

## **NEW ZEALAND DATA SHEET**

### **1. NAME OF MEDICINE**

VIMOVO™  
500 mg/20 mg modified-release tablets

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each modified-release tablet contains 500 mg naproxen and 20 mg esomeprazole (as magnesium trihydrate).

VIMOVO contains very low, non-preserving levels of 0.02 mg methyl parahydroxybenzoate and 0.01 mg propyl parahydroxybenzoate (see sections 4.4 and 6.1).

For a full list of excipients, see section 6.1.

### **3. PHARMACEUTICAL FORM**

Modified-release tablet containing enteric-coated (gastro-resistant) naproxen and film-coated esomeprazole.

Oval, biconvex, yellow tablet marked '500/20' in black ink.

### **4. CLINICAL PARTICULARS**

#### **4.1 INDICATIONS**

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

#### **4.2 DOSAGE AND ADMINISTRATION**

##### **Dosage in adults**

The dose is 1 tablet (500 mg/20 mg) twice daily.

Undesirable effects of naproxen may be minimised by using the lowest effective dose for the shortest duration possible (see section 4.4). In patients not treated with a NSAID previously, a lower daily dose of naproxen or of another NSAID should be considered. When total daily dose of 1000 mg of naproxen is not considered appropriate, alternative therapeutic regimens should be utilized.

Treatment should be continued to achieve individual treatment goals, reviewed at regular intervals and discontinued if no benefit seen.

Due to the delayed release of naproxen from the enteric-coated formulation, VIMOVO is not intended for the treatment of acute pain conditions (such as dental pain or gout). However, flares of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis may be treated with VIMOVO.

### **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 section 5.2).

### **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 sections 4.4 and 4.5). When total daily dose of 1000 mg of naproxen is considered not appropriate, alternative therapeutic regimens should be utilized.

VIMOVO is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/minute) because accumulation of naproxen metabolites has been seen in patients with severe renal failure and in those on dialysis (see sections 4.3 and 4.4).

#### 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 sections 4.4 and 5.2). When total daily dose of 1000 mg of naproxen is considered not appropriate, alternative therapeutic regimens should be utilized.

VIMOVO is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2).

#### Elderly (>65 years)

The elderly are at an increased risk of the serious consequences of adverse reactions (see sections 4.4 and 5.2). When total daily dose of 1000 mg of naproxen is considered not appropriate (e.g. in elderly with impaired renal function or low body weight), alternative therapeutic regimens should be utilized.

#### Children (≤18 years)

VIMOVO is not recommended for use in children, due to lack of data on safety and efficacy.

### **4.3 CONTRAINDICATIONS**

- Known hypersensitivity to naproxen, esomeprazole, substituted benzimidazoles, or to any of the excipients
- History of asthma, urticaria or allergic-type reactions induced by administration of aspirin or other NSAIDs (see section 4.4)
- Third trimester of pregnancy (see section 4.6)
- Severe hepatic impairment (e.g. Childs-Pugh C)
- Severe heart failure
- Severe renal impairment
- Active peptic ulceration (see section 4.4, gastrointestinal effects, *Naproxen*)
- Gastrointestinal bleeding, cerebrovascular bleeding or other bleeding disorders (see section 4.4, Haematological effects)
- VIMOVO must not be used concomitantly with atazanavir and nelfinavir (see sections 4.4 and 4.5).

## 4.4 WARNINGS AND PRECAUTIONS FOR USE

### General

The use of VIMOVO with other concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided. VIMOVO can be used with low dose aspirin. (See also section 4.5.)

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

When total daily dose of 1000 mg of naproxen is considered not appropriate, alternative therapeutic regimens should be utilized.

Risk-factors to develop NSAID related gastro-intestinal complications include high age, concomitant use of anticoagulants, corticosteroids, other NSAIDs including low-dose acetylsalicylic acid, debilitating cardiovascular disease, and a history of gastric and/or duodenal ulcers.

In patients with the following conditions, naproxen should only be used after a rigorous benefit-risk ratio:

- Inducible porphyries
- Systemic lupus erythematosus and mixed connective tissue disease. There may be an increased risk of aseptic meningitis in these patients.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

VIMOVO contains very low levels of methyl- and propyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed). (See sections 2 and 6.1).

