each treatment group were using low-dose aspirin (≤325 mg/day). The primary endpoint in these studies was incidence of gastric ulcers at any timepoint through the 6 months of treatment.

The inclusion criteria in both studies for defining patients at risk of GI toxicity were:

- patients 18 to 49 years old with a documented, uncomplicated gastric or duodenal ulcer (a mucosal break of at least 3 mm in diameter with depth, without any concurrent bleeding, clot or perforation) within 5 years of study enrolment
- patients 50 years of age or older regardless of ulcer history.

Some study participants also had other risk factors; smoking, concomitant low-dose aspirin or corticosteroids and comorbid disease. Because some patients would be randomized to treatment with naproxen in the absence of gastroprotection, patients with a documented history of a complicated upper gastrointestinal event (a recognised strongly predictive risk factor) were excluded from the studies. Patients were also screened for *H. Pylori* infection and patients testing positive were excluded from the studies. VIMOVO has not been studied in patients with *H. Pylori* infection.

Patients at risk of NSAID-associated gastric and duodenal ulcers and associated complications are defined in Australian clinical practice guidelines.

In the individual studies, a significantly lower proportion of patients on VIMOVO had gastric ulcers compared to those on EC-naproxen throughout 6 months (primary endpoint) and as early as the first month of treatment (ITT populations, p<0.001 for all comparisons).

Table 1 Cumulative observed incidence of arthritis[a] patients developing gastric ulcers throughout 6 months from Studies 301 and 302 (ITT population)

	Study 301		Study 302		Pooled	
	VIMOVO 500/20 mg bid (N=218)	**EC-naproxen** 500 mg bid (N=216)	**VIMOVO** 500/20 mg bid (N=210)	**EC-naproxen** 500 mg bid (N=210)	**VIMOVO** 500/20 mg bid (N=428)	**EC-naproxen** 500 mg bid (N=426)
0 to 1 month						
Incidence (%)	1.4	13.0	1.9	10.0	1.6	11.5
95% CI	(0.3 – 4.0)	(8.8 – 18.2)	(0.5 – 4.8)	(6.3 – 14.9)	(0.7 – 3.3)	(8.6 – 14.9)
p-value [b]	<0.001		<0.001		-	
0 to 3 months						
Incidence (%)	1.8	19.4	4.8	17.6	3.3	18.5
95% CI	(0.5 – 4.6)	(14.4–25.4)	(2.3 – 8.6)	(12.7–23.5)	(1.8 – 5.4)	(15.0–22.6)
p-value [b]	<0.001		<0.001		-	
0 to 6 months (primary endpoint)						
Incidence (%)	4.1	23.1	7.1	24.3	5.6	23.7
95% CI	(1.9 – 7.7)	(17.7–29.4)	(4.1 – 11.5)	(18.6–30.7)	(3.6 – 8.2)	(19.7–28.0)
p-value [b]	<0.001		<0.001		-	

[a] Studies also included 23% patients with chronic musculoskeletal conditions requiring ongoing NSAID therapy

[b] p values based on Fisher's exact test

A significantly lower proportion of patients who took VIMOVO compared to EC-naproxen had pre-specified NSAID-associated upper gastrointestinal adverse events and/or duodenal ulcer (53.3% vs 70.4%, p<0.001). In these trials, patients receiving VIMOVO had a mean duration of therapy of 152 days compared to 124 days in patients receiving EC-naproxen alone. A significantly higher proportion of patients taking EC-naproxen (12.0%) discontinued from the studies due to pre-specified NSAID-associated upper GI adverse events (including duodenal ulcers) compared to VIMOVO (4.0%) in both trials (p<0.001).

VIMOVO was effective across subgroups of patients considered to be at greater risk of GI side effects, increased age or concomitant use of low-dose ASA.

Table 2 Cumulative proportions of arthritis[a] patients with gastric ulcers at 6 months by risk factors from Studies 301 and 302 (pooled, ITT population)

	VIMOVO, 500/20 mg bid		EC-naproxen, 500 mg bid		
Subgroup	**N**	**% Gastric Ulcer (95% CI)**	**N**	**% Gastric Ulcer (95% CI)**	**p-value**
No history of ulcer- 5 years	395	5.3 (3.3 - 8.0)	390	21.5 (17.6 - 26.0)	p<0.001 [b]
Age 50 – 59 years	202	7.4 (4.2 – 12.0)	208	21.2 (15.8 – 27.3)	<0.001 [b]
Age 60 – 69 years	157	3.8 (1.4 – 8.1)	142	28.2 (20.9 – 36.3)	<0.001 [b]
Age <65years	294	7.5 (4.7 - 11.1)	303	21.8 (17.3 - 26.9)	<0.001 [b]
Age ≥65 years	134	1.5 (0.2 - 5.3)	123	28.5 (20.7 - 37.3)	<0.001 [b]
Age ≥70 years	55	0 (0.0 – 6.5)	67	22.4 (13.1 – 34.2)	<0.001 [b]
Used low-dose ASA	99	3.0 (0.6 - 8.6)	102	28.4 (19.9 - 38.2)	<0.001 [c]
Did not use low-dose ASA	329	6.4 (4.0 - 9.6)	324	22.2 (17.8 - 27.1)	<0.001 [c]

[a] Studies also included 23% patients with chronic musculoskeletal conditions requiring ongoing NSAID therapy

[b] p values based on CMH test stratified by low-dose ASA use at randomization

[c] p values based on Fisher's exact test

Dyspeptic symptoms, as measured by the Symptoms of Dyspepsia Assessment (SODA) for both abdominal pain and non-pain symptoms, and for satisfaction, were lower in those patients who took VIMOVO compared to those who took EC-naproxen. Significantly greater improvements versus baseline in abdominal pain and non-pain symptoms and satisfaction with dyspepsia related health, as measured by SODA, were achieved with VIMOVO compared to EC-naproxen (p<0.001 in all domains, combined analysis).

