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 \textit{in vivo}, with negligible conversion to the R-isomer. The chemical name is di-\((S)\)-5-methoxy-2-\([(4\text{-methoxy-3,5-dimethyl-2-pyridinyl})\text{methyl}]\text{sulfinyl}\)-1\(H\)-benzimidazole magnesium salt trihydrate.

The chemical structure of esomeprazole magnesium trihydrate is:

![Chemical structure of esomeprazole magnesium trihydrate]

CAS number: 217087-09-7

Molecular formula: \(C_{34}H_{38}N_6O_6S_2\text{Mg.3H}_2\text{O}\)

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\text{-methoxy-alpha-methyl-2-naphthaleneacetic acid. It is an odourless, white to off-white crystalline substance.}

The chemical structure of naproxen is:

![Chemical structure of naproxen]
CAS number: 2224531
Molecular formula: $\text{C}_{14}\text{H}_{14}\text{O}_3$
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 cyclooxygenase 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 $\text{H}^+\text{K}^+\text{-ATPase}$ (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 ($C_{\text{max}}$), minimum plasma concentration ($C_{\text{low}}$) and average plasma concentration over the dosing interval ($C_{\text{ave}}$), 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 C_{ss} 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 isofrom, 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-O-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* patients developing gastric ulcers throughout 6 months from Studies 301 and 302 (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>Study 301</th>
<th>Study 302</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VIMOVO</td>
<td>EC-naproxen</td>
<td>VIMOVO</td>
</tr>
<tr>
<td></td>
<td>500/20 mg bid (N=218)</td>
<td>500 mg bid (N=216)</td>
<td>500/20 mg bid (N=210)</td>
</tr>
<tr>
<td>0 to 1 month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>1.4</td>
<td>13.0</td>
<td>1.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.3 – 4.0)</td>
<td>(8.8 – 18.2)</td>
<td>(0.5 – 4.8)</td>
</tr>
<tr>
<td>p-value b</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>0 to 3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>1.8</td>
<td>19.4</td>
<td>4.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.5 – 4.6)</td>
<td>(14.4–25.4)</td>
<td>(2.3 – 8.6)</td>
</tr>
<tr>
<td>p-value b</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>0 to 6 months (primary endpoint)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>4.1</td>
<td>23.1</td>
<td>7.1</td>
</tr>
<tr>
<td>95% CI</td>
<td>(1.9 – 7.7)</td>
<td>(17.7–29.4)</td>
<td>(4.1 – 11.5)</td>
</tr>
<tr>
<td>p-value b</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

* 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* patients with gastric ulcers at 6 months by risk factors from Studies 301 and 302 (pooled, ITT population)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>VIMOVO, 500/20 mg bid</th>
<th>EC-naproxen, 500 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% Gastric Ulcer (95% CI)</td>
</tr>
<tr>
<td>No history of ulcer- 5 years</td>
<td>395</td>
<td>5.3 (3.3 - 8.0)</td>
</tr>
<tr>
<td>Age 50 – 59 years</td>
<td>202</td>
<td>7.4 (4.2 – 12.0)</td>
</tr>
<tr>
<td>Age 60 – 69 years</td>
<td>157</td>
<td>3.8 (1.4 – 8.1)</td>
</tr>
<tr>
<td>Age &lt;65years</td>
<td>294</td>
<td>7.5 (4.7 – 11.1)</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>134</td>
<td>1.5 (0.2 – 5.3)</td>
</tr>
<tr>
<td>Age ≥70 years</td>
<td>55</td>
<td>0.0 (0.0 – 6.5)</td>
</tr>
<tr>
<td>Used low-dose ASA</td>
<td>99</td>
<td>3.0 (0.6 – 8.6)</td>
</tr>
<tr>
<td>Did not use low-dose ASA</td>
<td>329</td>
<td>6.4 (4.0 – 9.6)</td>
</tr>
</tbody>
</table>

---

*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)