### Elderly

Naproxen: The elderly have an increased frequency of adverse reactions especially gastro-intestinal bleeding, and perforation, which may be fatal (see sections 4.2 and 5.2). The esomeprazole component of VIMOVO decreased the incidence of ulcers in elderly.

### Gastrointestinal effects:

Naproxen: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation with NSAIDs is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should begin treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5). The esomeprazole component of VIMOVO is a proton pump inhibitor.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving NSAIDs with concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (for information on use of VIMOVO with low-dose aspirin, see section 4.5).

Ulcer complications such as bleeding, perforation and obstruction were not studied in the VIMOVO trials.

When GI bleeding or ulceration occurs in patients receiving VIMOVO, the treatment should be withdrawn (see section 4.3).

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8 – Undesirable effects).

**Esomeprazole:** In 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 magnesium may alleviate symptoms and delay diagnosis.

Dyspepsia could still occur despite the addition of esomeprazole to the combination tablet (see section 5.1).

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* (see section 5.1).

Esomeprazole, as all acid-blocking medicines, might reduce the absorption of vitamin B<sub>12</sub> (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors of reduced vitamin B<sub>12</sub> absorption on long-term therapy.

### **Cardiovascular and cerebrovascular effects**

**Naproxen:** Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long-term treatment) may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Although data suggest that the use of naproxen (1000 mg daily) may be associated with a lower risk, some risk cannot be excluded.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with naproxen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

### **Renal effects**

**Naproxen:** Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin

formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, hypovolaemia, heart failure, liver dysfunction, salt depletion, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state (see also below, and sections 4.2 and 4.5).

### **Use in patients with impaired renal function**

As naproxen and its metabolites 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 contraindicated in patients having a baseline creatinine clearance of less than 30 ml/minute (see section 4.3).

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of protein binding.

Certain patients, specifically those whose renal blood flow is compromised, because of extracellular volume depletion, cirrhosis of the liver, sodium restriction, congestive heart failure, and pre-existing renal disease, should have renal function assessed before and during VIMOVO therapy. Some elderly patients in whom impaired renal function may be expected, as well as patients using diuretics, may also fall within this category. A reduction in daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in these patients.

### **Hepatic effects**

Borderline elevations of one or more liver tests may occur in patients taking NSAIDs. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

#### Hepatorenal syndrome

The use of NSAIDs may be associated with acute renal failure in patients with severe hepato-cirrhosis. These patients frequently also have concomitant coagulopathy related to inadequate synthesis of clotting factors. Antiplatelet effects associated with naproxen could further increase risk of severe bleeding in these patients

### **Haematological effects**

Naproxen: 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. dicoumarol derivatives) may be at increased risk of bleeding if given naproxen-containing products concurrently (see section 4.5).

Naproxen decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

When active and clinically significant bleeding from any source occurs in patients receiving VIMOVO, the treatment should be withdrawn.

**Eye effects**

*Naproxen*: Because of adverse eye findings in animal studies with NSAIDs, it is recommended that an ophthalmic examination be carried out if any change or disturbance in vision occurs.

**Dermatological effects**

*Naproxen*: Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring within the first month of treatment in the majority of cases. 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 angioedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps.

**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 section 4.3) and should be used with caution in patients with pre-existing asthma.

**Inflammation**

*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.

**Female fertility**

The use of VIMOVO, as with any drug known to inhibit cyclooxygenase / prostaglandin synthesis, may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of VIMOVO should be considered (see section 4.6).

**Combination with other medicinal products:**

Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus loading) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded and therefore VIMOVO must not be used concomitantly with atazanavir (see section 4.3).

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolised through CYP2C19

should be considered. An interaction is observed between clopidogrel and omeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

## 4.5 INTERACTIONS

### Contraindications of concomitant use (see section 4.3)

#### Antiretroviral agents

Omeprazole, the racemate of D+S omeprazole (esomeprazole), has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these 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 CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C<sub>max</sub> and C<sub>min</sub>). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC, C<sub>max</sub> and C<sub>min</sub> by 36–39% and mean AUC, C<sub>max</sub> and C<sub>min</sub> for the pharmacologically active metabolite M8 was reduced by 75-92%.

For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

No interaction study has been performed with VIMOVO and atazanavir. However, due to the similar pharmacodynamic and pharmacokinetic properties of omeprazole and esomeprazole, the concomitant use of atazanavir and nelfinavir with esomeprazole is not recommended and concomitant administration with VIMOVO is contraindicated (see section 4.3).