As well, a significantly greater proportion of patients taking VIMOVO reported heartburn resolution at 1, 3, and 6 months (63.7%, 71.0%, and 76.1% of patients) compared to those taking EC-naproxen (44.0%, 46.3%, and 53.8% of patients) ($p<0.001$ at all time points).

Studies with VIMOVO – Efficacy in Osteoarthritis

In two 3-month double-blind, placebo-controlled studies in patients (n=1219; 36/64 %M/F, 80/16/4 %Caucasian/Black/Other; median age 60 to 61 years (range 49 – 90 years)) with osteoarthritis of the knee (as per American College of Rheumatology (ACR) standards), some of whom were on low-dose ASA (n=282), VIMOVO was given as 500/20 mg twice daily, and was compared to celecoxib 200 mg given once daily. The primary endpoint in these studies was VAS pain assessment at week 12 using WOMAC Pain, WOMAC Function and PGA-VAS assessment.

VIMOVO was found to be non-inferior to celecoxib, as measured by the co-primary endpoints, change from baseline WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) scores on domains of pain and physical function as well as on Patient Global Assessment Scores.

Table 3 Comparison of VIMOVO vs celecoxib in WOMAC pain, function, and PGA-VAS, change from baseline at Week 12 from Studies 307 and 309 (ITT population)

	Study 307		Study 309		Pooled	
	VIMOVO 500/20 mg bid (N=246)	Celecoxib 200 mg od (N=242)	VIMOVO 500/20 mg bid (N=241)	Celecoxib 200 mg od (N=244)	VIMOVO 500/20 mg bid (N=487)	Celecoxib 200 mg od (N=486)
WOMAC Pain						
Week 12 LS mean change	-42.0	-41.8	-44.2	-42.9	-43.1	-42.3
% Change from baseline	60.4	60.3	63.2	61.3	61.7	60.7
WOMAC Function						
Week 12 LS mean change	-36.4	-36.3	-38.9	-36.8	-37.6	-36.6
% Change from baseline	54.6	54.4	58.0	54.9	56.3	54.7
PGA-VAS						

Table 3 Comparison of VIMOVO vs celecoxib in WOMAC pain, function, and PGA-VAS, change from baseline at Week 12 from Studies 307 and 309 (ITT population)

	Study 307		Study 309		Pooled	
	VIMOVO 500/20 mg bid (N=246)	Celecoxib 200 mg od (N=242)	VIMOVO 500/20 mg bid (N=241)	Celecoxib 200 mg od (N=244)	VIMOVO 500/20 mg bid (N=487)	Celecoxib 200 mg od (N=486)
Week 12 LS mean change	21.2	21.6	29.0	25.6	25.0	23.6
% Change from baseline	66.6	70.1	86.0	89.5	75.9	79.5

PGA-VAS Patient Global Assessment on a Visual Analogue Scale; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

VIMOVO treatment resulted in a significantly greater percentage of heartburn-free days than celecoxib (LS mean 76.4% VIMOVO vs 68.8% celecoxib) and significantly less rescue antacid use than celecoxib. The discontinuation rate due to adverse events was similar in patients receiving VIMOVO (6.9%) and celecoxib (7.8%).

INDICATIONS

VIMOVO is indicated for patients with an increased risk of gastrointestinal ulceration, who require NSAID therapy for symptomatic management of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis with an inflammatory component AND in whom lower doses of naproxen or other NSAIDs have proven insufficient.

If a total daily dose of 1 g of naproxen is not required, VIMOVO should NOT be used.

CONTRAINDICATIONS

In patients who are hypersensitive to naproxen or naproxen sodium or in whom acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory/analgesic agents induce allergic manifestations, e.g. asthma, nasal polyps, rhinitis and urticaria. Severe anaphylactic-like reactions to naproxen have been reported in such patients.

In patients with active, or a history of peptic or gastrointestinal ulceration, chronic dyspepsia or active gastrointestinal bleeding or perforation, related to previous NSAID therapy.

In patients with active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding) unrelated to previous NSAID therapy.

In patients 18 years of age or less since safety in this age group has not been established.

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any of the excipients.

History of asthma, urticaria or allergic-type reactions induced by administration of aspirin or other NSAIDs.

Third trimester of pregnancy.

Severe hepatic impairment (e.g. Childs-Pugh C).

Severe heart failure.

Severe renal failure.

Cerebrovascular bleeding or other bleeding disorders.

VIMOVO must not be used concomitantly with atazanavir and nelfinavir.

VIMOVO must not be used concomitantly with cilostazol.

PRECAUTIONS

Use in patients with upper gastrointestinal symptoms

VIMOVO treatment should not be initiated in patients with upper gastrointestinal symptoms. Such symptoms should be appropriately investigated and managed by other treatment before treatment with VIMOVO can be considered. If clinically indicated, testing and treatment for *H. Pylori* infection should be considered.

Use in treatment of acute pain

VIMOVO is not recommended for initial treatment of acute pain because, as with other modified release formulations of naproxen, the absorption of naproxen is delayed. However, flares of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis may be treated with VIMOVO.

Gastrointestinal effects

Naproxen

All NSAIDs can cause gastrointestinal discomfort and rarely serious, potentially fatal, gastrointestinal effects such as ulcers, irritation, bleeding and perforation which may increase with dose or duration of use, but can occur at any time without warning. Upper gastrointestinal ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 - 6 months and in about 2 - 4% of patients treated for one year. These trends continue with

longer duration of use, increasing the likelihood of developing a serious gastrointestinal event at some time during the course of therapy. However, even short term therapy is not without risk. VIMOVO has been formulated with esomeprazole to decrease the incidence of gastrointestinal side effects, including ulceration, from naproxen. While VIMOVO has been shown to significantly decrease the occurrence of gastric ulcers compared to naproxen alone, ulceration and associated complications can still occur (see Pharmacology). When gastrointestinal bleeding or ulceration occurs in patients receiving VIMOVO, the treatment should be withdrawn.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events e.g. elderly, debilitated patients, those with a history of serious gastrointestinal events, smoking and alcoholism.