<table>
<thead>
<tr>
<th></th>
<th>Study 307</th>
<th>Study 309</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VIMOVO 500/20 mg bid (N=246)</td>
<td>Celecoxib 200 mg od (N=242)</td>
<td>VIMOVO 500/20 mg bid (N=241)</td>
</tr>
<tr>
<td><strong>WOMAC Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12 LS mean change</td>
<td>-42.0</td>
<td>-41.8</td>
<td>-44.2</td>
</tr>
<tr>
<td>% Change from baseline</td>
<td>60.4</td>
<td>60.3</td>
<td>63.2</td>
</tr>
<tr>
<td><strong>WOMAC Function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12 LS mean change</td>
<td>-36.4</td>
<td>-36.3</td>
<td>-38.9</td>
</tr>
<tr>
<td>% Change from baseline</td>
<td>54.6</td>
<td>54.4</td>
<td>58.0</td>
</tr>
</tbody>
</table>

**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)

<table>
<thead>
<tr>
<th></th>
<th>Study 307</th>
<th>Study 309</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VIMOVO</td>
<td>Celecoxib</td>
<td>VIMOVO</td>
</tr>
<tr>
<td></td>
<td>500/20 mg</td>
<td>200 mg od</td>
<td>500/20 mg</td>
</tr>
<tr>
<td>bid (N=246)</td>
<td>(N=242)</td>
<td>(N=241)</td>
<td>(N=244)</td>
</tr>
<tr>
<td>Week 12 LS mean change</td>
<td>21.2</td>
<td>21.6</td>
<td>29.0</td>
</tr>
<tr>
<td>% Change from baseline</td>
<td>66.6</td>
<td>70.1</td>
<td>86.0</td>
</tr>
</tbody>
</table>

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 dosedependent 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, ACE inhibitors or angiotensin II receptor antagonists, and the elderly. Discontinuation of naproxen is usually followed by recovery to the pretreatment 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

The combination of VIMOVO 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 ADMINISTRATION 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 ADMINISTRATION). 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, ACE inhibitors or angiotensin II receptor antagonists 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 tumorigenicity 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/m² 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, H₂-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.

Fertility

The use of NSAIDs like naproxen may impair female fertility. VIMOVO should not be used in women attempting to conceive.

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 in women attempting to conceive or 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.

**ACE-inhibitors/Angiotensin II receptor antagonists**

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors and angiotensin II receptor antagonists. NSAIDs may also increase the risk of renal impairment associated with the use of ACE-inhibitors or angiotensin II receptor antagonists. The combination of NSAIDs and ACE-inhibitors or angiotensin II receptor antagonists should be given with caution in patients who are elderly, volume depleted, or with impaired renal function (see PRECAUTIONS).

**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.

Cyclosporin
As with all NSAIDs caution is advised when cyclosporin is co-administered with naproxen because of the increased risk of nephrotoxicity.

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-O-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 ($t_{1/2}$) 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.

Tacrolimus
Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus. As with all NSAIDs caution is advised when tacrolimus is co-administered because of the increased risk of nephrotoxicity.

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).

Amoxicillin 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 artifactualy 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)

<table>
<thead>
<tr>
<th>Preferred term (sorted by SOC)</th>
<th>VIMOVO 500/20 mg twice daily (n=428) %</th>
<th>EC-Naproxen 500 mg twice daily (n=426) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastritis Erosive</td>
<td>19.4</td>
<td>38.0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>18.0</td>
<td>26.8</td>
</tr>
<tr>
<td>Gastritis</td>
<td>17.1</td>
<td>14.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Gastric Ulcer</td>
<td>5.6</td>
<td>23.7</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>5.6</td>
<td>8.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>5.1</td>
<td>4.9</td>
</tr>
<tr>
<td>Hiatus Hernia</td>
<td>4.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Preferred term</td>
<td>VIMOVO 500/20 mg twice daily (n=428) %</td>
<td>EC-Naproxen 500 mg twice daily (n=426) %</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Abdominal Distension</td>
<td>3.7</td>
<td>3.8</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3.7</td>
<td>3.1</td>
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<tr>
<td>Esophagitis</td>
<td>3.5</td>
<td>7.5</td>
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<tr>
<td>Constipation</td>
<td>2.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Erosive Duodenitis</td>
<td>2.1</td>
<td>11.7</td>
</tr>
<tr>
<td>Abdominal pain lower</td>
<td>2.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>1.4</td>
<td>7.3</td>
</tr>
<tr>
<td>Gastritis hemorrhagic</td>
<td>1.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>0.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>0.7</td>
<td>5.4</td>
</tr>
<tr>
<td>Erosive esophagitis</td>
<td>0.5</td>
<td>5.6</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0.9</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1.2</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>2.3</td>
<td>2.6</td>
</tr>
</tbody>
</table>