### Concomitant use with precaution

#### Other analgesics including cyclooxygenase-2 selective inhibitors:

Concomitant use of two or more NSAIDs should be avoided as this may increase the risk of adverse effects, especially gastrointestinal ulcers and bleeding. The concomitant use of VIMOVO with other NSAIDs, except for low-dose aspirin ( $\leq 325$  mg/day), is not recommended (see section 4.4).

#### Aspirin

VIMOVO can be administered with low-dose aspirin ( $\leq 325$  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 section 5.1). However, the concurrent use of aspirin and VIMOVO may still increase the risk of serious adverse events (see sections 4.4 and 4.8).

### Cyclosporin and tacrolimus

As with other non-steroidal anti-inflammatory drugs, caution is advised when cyclosporin is co-administered because of the increased risk of nephrotoxicity.

There is a possible risk of nephrotoxicity when NSAIDs are given with tacrolimus.

### 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 section 4.4).

### Selective Serotonin Reuptake Inhibitors (SSRIs)

Concomitant use of NSAIDs, including COX-2 selective inhibitors, and SSRIs increases the risk of gastrointestinal bleeding (see section 4.4).

### 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 section 4.4).

### ACE-inhibitors

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors, and may increase the risk of renal impairment associated with the use of ACE-inhibitors. Therefore, the combination should be given with caution in patients with impaired renal function, especially elderly patients.

### Digoxin

NSAIDs may increase plasma cardiac glycoside levels when co-administered with cardiac glycosides such as digoxin.

### Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. 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

Caution is advised where methotrexate is administered concurrently because of possible enhancement of its toxicity, since naproxen, in common with other non-steroidal anti-inflammatory medicines, has been reported to reduce the tubular secretion of methotrexate in an animal model.

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.

Clopidogrel

In a crossover clinical study, clopidogrel (300-mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) with 5 µM ADP was diminished by 47% (24 hours) and 30% (Day 5) when clopidogrel and omeprazole were administered together. In another study it was shown that administering clopidogrel and omeprazole different times apart did not prevent their interaction that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19.

Inconsistent data on the clinical implications of this PK/ PD interaction in terms of major cardiovascular events have been reported from both observational and clinical studies..

Anti-coagulants and thrombocyte aggregation inhibitors

NSAIDs may enhance the effects of oral anti-coagulants (e.g. warfarin, dicoumarol) heparins and thrombocyte aggregation inhibitors (see section 4.4).

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 marketed 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 coumarine derivatives.

Beta receptor-blockers

Naproxen and other NSAIDs can reduce the antihypertensive effect of propranolol and other beta-blockers.

Probenecid

Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

Medicines with gastric pH-dependent absorption

The gastric acid suppression during treatment with esomeprazole – and other PPIs, might decrease or increase the absorption of medicines with a gastric pH dependent absorption. . Like with other medicines that decrease the intragastric acidity, the absorption of medicines, such as ketoconazole, itraconazole, posaconazole and erlotinib can decrease while the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant use with posaconazole and erlotinib should be avoided. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by up to 10% (up to 30% in two out of ten subjects).

### Other Information Concerning Drug Interactions

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.

As with other NSAIDs, concomitant administration of cholestyramine can delay the absorption of naproxen.

In healthy volunteers, concomitant administration of 40 mg esomeprazole 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 also section 4.4).

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin and quinidine.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Esomeprazole is also metabolised by CYP3A4. The following have been observed in relation to these enzymes:

- Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.
- Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients.
- 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.
- Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to esomeprazole.

Dose adjustment of esomeprazole is not required in any of these cases.

Medicines 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 the esomeprazole metabolism.

Omeprazole as well as esomeprazole act as inhibitors of CYP 2C19. 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.

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking quinolones may have an increased risk of developing convulsions.

### Drug/Laboratory Test Interaction

Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-di-

nitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

## 4.6 PREGNANCY AND LACTATION

### Pregnancy

#### Naproxen:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

#### Esomeprazole:

There are limited amount of data from the use of esomeprazole in pregnant women. With the racemic mixture omeprazole data on a larger number of exposed pregnancies stemming from epidemiological studies indicate no malformative nor foetotoxic effects. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/foetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development.