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis; Crohn's disease) as their condition may be exacerbated. Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment. When gastrointestinal bleeding or ulceration occurs in patients receiving NSAIDs, treatment should be withdrawn immediately. Physicians should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

Studies to date have not identified any subset of patients not at risk of developing peptic ulcer and bleeding. However, the elderly have an increased frequency of adverse effects to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal. Debilitated patients do not seem to tolerate ulceration or bleeding as well as others. Most of the fatal gastrointestinal events associated with NSAIDs occurred with the elderly and/or debilitated patients.

In patients with active peptic ulcer or inflammatory disease of the gastrointestinal tract and active rheumatoid arthritis, an attempt might be made to treat the arthritis with a non-ulcerogenic drug.

Caution is advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding (see **PRECAUTIONS - Interactions with Other Medicines**). The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

Patients with risk factors should commence treatment on the lowest dose available. If a total daily dose of 1g of naproxen is not considered appropriate, alternative therapeutic regimens should be utilised.

Esomeprazole

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be

excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Cardiovascular thrombotic effects

Naproxen

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest-effective dose should be used for the shortest possible duration (see DOSAGE AND ADMINISTRATION). If a total daily dose of 1g of naproxen is not considered appropriate, alternative therapeutic regimens should be utilised.

There is no consistent evidence to suggest that concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and long term treatment) may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). The data suggest that naproxen (1,000 mg daily) may be associated with a lower risk for arterial thrombotic events than COX-2 selective inhibitors, but a small risk cannot be excluded. Overall, the data do not support a cardioprotective effect.

Hypertension

Naproxen

NSAIDs may lead to onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing VIMOVO to patients with hypertension. Blood pressure should be monitored closely during initiation of VIMOVO treatment and at regular intervals thereafter.

Heart Failure

Naproxen

Fluid retention and oedema have been observed in some patients taking NSAIDs, therefore, caution is advised in patients with fluid retention or heart failure.

Fluid Retention and Oedema

Naproxen

Peripheral oedema has been observed in some patients taking naproxen or other NSAIDs. Although sodium retention has not been reported in metabolic studies, it is possible that patients with compromised cardiac function may be at greater risk when taking naproxen. For this reason, VIMOVO should be used with caution in patients with fluid retention and hypertension. VIMOVO is contraindicated in patients with heart failure (see CONTRAINDICATIONS).

Renal effects

Naproxen

There have been reported cases of impaired renal function, renal failure, acute interstitial nephritis, haematuria, proteinuria, renal papillary necrosis, and occasionally nephritic syndrome associated with naproxen.

VIMOVO should not be given to patients with creatinine clearance less than 30 mL/min because accumulation of naproxen metabolites has been seen in such patients.

As with other NSAIDs, naproxen should be used with caution in patients with impaired renal function or a history of kidney disease because naproxen is an inhibitor of prostaglandin synthesis. Caution should be observed in patients with conditions leading to a reduction in blood volume and/or renal blood flow as prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of naproxen or other NSAIDs may cause a dose-dependent reduction in renal prostaglandin formation and may precipitate overt renal decompensation or failure. Patients at greatest risk are those with impaired renal function, hypovolaemia, heart failure, liver dysfunction, salt depletion, those taking diuretics and the elderly. Discontinuation of naproxen is usually followed by recovery to the pre-treatment state; however, serious adverse events may persist. Thus, VIMOVO should be used with great caution in such patients and the monitoring of serum creatinine and/or creatinine clearance is advised. A reduction of daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in these patients. If a total daily dose of 1g of naproxen is not considered appropriate, alternative therapeutic regimens should be utilised.

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding.

Esomeprazole

No studies have been performed with esomeprazole in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites

of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Interstitial nephritis has been reported as a very rare event from postmarketing data for esomeprazole (see ADVERSE EVENTS).

Naproxen and esomeprazole

The patient populations in the VIMOVO clinical studies were not large enough to detect a rare adverse event signal and so it is not known if the combination of naproxen and esomeprazole increases the risk of acute renal injury. Physicians should therefore be alert to the possibility of renal injury. VIMOVO should be used with great caution in patients at increased risk of renal injury (see Renal effects, naproxen) and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients.

Hepatic Impairment

Naproxen

As with other NSAIDs elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may resolve with continued therapy. The ALT test is probably the most sensitive indicator of liver dysfunction. Meaningful elevations (three times the upper limit of normal) of ALT or AST occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting hepatic dysfunction, or in whom an abnormal hepatic test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with naproxen containing products.

Hepatic abnormalities may be the result of hypersensitivity or direct toxicity. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with naproxen as with other NSAIDs. Cross reactivity has been reported. Although such reactions are rare, if abnormal hepatic tests persist or worsen, if clinical signs and symptoms consistent with hepatic disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), VIMOVO should be discontinued.

Chronic alcoholic hepatic disease and potentially other forms of cirrhosis reduce the total plasma concentration of naproxen; however the plasma concentration of unbound naproxen is increased. The implication of this finding for naproxen dosing is unknown.

In patients with impaired hepatic function, the lowest effective dose is recommended. If a total daily dose of 1g of naproxen is not considered appropriate, alternative therapeutic regimens should be utilised. Patients with severe hepatic insufficiency should not receive VIMOVO (see CONTRAINDICATIONS).

Haematological

Naproxen

Naproxen decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined (see PRECAUTIONS – Effects on Laboratory Tests).

