PACKAGE LEAFLET TEXT
Issued to the Medical Profession Only

VIMOVO

NAME OF THE MEDICINAL PRODUCT

VIMOVO tablets 500 mg/20 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

VIMOVO 500 mg/20 mg: Each tablet contains 500 mg naproxen and 20 mg esomeprazole (as magnesium trihydrate).

PHARMACEUTICAL FORM

Film-coated tablet

500 mg/20 mg: Oval, biconvex, yellow tablet marked '500/20' in black ink, containing enteric-coated (gastro-resistant) naproxen and film-coated esomeprazole.

CLINICAL PARTICULARS

Therapeutic indications

Relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing Non-Steroidal Anti-inflammatory Drugs (NSAID) associated gastric ulcers. VIMOVO is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen-containing products. Controlled studies do not extend beyond 6 months.

Posology and method of administration

Carefully consider the potential benefits and risks of VIMOVO and other treatment options before deciding to use VIMOVO. Use the lowest effective dose for the shortest duration

consistent with individual patient treatment goals. VIMOVO does not allow for administration of a lower daily doses of naproxen or esomeprazole. If a lower daily dose of either naproxen (i.e. < 1000 mg/day) or immediate release (IR) esomeprazole (i.e. < 40mg/day) is more appropriate, alternate therapy should be considered.

Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis
The dosage is one tablet twice daily of VIMOVO 500 mg naproxen and 20 mg of esomeprazole.

The tablets are to be swallowed whole with liquid. Do not split, chew, crush or dissolve the tablet. VIMOVO is to be taken at least 30 minutes before meals.

Geriatric Patients
Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Use caution when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly use the lowest effective dose (see section Pharmacokinetic properties).

Patients With Moderate to Severe Renal Impairment
Naproxen-containing products are not recommended for use in patients with moderate to severe or severe renal impairment (creatinine clearance <30 mL/min) (see sections Special warnings and special precautions for use and Pharmacokinetic properties).

Hepatic Insufficiency
Monitor patients with mild to moderate hepatic impairment closely and consider a possible dose reduction based on the naproxen component of VIMOVO.
VIMOVO is not recommended in patients with severe hepatic impairment because esomeprazole doses should not exceed 20 mg daily in these patients (see sections Special warnings and special precautions for use and Pharmacokinetic properties).

Pediatric Patients
The safety and efficacy of VIMOVO in children younger than 18 years has not been established. VIMOVO is therefore not recommended for use in children.

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 Special warnings and special precautions for use)

- Third trimester of pregnancy (see section Pregnancy and lactation)

- Severe hepatic impairment (e.g. Childs-Pugh C)
- Use during the peri-operative period in the setting of coronary artery bypass graft (CABG) surgery.
- Severe heart failure
- Severe renal impairment
- Active peptic ulceration
- Gastrointestinal bleeding, cerebrovascular bleeding or other bleeding disorders

Special warnings and special precautions for use

Elderly
Naproxen: The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding, ulceration and perforation, which may be fatal (see sections Posology and method of administration and Pharmacokinetic properties).

Gastrointestinal effects
Naproxen: Gastrointestinal 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 gastrointestinal events. 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 section Pharmacodynamic properties).

The risk of gastrointestinal bleeding, ulceration or perforation with NSAIDs is higher with increasing doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly. These patients should begin treatment on the lowest dose available.

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.

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 Interaction with other medicinal products and other forms of interaction).

When gastrointestinal bleeding or ulceration occurs in patients receiving VIMOVO, the treatment should be withdrawn.

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 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.

Cardiovascular and cerebrovascular effects

Naproxen: As with all NSAIDs, appropriate monitoring and advice are required for patients with a history of hypertension and/or congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

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).

Clinical trial and epidemiological 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.

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, hypovolemia, 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 section Posology and method of administration and Interaction with other medicinal products and other forms of interaction).

Use in patients with impaired renal function

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/minute.

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.