During the first and second trimester of pregnancy, VIMOVO should not be given unless clearly necessary. If VIMOVO is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the duration of treatment should be kept as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, VIMOVO is contraindicated during the third trimester of pregnancy.

## Fertility

The use of NSAIDs like naproxen may impair female fertility. The use of VIMOVO is not recommended in women attempting to conceive (see section 4.4).

## Breastfeeding

Naproxen is excreted in low quantities in human milk. It is unknown whether esomeprazole is excreted in human milk. A published case report on the racemic mixture omeprazole indicated excretion of low quantities in the human breast milk (weight adjusted dose < 7%). VIMOVO should not be used during breastfeeding.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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.

## 4.8 ADVERSE EFFECTS

### Summary of safety profile

Immediate release esomeprazole has been included in the tablet formulation to decrease the incidence of gastrointestinal side effects from naproxen. VIMOVO has been shown to significantly decrease the occurrence of gastric ulcers and NSAID associated upper gastrointestinal adverse events compared to naproxen alone (see section 5.1).

No new safety findings were identified during VIMOVO treatment in the overall study population (n=1157) compared to the well-established safety profiles of the individual active substances naproxen and esomeprazole.

### Tabulated summary of adverse reactions

Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are defined according to the following convention: Very common ( $\geq 1/10$ ), Common ( $\geq 1/100$  to  $< 1/10$ ), Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), Very rare ( $< 1/10,000$ ), Not known (cannot be estimated from the available data)

### VIMOVO

The following adverse experiences have been reported in patients taking VIMOVO during clinical trials

	Very Common	Common	Uncommon	Rare
<b>Infections and infestations</b>			infection	diverticulitis
<b>Blood and lymphatic system disorders</b>				eosinophilia, leucopenia
<b>Immune system disorders</b>				hypersensitivity reactions

	<b>Very Common</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>
<b>Metabolism and nutrition disorders</b>			appetite disorder	fluid retention, hyperkalaemia, hyperuricaemia
<b>Psychiatric disorders</b>			anxiety, depression, insomnia	confusion, dream abnormalities
<b>Nervous system disorders</b>		dizziness, headache, taste disturbance	paraesthesia, syncope	somnolence, tremor
<b>Ear and labyrinth disorders</b>			tinnitus, vertigo	
<b>Cardiac disorders</b>			arrhythmia, palpitations	myocardial infarction, tachycardia
<b>Vascular disorders</b>		hypertension		
<b>Respiratory, thoracic and mediastinal disorders</b>			asthma, bronchospasm, dyspnoea	
<b>Gastrointestinal disorders</b>	dyspepsia	abdominal pain, constipation, diarrhoea, oesophagitis , flatulence, gastric/duodenal ulcers*, gastritis, nausea, vomiting	dry mouth, eructation, gastrointestinal bleeding, stomatitis	glossitis, haematemesis , rectal bleeding
<b>Skin and subcutaneous tissue disorders</b>		skin rashes	dermatitis, hyperhidrosis, pruritis, urticaria	alopecia, ecchymoses
<b>Musculoskeletal and connective tissue disorders</b>		arthralgia	myalgia	
<b>Renal and urinary disorders</b>				proteinuria, renal failure
<b>Reproductive system and breast disorders</b>				menstrual disorder
<b>General disorders and administration site disorders</b>		oedema	asthenia, fatigue, pyrexia	
<b>Investigations</b>			abnormal liver function tests, raised serum creatinine	

\*as detected by scheduled routine endoscopy

Naproxen

The following adverse experiences have been reported in patients taking naproxen during clinical trials and through postmarketing reports.