Patients who have coagulation disorders or are receiving drug therapy that interferes with haemostasis should be carefully observed if naproxen-containing products are administered. Patients at high risk of bleeding and those on full anti-coagulation therapy (e.g. heparin or dicoumarol derivates) may be at increased risk of bleeding if given naproxen-containing products concurrently (see Interactions with other Medicines). Therefore, the benefits of prescribing VIMOVO should be weighed against these risks.

Patients with initial haemoglobin values of 10 grams or less, and who are to receive long-term therapy should have haemoglobin values determined frequently.

Patients on other drugs such as hydantoins, sulfonamides, sulfonylureas or methotrexate should be observed for increased effect or toxicity (see PRECAUTIONS – Interactions with Other Medicines).

When active and clinically significant bleeding from any source occurs in patients receiving VIMOVO, the treatment should be withdrawn.

Dermatological effects

Naproxen

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their physician at the first appearance of a skin rash or any other sign of hypersensitivity. VIMOVO should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Anaphylactic (anaphylactoid) reactions

Naproxen

Hypersensitivity reactions may occur in susceptible individuals. Anaphylactic (anaphylactoid) reactions may occur both in patients with and without a history of hypersensitivity or exposure to aspirin, other NSAIDs or naproxen-containing products. They may also occur in individuals with a history of angio-oedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome. Bronchospasm may be precipitated in patients suffering from, or with a history of, asthma or allergic disease or aspirin sensitivity.

Pre-existing asthma

Naproxen

The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, VIMOVO should not be administered to patients with this form of aspirin sensitivity (see CONTRAINDICATIONS) and should be used with caution in patients with pre-existing asthma.

Inflammation, including infection

Naproxen

The anti-pyretic and anti-inflammatory activities of naproxen may reduce fever and other signs of inflammation, thereby diminishing their utility as diagnostic signs.

Ocular events

Naproxen

Adverse ophthalmological effects have been observed with NSAIDs. In rare cases, adverse ocular disorders including papillitis, retrobulbar optic neuritis and papilloedema have been reported in users of NSAIDs including naproxen, although a cause-and-effect relationship cannot be established; accordingly, patients who develop visual disturbances during treatment with naproxen should have an ophthalmological examination.

Combination with other medicinal products

Naproxen

The combination of naproxen and other non-aspirin NSAIDs including cyclooxygenase-2 selective inhibitors is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events. Non-aspirin NSAIDs should be discontinued on commencement of VIMOVO treatment.

Esomeprazole

The combination of esomeprazole and other gastroprotective medications such as other proton pump inhibitors or H2 receptor antagonists is not recommended because of the cumulative risks of adverse events. Other gastroprotective medications should be discontinued on commencement of VIMOVO treatment.

General

When total daily dose of 1g of naproxen is considered not appropriate, alternative therapeutic regimens should be utilized.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance. Controlled studies assessing the efficacy and safety of VIMOVO do not extend beyond 6 months of treatment.

VIMOVO contains methyl- and propyl hydroxybenzoate, which may cause allergic reactions (possibly delayed).

Special patient populations

CYP2C19 enzyme

Esomeprazole

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were about 60% higher. These findings have no implications for the Dosage and Administration of VIMOVO.

Elderly

Naproxen

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding, ulceration and perforation, which may be fatal. (see DOSAGE AND ADMINSTRATION and PHARMACOLOGY). In clinical trials with VIMOVO the elderly did not have increased rates of gastroduodenal ulcers compared with patients under the age of 60 and ulcer risk reduction was maintained in this elderly population. However, ulcer complications such as bleeding, perforation and obstruction were not studied in these VIMOVO trials.

Esomeprazole

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Gender

Esomeprazole

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of VIMOVO.

Hepatic insufficiency

The pharmacokinetics of VIMOVO have not been determined in patients with impaired hepatic function.

Naproxen

The pharmacokinetics of naproxen have not been determined in subjects with hepatic impairment. Chronic alcoholic liver disease and probably also other forms of cirrhosis reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. The implication of this finding for the naproxen component of VIMOVO dosing is unknown but it is prudent not to

exceed the recommended dose (see DOSAGE AND ADMINSTRATION). Patients with severe hepatic insufficiency should not receive VIMOVO (see CONTRAINDICATIONS).

Esomeprazole

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Patients with severe hepatic insufficiency should not receive VIMOVO (see CONTRAINDICATIONS).

Renal impairment

Naproxen

As naproxen is eliminated to a large extent (95%) by urinary excretion via glomerular filtration, it should be used with great caution in patients with impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients. VIMOVO is not recommended in patients having a baseline creatinine clearance of less than 30 mL/min.

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of protein binding.

Certain patients, specifically those whose renal blood flow is compromised, because of extracellular volume depletion, cirrhosis of the liver, sodium restriction, congestive heart failure, and pre-existing renal disease, should have renal function assessed before and during VIMOVO therapy. Some elderly patients in whom impaired renal function may be expected, as well as patients using diuretics, may also fall within this category. A reduction in daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in these patients. Should a reduction to below 1 g daily be considered necessary, alternative therapeutic regimens should be utilised.

Carcinogenicity

No non-clinical data on the combination of the active substances are available. There are no known interactions between naproxen and esomeprazole that would indicate any novel or synergistic adverse pharmacology, pharmaco/ toxicokinetics, toxicity, physical/chemical interaction or tolerability issues as a result of their combination.

Naproxen

Limited non-clinical data are available to assess the carcinogenic potential of naproxen. There was no evidence of tumerogenicity in a 2 year dietary study in

rats, at doses up to 24 mg/kg/day (exposure approximately 5-fold lower than the anticipated daily exposure to naproxen with VIMOVO tablets). The potential carcinogenicity of naproxen at clinically relevant exposures is unknown.