Haematological
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 derivates) may be at increased risk of bleeding if given naproxen-containing products concurrently (see section Interaction with other medicinal products and other forms of interaction).

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.

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 Undesirable effects). 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.

Eye effects
It is recommended that ophthalmic examinations be carried out if any change or disturbance in vision occurs**.**

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.

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 Contraindications) 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.

Combination with other medicinal products

Naproxen: The combination of naproxen and non-aspirin NSAIDs including cyclooxygenase-2 selective inhibitors is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events.

Esomeprazole: Concomitant administration with esomeprazole and drugs such as atazanavir and nelfinavir is not recommended (see section Interaction with other medicinal products and other forms of interaction).

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

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.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

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

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

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

Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Antiretroviral agents

Omeprazole, the racemate of 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. Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is therefore not recommended. 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. Due to the similar pharmacodynamic and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as atazanavir and nelfinavir is not recommended (see section Special warnings and special precautions for use).

Concomitant use with precaution

Aspirin

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 section Pharmacodynamic properties). However, the concurrent use of aspirin and VIMOVO may still increase the risk of serious adverse events (see section Special warnings and special precautions for use and Undesirable 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.

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 Special warnings and special precautions for use).

Selective Serotonin Reuptake Inhibitors (SSRIs)

Epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the

occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of and NSAID or aspirin potentiated the risk of bleeding. Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Therefore, caution should be used when NSAIDs, including COX-2 selective inhibitors, are administered concomitantly with SSRIs (see section Special warnings and special precautions for use).

ACE-inhibitors
Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Lithium
NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate
When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model. This may indicate that both esomeprazole and naproxen could enhance the toxicity of methotrexate. The clinical relevance is likely to be greater in patients receiving high doses of methotrexate and in patients with renal dysfunction. Caution should be used when VIMOVO is administered concomitantly with methotrexate. In high-dose methotrexate administration a temporary withdrawal of VIMOVO is recommended.

Sulphonylureas, Hydantoins
Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as sulphonylureas, and hydantoins. Patients simultaneously receiving naproxen and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

Anti-coagulants
NSAIDs may increase the anticoagulant effects of oral agents (e.g. warfarin and dicoumarol) and heparins (see section Special warnings and special precautions for use).

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 coumarine derivatives.

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

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

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

Drugs with gastric pH-dependent absorption
The gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of drugs with a gastric pH dependent absorption. Like with other drugs that decrease the intragastric acidity, the absorption of drugs, such as ketoconazole, itraconazole and erlotinib can decrease while 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).

Other Information Concerning Drug Interactions
Studies evaluating concomitant administration of esomeprazole and either naproxen 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.

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 esomprazole is not required any of these cases.

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 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.

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).

Pregnancy and lactation

There are no data on the use of VIMOVO in pregnant women. Therefore the following information on the individual active substances is provided.

Pregnancy
Naproxen:
Use of naproxen in the last trimester of pregnancy is contraindicated because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition. NSAIDs should not be used during the first two trimester of pregnancy, unless the potential benefit to patient outweighs the potential risk to fetus.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryofetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Naproxen-containing products are not recommended in labour and delivery because, through their prostaglandin synthesis inhibitory effect, may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage.

Esomeprazole:
For esomeprazole, limited clinical data on exposed pregnancies are available. 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. Nevertheless, caution should be exercised when prescribing to pregnant women.

Breastfeeding
Naproxen is excreted in human milk. It is unknown whether esomeprazole is excreted in human milk, since no studies in lactating women have been performed.
VIMOVO should not be used during breast-feeding.

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.

Undesirable 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 Pharmacodynamic Properties).