	<b>Common</b>	<b>Uncommon/Rare</b>
<b>Infections and infestations</b>	diverticulitis	aseptic meningitis, infection, sepsis
<b>Blood and lymphatic system disorders</b>		agranulocytosis, aplastic anaemia, eosinophilia, granulocytopenia, haemolytic anaemia, leucopenia, lymphadenopathy, pancytopenia, thrombocytopenia
<b>Immune system disorders</b>		anaphylactic reactions, anaphylactoid reactions, hypersensitivity reactions
<b>Metabolism and nutrition disorders</b>		appetite disorder, fluid retention, hyperglycaemia, hyperkalaemia, hyperuricaemia, hypoglycaemia, weight changes
<b>Psychiatric disorders</b>	depression, insomnia	agitation, anxiety, confusion, dream abnormalities, hallucinations, nervousness
<b>Nervous system disorders</b>	dizziness, drowsiness, headache, lightheadedness, vertigo	cognitive dysfunction, coma, convulsions, inability to concentrate, optic neuritis, paraesthesia, syncope, tremor
<b>Eye disorders</b>	visual disturbances	blurred vision, conjunctivitis, corneal opacity, papilloedema, papillitis
<b>Ear and labyrinth disorders</b>	tinnitus, hearing disturbances	hearing impairment
<b>Cardiac disorders</b>	palpitations	arrhythmia, congestive heart failure, myocardial infarction, tachycardia
<b>Vascular disorders</b>		hypertension, hypotension, vasculitis
<b>Respiratory, thoracic and mediastinal disorders</b>	Dyspnoea	asthma, bronchospasm, eosinophilic pneumonitis, pneumonia, pulmonary oedema, respiratory depression
<b>Gastrointestinal disorders</b>	dyspepsia, abdominal pain, nausea, vomiting diarrhoea, constipation, heartburn, peptic ulcers, stomatitis	dry mouth, oesophagitis, gastric ulcers, gastritis, glossitis, eructation, flatulence, gastric/duodenal ulcers, gastrointestinal bleeding and/or perforation, melaena, haematemesis, pancreatitis, colitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease), nonpeptic gastrointestinal ulceration, rectal bleeding, ulcerative stomatitis
<b>Hepatobiliary disorders</b>		cholestasis, hepatitis, jaundice, liver failure

	Common	Uncommon/Rare
<b>Skin and subcutaneous tissue disorders</b>	pruritis, ecchymoses, purpura, skin rashes	alopecia, exanthema, urticaria, bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN), erythema multiforme, erythema nodosum, fixed drug eruption, lichen planus, systemic lupus erythematoses, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria), exfoliative dermatitis, angioneurotic edema, pustular reaction
<b>Musculoskeletal and connective tissue disorders</b>		muscle weakness, myalgia
<b>Renal and urinary disorders</b>		glomerular nephritis, haematuria, interstitial nephritis, nephrotic syndrome, oliguria/polyuria, proteinuria, renal failure, renal papillary necrosis, tubular necrosis
<b>Reproductive system and breast disorders</b>		infertility, menstrual disorder
<b>General disorders and administration site disorders</b>	fatigue, oedema, sweating, thirst	asthenia, malaise, pyrexia
<b>Investigations</b>		abnormal liver function tests, increased bleeding time, raised serum creatinine

Esomeprazole:

The following adverse drug reactions have been identified or suspected in the clinical trials programme for enteric-coated esomeprazole and/or from post-marketing use. None were found to be dose-related.

	Common	Uncommon	Rare	Very rare
<b>Blood and lymphatic system disorders</b>			leukopenia, thrombocytopenia	agranulocytosis, pancytopenia
<b>Immune system disorders</b>			hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock	
<b>Metabolism and nutrition disorders</b>		peripheral oedema	hyponatraemia	hypomagnesaemia
<b>Psychiatric disorders</b>		insomnia	agitation, confusion, depression	aggression, hallucinations

	Common	Uncommon	Rare	Very rare
<b>Nervous system disorders</b>	headache	dizziness, paraesthesia, somnolence	taste disturbance	
<b>Eye disorders</b>			blurred vision	
<b>Ear and labyrinth disorders</b>		vertigo		
<b>Respiratory, thoracic and mediastinal disorders</b>			bronchospasm	
<b>Gastrointestinal disorders</b>	abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation	dry mouth	stomatitis, gastrointestinal candidiasis	Microscopic colitis
<b>Hepatobiliary disorders</b>		increased liver enzymes	hepatitis with or without jaundice	hepatic failure, hepatic encephalopathy in patients with pre-existing liver disease
<b>Skin and subcutaneous tissue disorders</b>		dermatitis, pruritus, urticaria, rash	alopecia, photosensitivity	erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
<b>Musculoskeletal and connective tissue disorders</b>			arthralgia, myalgia	muscular weakness
<b>Renal and urinary disorders</b>				Interstitial nephritis
<b>Reproductive system and breast disorders</b>				gynaecomastia
<b>General disorders and administration site disorders</b>			malaise, increased sweating	

### Description of selected adverse reactions

#### Naproxen

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long-term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Although data suggest that the use of naproxen (1000 mg daily) may be associated with a lower risk, some risk cannot be excluded (see section 4.4).