Esomeprazole

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m^2 basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H_2-receptor antagonists and by partial fundectomy.

Genotoxicity

No non-clinical data on the combination of the active substances are available. There are no known interactions between naproxen and esomeprazole that would indicate any novel or synergistic adverse pharmacology, pharmaco/ toxicokinetics, toxicity, physical/chemical interaction or tolerability issues as a result of their combination.

Naproxen

Limited non-clinical data are available to assess the genotoxic potential of naproxen. Naproxen was not mutagenic in bacterial reverse mutation assays, although the validity of these assays was uncertain. Analysis of the clastogenic potential of naproxen has not been adequately investigated in nonclinical studies.

Esomeprazole

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

Naproxen

The use of naproxen, as with any drug known to inhibit cyclo-oxygenase/ prostaglandin synthesis, may impair fertility and is not recommended in women

attempting to conceive. In women who have difficulty conceiving or are undergoing investigation of infertility, withdrawal of VIMOVO should be considered.

Esomeprazole

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category C

VIMOVO is contraindicated in the third trimester of pregnancy.

Naproxen

Animal studies with naproxen do not indicate direct or indirect harmful effects with respect to embryonal/foetal development. Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. As with other drugs of this type, naproxen produces delay in parturition in animals and also affects the human foetal cardiovascular system (closure of ductus arteriosus). Use of VIMOVO in the last trimester of pregnancy is contraindicated (see CONTRAINDICATIONS). NSAIDs should not be used during the first two trimesters of pregnancy unless the potential benefit to the patient outweighs the potential risk to the foetus.

Naproxen containing products are not recommended in labour and delivery because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect foetal circulation and inhibit contractions with an increased bleeding tendency in both mother and child.

Esomeprazole

For esomeprazole limited clinical data on exposed pregnancies are available. VIMOVO should only be given to pregnant women if its use is considered essential. VIMOVO is contraindicated in the last trimester of pregnancy.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg/day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced foetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the foetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

Naproxen is excreted in human milk at levels approximately 1% of plasma concentrations. It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore VIMOVO should not be used during breast feeding.

Effects on ability to drive and operate machinery

When driving vehicles or operating machines it should be taken into account that some of the adverse effects (e.g. dizziness) reported following the use of VIMOVO may reduce the ability to react.

Interactions with other medicines

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2-selective NSAID) did not identify any clinically relevant interaction.

VIMOVO can be administered with low-dose aspirin (≤325 mg/day) therapy. In clinical trials, patients taking VIMOVO in combination with low-dose aspirin did not have an increased occurrence of gastric ulcers compared to patients taking VIMOVO alone (see PHARMACOLOGY). However, the concurrent use of aspirin and VIMOVO may still increase the risk of serious adverse events (see ADVERSE EFFECTS).

When naproxen is administered with high doses of aspirin, its protein binding is reduced, although the clearance of free naproxen is not altered. The clinical significance of this interaction is not known.

Naproxen interactions

Other NSAIDs

Combination of naproxen-containing products and other NSAIDs, including cyclooxygenase-2 (COX-2) selective inhibitors, is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events.

Sodium Bicarbonate

Sodium bicarbonate may enhance the rate of naproxen absorption.

Zidovudine

In vitro studies have shown that naproxen may interfere with the metabolism of zidovudine, resulting in higher zidovudine plasma levels. Therefore, to avoid the potential side effects associated with increased zidovudine plasma levels, dose reduction should be considered. Should a reduction to below 1 g daily be considered necessary, alternative therapeutic regimens should be utilised.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time (triple whammy) increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the initiation of the combination. The

combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Cholestyramine

As with other NSAIDs, concomitant administration of cholestyramine can delay the absorption of naproxen.

Diuretics

Clinical studies, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy (see PRECAUTIONS).

Selective Serotonin Reuptake Inhibitors (SSRIs)

Epidemiological studies, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. Therefore, caution should be used when NSAIDs, including COX-2 selective inhibitors, are administered concomitantly with SSRIs (see PRECAUTIONS).

Corticosteroids

There is an increased risk of gastrointestinal bleeding when corticosteroids are combined with NSAIDs including COX–2 selective inhibitors. Caution should be used when NSAIDs are administered concomitantly with corticosteroids (see PRECAUTIONS). If steroid dosage is reduced or eliminated during VIMOVO therapy, the steroid dosage should be reduced slowly and the patients must be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of underlying disease.

Cyclosporin

As with all NSAIDs caution is advised when cyclosporin is co-administered with naproxen because of the increased risk of nephrotoxicity.

ACE-inhibitors

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model. This may indicate that both esomeprazole and naproxen could enhance the toxicity of methotrexate. The clinical relevance is likely to be greater in patients receiving high doses of methotrexate and in patients with renal dysfunction. Caution should be used when VIMOVO is administered concomitantly with methotrexate. In high-dose methotrexate administration a temporary withdrawal of VIMOVO is recommended.

Sulphonylureas, Hydantoins

Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as sulphonylureas, and hydantoins. Patients simultaneously receiving naproxen and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone. No significant interactions have been observed in clinical studies with naproxen and coumarin-type anticoagulants. However, caution is advised since interactions have been seen with other nonsteroidal agents of this class. The free fraction of warfarin may increase substantially in some subjects and naproxen interferes with platelet function(see section PRECAUTIONS).

Anticoagulants/ Antiplatelets Agents

Patients who have coagulation disorders or are receiving drug therapy that interferes with haemostasis should be carefully observed if naproxen is administered. Patients on full anticoagulation therapy (e.g., heparin or dicoumarol derivatives) may be at increased risk of bleeding if given naproxen concurrently. Thus, the benefits should be weighed against these risks.

There is an increased risk of gastrointestinal bleeding when anti-platelet agents are combined with NSAIDs.