*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)

<table>
<thead>
<tr>
<th>Preferred term (sorted by SOC)</th>
<th>VIMOVO 500 mg/20 mg twice daily (n=490) %</th>
<th>Celecoxib 200 mg once daily (n=488) %</th>
<th>Placebo (n=246) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8.4</td>
<td>10.7</td>
<td>12.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.5</td>
<td>2.9</td>
<td>3.7</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>4.1</td>
<td>4.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>3.5</td>
<td>2.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.5</td>
<td>3.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.1</td>
<td>0.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Headache</td>
<td>2.7</td>
<td>3.7</td>
<td>5.3</td>
</tr>
<tr>
<td>General disorders and...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>3.1</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Musculoskeletal and...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1.4</td>
<td>2.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Back pain</td>
<td>1.2</td>
<td>2.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Respiratory, thoracic and...</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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, melena, 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, melena, 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; severe hypomagnesaemia may result in hypocalcaemia

**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

<table>
<thead>
<tr>
<th>E total n=519</th>
<th>E 40 n=173</th>
<th>E 20 n=179</th>
<th>E 10 n=167</th>
<th>Placebo n=169</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean exposure time (days):</td>
<td>136</td>
<td>147</td>
<td>144</td>
<td>115</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>44 (8.5)</td>
<td>16 (9.2)</td>
<td>17 (9.5)</td>
<td>11 (6.6)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>35 (6.7)</td>
<td>13 (7.5)</td>
<td>9 (5.0)</td>
<td>13 (7.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>34 (6.6)</td>
<td>11 (6.4)</td>
<td>14 (7.8)</td>
<td>9 (5.4)</td>
</tr>
<tr>
<td>Gastritis/gastritis (aggravated)</td>
<td>32 (6.2)</td>
<td>11 (6.4)</td>
<td>13 (7.3)</td>
<td>8 (4.8)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>26 (5.0)</td>
<td>13 (7.5)</td>
<td>7 (3.9)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>Nausea/nausea (aggravated)</td>
<td>25 (4.8)</td>
<td>11 (6.4)</td>
<td>8 (4.5)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>22 (4.2)</td>
<td>8 (4.6)</td>
<td>10 (5.6)</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19 (3.7)</td>
<td>4 (2.3)</td>
<td>9 (5.0)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>Accident and/or injury</td>
<td>19 (3.7)</td>
<td>3 (1.7)</td>
<td>6 (3.4)</td>
<td>10 (6.0)</td>
</tr>
<tr>
<td>Infection viral</td>
<td>19 (3.7)</td>
<td>7 (4.0)</td>
<td>7 (3.9)</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td>Vomiting/vomiting (aggravated)</td>
<td>17 (3.3)</td>
<td>6 (3.5)</td>
<td>3 (1.7)</td>
<td>8 (4.8)</td>
</tr>
<tr>
<td>Hypertension/hypertension (aggravated)</td>
<td>14 (2.7)</td>
<td>2 (1.2)</td>
<td>6 (3.4)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>Gastrin serum increased</td>
<td>13 (2.5)</td>
<td>6 (3.5)</td>
<td>6 (3.4)</td>
<td>1 (0.6)</td>
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<tr>
<td>Tooth disorder</td>
<td>13 (2.5)</td>
<td>4 (2.3)</td>
<td>6 (3.4)</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Back pain</td>
<td>10 (1.9)</td>
<td>3 (1.7)</td>
<td>2 (1.1)</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td>Epigastric pain/epigastric pain (aggravated)</td>
<td>9 (1.7)</td>
<td>2 (1.2)</td>
<td>2 (1.1)</td>
<td>5 (3.0)</td>
</tr>
</tbody>
</table>

**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 NSAIIDs, 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, alkalization 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 packed in HDPE bottles containing 6, 60, or 500* tablets or in aluminium foil blister strip packs* containing 10, 30 or 100 tablets. All bottle sizes have child-resistant caps except for the 500 tablet bottle which is a dispensing pack. The sachet containing the dessicant is not meant to be consumed.
*The 500 tablet bottle and all blister presentations are not available in Australia.

NAME AND ADDRESS OF SPONSOR
AstraZeneca Pty Ltd
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NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE
S4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)
25th October 2011

DATE OF MOST RECENT AMENDMENT
22nd October 2012

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