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4 - Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

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 and/or duodenal ulcers and NSAID associated upper gastrointestinal adverse events compared to naproxen alone.

## 4.9 OVERDOSE

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, hypoprothrombinaemia, renal dysfunction, metabolic acidosis, apnoea, 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.

### 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.

Haemodialysis 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, alkalinisation of urine or haemoperfusion 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.

**5. PHARMACOLOGICAL PROPERTIES****5.1 PHARMACODYNAMIC PROPERTIES**

Pharmacotherapeutic group: naproxen and esomeprazole ATC code: MO1AE52

**Mechanism of action**

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 providing protection against possible local gastric toxicity of naproxen.

Due to the delayed-release of naproxen, VIMOVO is not intended for, and has not been studied in, acute pain.

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

Esomeprazole is the S-enantiomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H<sup>+</sup>K<sup>+</sup>-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

**Pharmacodynamic effects**Effect on gastric acid secretion

An optimal effect (maintenance of high gastric pH) was achieved with VIMOVO formulation containing 20 mg of esomeprazole. After 9 days of dosing twice daily with VIMOVO, intragastric pH above 4 was maintained for a mean time of 17.1 hours (SD 3.1) in healthy volunteers. The corresponding value for NEXIUM 20 mg was 13.6 hours (SD 2.4).

Other effects related to acid inhibition

During treatment with antisecretory drugs, serum gastrin increases in response to the decreased acid secretion. Also chromogranin A (CgA) increases due to decreased gastric acidity.

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 at a somewhat increased frequency. These changes are a physiological

consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

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*.

### **Clinical safety and efficacy**

In all of the clinical studies, VIMOVO was taken by 491 patients for 6 months and 135 for 12 months. In two randomised, double-blind, active-controlled studies, the incidence of gastric and duodenal ulcers was significantly lower after VIMOVO treatment compared to enteric-coated naproxen 500 mg twice daily (without esomeprazole or other PPI) during a 6-month treatment period. The participants were at risk a priori for developing NSAID-associated ulcers, due to advanced age, or prior history of gastric or duodenal ulcers. Patients who tested positive for *H pylori* were excluded from these trials.

The gastric ulcer incidences for VIMOVO were 5.6%, and for enteric-coated naproxen 23.7% (pooled data). VIMOVO also significantly reduced the occurrence of duodenal ulcers relative to enteric-coated naproxen (0.7 versus 5.4%) (pooled data).

VIMOVO also significantly reduced the occurrence of pre-specified NSAID associated upper gastrointestinal adverse events compared to enteric-coated naproxen during these trials (53.3% vs 70.4% (pooled data)).

In the VIMOVO trials, only patients at risk to develop NSAID-related gastroduodenal ulcers such as >50 years of age or prior uncomplicated ulcer were included; concomitant users of low-dose aspirin (LDA) were permitted. Subgroup analyses confirmed the same trend as observed for overall population regarding efficacy of GI ulcer prevention by VIMOVO. In users of LDA, the incidence of gastroduodenal ulcers was 4.0% (95% CI 1.1-10.0%) in the VIMOVO group (n=99) versus 32.4% (95% CI 23.4-42.3%) in the EC Naproxen-only group (n=102). In elderly  $\geq$  60 years of age, the incidence of gastroduodenal ulcers was 3.3% (95% CI 1.3-6.7%) versus 30.1% (95% CI 24.0-36.9%) in the VIMOVO group (n=212) and in the EC Naproxen-only group (n=209), respectively.

In two clinical trials, VIMOVO had less upper abdominal discomfort over a 6-month period compared with enteric-coated naproxen as measured by dyspepsia symptoms. A significantly lower proportion of patients taking VIMOVO prematurely discontinued the studies due to adverse events compared to patients taking enteric-coated naproxen alone (7.9% vs. 12.5% respectively); 4.0% and 12.0% of discontinuations were due to upper gastric-related adverse events, including duodenal ulcers, respectively). Patients on VIMOVO had a mean duration of therapy of 152 days compared to 124 days in patients receiving enteric-coated naproxen alone.

In two 12-week studies in patients with osteoarthritis of the knee, VIMOVO (500 mg/20 mg given twice daily) had similar improvement in pain and function, time to onset of pain relief, and discontinuation due to adverse events compared to celecoxib 200 mg once daily.