Beta receptor-blockers

Naproxen and other NSAIDs can reduce the antihypertensive effect of propranolol and other beta-blockers.

Probenecid

Probenecid significantly prolongs the half-life of naproxen (from 14 to 37 hrs). This is associated with a decrease in conjugated metabolites and an increase in 6-0-desmethyl naproxen.

Esomeprazole interactions

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19, the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Other drugs that affect esomeprazole

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's Wort) may lead to decreased esomeprazole serum levels by increasing esomeprazole metabolism.

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{½}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively. (See CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model. This may indicate that both esomeprazole and naproxen could enhance the toxicity of methotrexate. The clinical relevance is likely to be greater in patients receiving high doses of methotrexate and in patients with renal dysfunction. Caution should be used when VIMOVO is administered concomitantly with methotrexate. In high-dose methotrexate administration a temporary withdrawal of VIMOVO is recommended.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and

nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Amoxycillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effects on laboratory tests

Naproxen

Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-di-nitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

Esomeprazole

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference, VIMOVO treatment should be temporarily stopped five days before CgA measurements.

ADVERSE EFFECTS

VIMOVO contains both naproxen and esomeprazole and the same pattern of undesirable effects as reported for both of these individual active substances may occur. Gastrointestinal undesirable effects such as dyspepsia, stomach pain, nausea and vomiting are the most commonly reported undesirable effects in patients treated with naproxen alone. VIMOVO has been developed with esomeprazole to decrease the incidence of gastrointestinal side effects from naproxen and has been shown to significantly decrease the occurrence of gastric ulcers and NSAID associated upper gastrointestinal adverse events compared to naproxen alone.

VIMOVO clinical trials

Adverse event data is provided from controlled studies using VIMOVO, involving 2317 patients ranging in duration from 3-12 months. Patients received either 500/20 mg of VIMOVO twice daily (n=1157), 500 mg of enteric-coated (EC) naproxen twice daily (n=426), 200 mg of celecoxib once daily (n=488), or placebo (n=246).

All adverse reactions, regardless of causality, occurring in ≥2% of patients from two 6-month randomized, double-blind, parallel-group controlled clinical studies (Study 301 and 302) conducted in patients at risk of developing NSAID-associated ulcers compared to EC-naproxen are presented in Table 4 below.

Table 4 Adverse Reactions, regardless of causality, occurring ≥2% in arthritis[a] patients at risk of NSAID-induced ulcers from Studies 301 and 302 (pooled, 6 months duration)

Preferred term (sorted by SOC)	VIMOVO 500/20 mg twice daily (n=428) %	EC-Naproxen 500 mg twice daily (n=426) %
Gastrointestinal Disorders		
Gastritis Erosive	19.4	38.0
Dyspepsia	18.0	26.8
Gastritis	17.1	14.1
Diarrhea	6.1	5.2
Gastric Ulcer	5.6	23.7
Abdominal Pain Upper	5.6	8.7
Nausea	5.1	4.9
Hiatus Hernia	4.2	5.9
Abdominal Distension	3.7	3.8
Flatulence	3.7	3.1

Preferred term (sorted by SOC)	VIMOVO 500/20 mg twice daily (n=428) %	EC-Naproxen 500 mg twice daily (n=426) %
Esophagitis	3.5	7.5
Constipation	2.6	2.8
Abdominal pain	2.3	1.6
Erosive Duodenitis	2.1	11.7
Abdominal pain lower	2.1	2.6
Duodenitis	1.4	7.3
Gastritis hemorrhagic	1.2	2.1
Gastroesophageal reflux disease	0.9	3.5
Duodenal ulcer	0.7	5.4
Erosive esophagitis	0.5	5.6
Infections and infestations		
Upper respiratory tract infection	4.9	3.8
Bronchitis	2.3	1.9
Urinary tract infection	2.3	1.4
Sinusitis	1.9	2.1
Nasopharyngitis	0.9	2.3
Musculoskeletal and connective tissue disorders		
Arthralgia	1.2	2.3
Nervous system disorders		
Headache	2.6	1.4
Dysgeusia	2.1	1.4
Respiratory, thoracic and mediastinal disorders		
Cough	2.3	2.6

[a] Studies also included 23% patients with chronic musculoskeletal conditions requiring ongoing NSAID therapy

Patients taking VIMOVO had significantly fewer pre-specified NSAID-associated upper GI adverse events (including duodenal ulcers) (53.3%) compared to patients taking EC naproxen alone (70.4%).

As well, patients taking VIMOVO had significantly less discontinuations due to adverse reactions compared to patients taking EC-naproxen alone (7.9% vs. 12.5% respectively). The most common reasons for discontinuations due to adverse events in the VIMOVO treatment group were upper abdominal pain (1.2%, n=5), duodenal ulcer (0.7%, n=3) and erosive gastritis (0.7%, n=3). Among patients receiving naproxen alone, the most common reasons for discontinuations due to adverse events were duodenal ulcer 5.4% (n=23), dyspepsia 2.8% (n=12) and upper abdominal pain 1.2% (n=5). The proportion of patients discontinuing treatment due to pre-specified NSAID-associated upper gastrointestinal adverse events (including duodenal ulcers) in patients treated with VIMOVO was 4.0% compared to 12.0% for patients taking EC-naproxen (p<0.001).

Adverse reaction data for VIMOVO, regardless of causality, occurring in ≥2% of patients, and greater than placebo from two 3-month randomized double-blind, placebo-controlled clinical studies (studies 307 and 309) conducted in patients with osteoarthritis of the knee are presented in Table 5 below.

Table 5 Adverse Reactions, regardless of causality, occurring ≥2% in patients with osteoarthritis of the knee from Studies 307 and 309 (3 months duration)

Preferred term (sorted by SOC)	VIMOVO 500 mg/20 mg twice daily (n=490) %	Celecoxib 200 mg once daily (n=488) %	Placebo (n=246) %
Gastrointestinal Disorders			
Dyspepsia	8.4	10.7	12.2
Diarrhea	5.5	2.9	3.7
Abdominal Pain Upper	4.1	4.3	3.3
Constipation	3.5	2.0	1.2
Nausea	3.5	3.1	3.7
Nervous System Disorders			
Dizziness	3.1	0.8	2.0
Headache	2.7	3.7	5.3
General disorders and administration site conditions			
Peripheral edema	3.1	1.2	1.2
Musculoskeletal and connective tissue disorders			
Arthralgia	1.4	2.9	1.6
Back pain	1.2	2.9	2.0
Respiratory, thoracic and mediastinal disorders			

Preferred term (sorted by SOC)	VIMOVO 500 mg/20 mg twice daily (n=490) %	Celecoxib 200 mg once daily (n=488) %	Placebo (n=246) %
Cough	1.4	0.6	2.8
Infections and infestations			
Sinusitis	1.0	1.2	2.4

Similar percentages of subjects receiving either VIMOVO or celecoxib withdrew from these studies due to treatment emergent adverse events (6.9% and 7.8% respectively). There were no adverse reactions in which more than 1% of subjects withdrew from any treatment group.

The long-term safety of VIMOVO was evaluated in an open label clinical trial of 239 patients, of which 135 patients received 500/20 mg of VIMOVO for 12 months. There were no differences in frequency or types of adverse reactions seen in the long-term safety study compared to shorter-term treatment in the randomized controlled studies above.

In the pooled data from all VIMOVO clinical trials in patients (n=2317), there were 4 reports of atrial fibrillation/flutter. All 4 events occurred in patients assigned to VIMOVO but all were assessed as unrelated or unlikely to be related to study drug.

Adverse effects for naproxen and esomeprazole monocomponents

The following adverse effects information has been reported in clinical trials and in post-marketing for esomeprazole and naproxen, taken alone.

Naproxen

Adverse effects reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis and osteoarthritis are listed below. In general, these effects were reported 2 to 10 times more frequently than they were in studies of 962 patients treated for mild to moderate pain.

Incidence between 3% and 9%

Gastrointestinal: The most frequently reported adverse events were related to the gastrointestinal tract. These were: constipation, heartburn, abdominal pain, nausea.

Central Nervous System: headache, dizziness, drowsiness

Dermatologic: itching (pruritis), skin eruption, ecchymoses

Special Senses: tinnitus

Cardiovascular: oedema, dyspnoea

Incidence between 1% and less than 3%

Gastrointestinal: dyspepsia, diarrhoea, stomatitis

Central Nervous System: light-headedness, vertigo

Dermatologic: sweating, purpura

Special Senses: hearing disturbances, visual disturbances

Cardiovascular: palpitations

General: thirst

Incidence less than 1%

PROBABLE CAUSAL RELATIONSHIP:

The following adverse effects were reported less frequently than 1% during controlled clinical trials and in post marketing reports. The probability of a causal relationship exists between naproxen and these adverse effects.

Gastrointestinal: abnormal liver function tests, gastrointestinal bleeding, haematemesis, jaundice, melaena, peptic ulceration with bleeding and/or perforation, non-peptic gastrointestinal ulceration, vomiting, ulcerative stomatitis, colitis, fatal hepatitis

Renal: glomerular nephritis, haematuria, interstitial nephritis, renal papillary necrosis, nephrotic syndrome, renal disease, hyperkalaemia, renal failure

Haematologic: eosinophilia, granulocytopenia, leukopenia, thrombocytopenia

Central Nervous System: depression, dream abnormalities, inability to concentrate, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis

Dermatologic: porphyria cutanea tarda, epidermolysis bullosa, alopecia, skin rashes, epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome (SJS), photosensitivity reactions including rare cases in which the skin resembles porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa

Special Senses: hearing impairment

Cardiovascular: vasculitis, congestive heart failure

General: menstrual disorders, pyrexia (chills and fever), eosinophilic pneumonitis, anaphylactoid reactions (see **PRECAUTIONS** – **Anaphylactic Reactions**)

CAUSAL RELATIONSHIP UNKNOWN:

Other reactions have been reported in circumstances in which a causal relationship could not be established. Although rarely reported, the physician should be alerted to these.

Haematologic: agranulocytosis, aplastic anaemia, haemolytic anaemia

Central and Peripheral Nervous System: cognitive dysfunction, convulsions, paraesthesia

Dermatologic: urticaria, photosensitivity

Mouth and Throat: sore throat

General: angioneurotic oedema, hyperglycaemia, hypoglycaemia, hyperkalaemia

Reproductive: female infertility

Post-Marketing Experience

The following adverse effects have been reported with NSAIDs and NAPROSYN:

Gastrointestinal: peptic ulcers, perforation, gastrointestinal bleeding, heartburn, nausea, oesophagitis, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, non-peptic gastrointestinal ulceration, melaena, haematemesis, stomatitis, ulcerative stomatitis, exacerbation of ulcerative colitis and Crohn's disease, pancreatitis, gastritis

Infection: aseptic meningitis

Blood and Lymphatic System Disorders: agranulocytosis, aplastic anaemia, eosinophilia, haemolytic anaemia, leucopenia, thrombocytopenia

Immune System Disorders: anaphylactoid reactions

Metabolic and Nutrition Disorders: hyperkalaemia

Psychiatric Disorders: depression, dream abnormalities, insomnia

Nervous System Disorders: dizziness, drowsiness, headache, light-headedness, retrobulbar optic neuritis, convulsions, cognitive dysfunction, inability to concentrate

Eye Disorders: visual disturbances, corneal opacity, papillitis, papilloedema

Ear and Labyrinth Disorders: hearing impairment, hearing disturbances, tinnitus, vertigo

Cardiac Disorders: palpitations, cardiac failure, congestive heart failure

Vascular Disorders: hypertension, vasculitis

Respiratory, Thoracic and Mediastinal Disorders: dyspnoea, pulmonary oedema, asthma, eosinophilic pneumonitis

Hepatobiliary Disorders: hepatitis, jaundice

Skin and Subcutaneous Tissue Disorder: ecchymoses, itching (pruritus), purpura, skin eruptions, sweating, alopecia, epidermal necrolysis, very rarely toxic epidermal necrolysis (TEN), erythema multiforme, bullous reactions (including SJS), erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, skin rashes, systemic lupus erythematosus (SLE), urticaria, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa or angioneurotic oedema

If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and patient monitored.