## 5.2 PHARMACOKINETIC PROPERTIES

### 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 enteric-coated naproxen, based on both area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C<sub>max</sub>) of naproxen, 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. After repeated twice daily dosing of VIMOVO, the C<sub>max</sub> was 2-3 times higher, and the AUC 4-5 times higher, as compared to the first day of dosing. 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).

Even though the AUC range at steady state was comparable for NEXIUM 20 mg once daily and VIMOVO twice daily: 292.0 - 2279.0 ng/ml and 189.0 - 2931.0 ng/ml, respectively, the mean exposure was 60% higher (CI: 1.28 - 1.93) for VIMOVO. This could be expected due to the different total dose of esomeprazole given as VIMOVO or NEXIUM (40 vs 20 mg). C<sub>max</sub> was 60% higher (CI: 1.27 - 2.02), for VIMOVO, which was expected for an IR formulation.

### **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 does not delay the absorption of esomeprazole but 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 section 4.2).

## 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<sub>ss</sub> 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 section 4.6).

### *Esomeprazole*

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

## Metabolism

### Naproxen

30% of naproxen is metabolized in the liver by the cytochrome P450 system (CYP), primarily CYP2C9, to 6-O-desmethyl naproxen. Neither the parent drug nor the metabolites induce metabolizing enzymes. Both naproxen and 6-O-desmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites.

### Esomeprazole

Esomeprazole is completely metabolised by the CYP system. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma. The major metabolites of esomeprazole have no effect on gastric acid secretion.

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 section 4.4).

### 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 of esomeprazole is about 17 l/h after a single dose and about 9 l/h after repeated administration.

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 has not been determined in patients with renal impairment.

Naproxen: Naproxen pharmacokinetics has 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 contraindicated for use in patients with severe renal impairment (creatinine clearance <30 ml/min) (see section 4.3).

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 has not been determined in patients with impaired hepatic function.

Naproxen: The pharmacokinetics of naproxen has 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 to use the lowest effective dose.

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.

Patients with severe hepatic insufficiency should not receive VIMOVO (see section 4.3).

### Elderly

There is 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. 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 posology 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.

## **5.3 PRECLINICAL SAFETY DATA**

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, pharmacokinetics, toxicity, physical/chemical interaction or tolerability issues as a result of their combination.

### Naproxen

Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity, carcinogenic potential, embryo-foetal toxicity and fertility. The principal findings at high doses in oral repeat-dose toxicity studies in animals were GI irritation and renal injury, both of which are attributed to inhibition of prostaglandin synthesis. Oral administration of naproxen to pregnant rats in the third trimester of pregnancy in peri- and postnatal studies resulted in difficult labour. This is a known effect for this class of compounds.

### Esomeprazole

Non-clinical bridging studies reveal no particular hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction. Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

#### Tablet core

- Croscarmellose sodium
- Magnesium stearate
- Povidone K90
- Silica, colloidal anhydrous

#### Coating

- Carnauba wax
- Glycerol monostearate 40-55
- Hypromellose
- Iron oxide E172 (yellow)
- Macrogol 8000
- Methacrylic acid-ethyl acrylate copolymer (1:1)
- Methyl parahydroxybenzoate E218\*
- Polydextrose
- Polysorbate 80
- Propyl parahydroxybenzoate E216\*
- Sodium laurilsulfate
- Titanium dioxide E171
- Triethyl citrate

#### Printing ink

- Hypromellose
- Iron oxide E172 (black)
- Propylene glycol

\*These preservatives are present in a film coating mixture and will carry through into the finished product at very low, non-functional levels.

### **6.2 INCOMPATIBILITIES**

Not applicable.

### **6.3 SHELF LIFE AND STORAGE CONDITION**

2 years.

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Do not store above 30°C.

Bottle: Store in the original package and keep the bottle tightly closed in order to protect from moisture.

### **6.5 NATURE AND CONTENTS OF CONTAINER**

HDPE bottles containing silica-gel desiccant with either a child resistant or non-child resistant (dispensing pack) polypropylene closure with an induction seal.  
Pack sizes: 6 or 60 modified-release tablets.

## **6.6 MEDICINE CLASSIFICATION**

Prescription Medicine.

## **7. NAME AND ADDRESS**

AstraZeneca Limited  
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## **8. DATE OF PREPARATION**

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