Musculoskeletal and Connective Tissue Disorders: myalgia, muscle weakness

Renal and Urinary Disorders: haematuria, interstitial nephritis, nephritic syndrome, renal disease, renal failure, renal papillary necrosis

Reproductive System: female infertility

General Disorders: oedema, thirst

Investigations: abnormal liver function tests, raised serum creatinine

Esomeprazole

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None were found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia
Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: peripheral oedema
Rare: hyponatraemia
Very rare: hypomagnesaemia

Psychiatric disorders

Uncommon: insomnia
Rare: agitation, confusion, depression
Very rare: aggression, hallucination

Nervous system disorders

Common: headache
Uncommon: dizziness, paraesthesia, somnolence
Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon: dry mouth
Rare: stomatitis, gastrointestinal candidiasis
Very rare: Microscopic colitis

Hepatobiliary disorders

Uncommon: increased liver enzymes
Rare: hepatitis with or without jaundice
Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash
Rare: alopecia, photosensitivity
Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia
Very rare: muscular weakness

Renal and urinary disorders

Very rare: interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 6 Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies

	E total n=519	E 40 n=173	E 20 n=179	E 10 n=167	Placebo n=169
Mean exposure time (days):	**136**	**147**	**144**	**115**	**58**
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

When prescribing an NSAID or a PPI, the harm/benefit ratio for each individual patient should be assessed and the lowest effective doses used for the shortest possible duration. If a total daily dose of 1 g of naproxen is not required, VIMOVO should not be used and alternative therapeutic regimens should be utilised. Since VIMOVO tablets cannot be divided and once daily dosing has not been studied, different therapeutic regimens would be achieved using medicines separately containing naproxen and esomeprazole as monotherapies.

Existing treatment with non-aspirin NSAIDs, including COX-2 selective inhibitors, and gastroprotective medications such as a proton pump inhibitors or H2 receptor antagonists, should be discontinued on commencement of treatment with VIMOVO.

Adults

The dose is 1 tablet (500 mg/20 mg) twice daily. Controlled studies assessing the efficacy and safety of VIMOVO do not extend beyond 6 months of treatment.

Method of administration

VIMOVO must be swallowed whole with water, and not split, chewed or crushed.

It is recommended that VIMOVO is taken at least 30 minutes prior to food intake (see Pharmacokinetics).

Special populations

Patients with renal impairment

In patients with mild to moderate renal impairment, VIMOVO should be used cautiously and renal function should be monitored closely. A reduction in the total daily naproxen dose should be considered (see PRECAUTIONS). When total daily dose of 1g of naproxen is considered not appropriate, alternative therapeutic regimens should be utilized.

VIMOVO is not recommended in patients with severe renal impairment (creatinine clearance <30 mL/min) because accumulation of naproxen metabolites has been seen in patients with severe renal failure and in those on dialysis (see section PRECAUTIONS).

Patients with hepatic impairment

In patients with mild to moderate hepatic impairment VIMOVO should be used cautiously and hepatic function should be monitored closely. A reduction in the total daily naproxen dose should be considered (see PRECAUTIONS). When total daily dose of 1 g of naproxen is considered inappropriate, alternative therapeutic regimens should be utilized.

VIMOVO is contraindicated in patients with severe hepatic impairment because these patients should not receive more than 20 mg esomeprazole per day (see CONTRAINDICATIONS).

Elderly (>65 years)

The elderly are at an increased risk of the serious consequences of adverse reactions (see PRECAUTIONS).

Children and adolescents (≤18 years)

VIMOVO is not recommended for use in children, due to lack of data on safety and efficacy.

OVERDOSAGE

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

There is no clinical data on overdose with VIMOVO.

Any effects of an overdose with VIMOVO would be expected to primarily reflect the effects of an overdose with naproxen.

Symptoms

Related to naproxen overdose

Significant naproxen overdosage may be characterized by lethargy, dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea, disorientation or vomiting. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose. A few patients have experienced convulsions, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening.

Related to esomeprazole overdose

The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg esomeprazole were uneventful. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness.

Management of overdose

Related to naproxen

Patients should be managed by symptomatic and supportive care following a NSAID overdose, particularly with respect to GI effects and renal damage. There are no specific antidotes. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine or hemoperfusion may not be useful due to high protein binding.

Related to esomeprazole

No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

PRESENTATION AND STORAGE CONDITIONS

VIMOVO modified release tablets: store below 25°C.

Oval, biconvex, yellow tablet marked ‘500/20’ in black ink, containing enteric-coated (gastro-resistant) naproxen and film-coated esomeprazole.

VIMOVO tablets are available in HDPE bottles. The bottles contain 6, 60, or 500 tablets. All bottle sizes have child-resistant caps except for the 500 tablet bottle which is a dispensing pack.

VIMOVO tablets are also available in aluminium foil blister strips. The blister packs contain 10, 30, or 100 tablets.

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

Date of TGA approval: 25th October 2011

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au