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 (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥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**
Infections and infestations			infection	diverticulitis
Blood and lymphatic system disorders				eosinophilia, leucopenia
Immune system disorders				hypersensitivity reactions
Metabolism and nutrition disorders			appetite disorder	fluid retention, hyperkalemia, hyperuricemia
Psychiatric disorders			anxiety, depression, insomnia	confusion, dream abnormalities
Nervous system disorders		dizziness, headache, taste disturbance	paraesthesia, syncope	somnolence, tremor
Ear and labyrinth disorders			tinnitus, vertigo	
Cardiac disorders			arrhythmia, palpitations	myocardial infarction, tachycardia
Vascular disorders		hypertension		
Respiratory, thoracic and mediastinal disorders			asthma, bronchospasm, dyspnea	
Gastrointestinal disorders	dyspepsia	abdominal pain, constipation, diarrhoea, esophagitis, flatulence, gastric/duodenal ulcers*, gastritis, nausea, vomiting	dry mouth, eructation, gastrointestinal bleeding, stomatitis	glossitis, hematemesis, rectal bleeding
Skin and subcutaneous tissue disorders		skin rashes	dermatitis, hyperhidrosis, pruritis, urticaria	alopecia, ecchymoses

Musculoskeletal and connective tissue disorders		arthralgia	myalgia	
Renal and urinary disorders				proteinuria, renal failure
Reproductive system and breast disorders				menstrual disorder
General disorders and administration site disorders		oedema	asthenia, fatigue, pyrexia	
Investigations			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.

	Common	**Uncommon/Rare**
Infections and infestations	diverticulitis	aseptic meningitis, infection, sepsis
Blood and lymphatic system disorders		agranulocytosis, aplastic anemia, eosinophilia, granulocytopenia, hemolytic anemia, leucopenia, lymphadenopathy, pancytopenia, thrombocytopenia
Immune system disorders		anaphylactic reactions, anaphylactoid reactions, hypersensitivity reactions
Metabolism and nutrition disorders		appetite disorder, fluid retention, hyperglycemia, hyperkalemia, hyperuricemia, hypoglycemia, weight changes
Psychiatric disorders	depression, insomnia	agitation, anxiety, confusion, dream abnormalities, hallucinations, nervousness
Nervous system disorders	dizziness, drowsiness,	cognitive dysfunction, coma,

	headache, lightheadedness, vertigo	convulsions, inability to concentrate, optic neuritis, paresthesia, syncope, tremor
Eye disorders	visual disturbances	blurred vision, conjunctivitis, corneal opacity, papilloedema, papillitis
Ear and labyrinth disorders	tinnitus, hearing disturbances	hearing impairment
Cardiac disorders	palpitations	arrhythmia, congestive heart failure, myocardial infarction, tachycardia
Vascular disorders		hypertension, hypotension, vasculitis
Respiratory, thoracic and mediastinal disorders	dyspnea	asthma, bronchospasm, eosinophilic pneumonitis, pneumonia, pulmonary edema, respiratory depression
Gastrointestinal disorders	dyspepsia, abdominal pain, nausea, vomiting, diarrhoea, constipation, heartburn, peptic ulcers, stomatitis	dry mouth, esophagitis, gastric ulcers, gastritis, glossitis, eructation, flatulence, gastric/duodenal ulcers, gastrointestinal bleeding and/or perforation, melena, hematemesis, pancreatitis, colitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease), nonpeptic gastrointestinal ulceration, rectal bleeding, ulcerative stomatitis
Hepatobiliary disorders		cholestasis, hepatitis, jaundice, liver failure
Skin and subcutaneous tissue disorders	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
Musculoskeletal and connective tissue disorders		muscle weakness, myalgia
Renal and urinary disorders		glomerular nephritis, hematuria, interstitial nephritis, nephrotic syndrome, oliguria/polyuria, proteinuria, renal failure, renal papillary necrosis, tubular necrosis
Reproductive system and breast disorders		infertility, menstrual disorder
General disorders and administration site disorders	fatigue, oedema, sweating, thirst	asthenia, malaise, pyrexia
Investigations		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**
Blood and lymphatic system disorders			leukopenia, thrombocytopenia	agranulocytosis, pancytopenia
Immune system disorders			hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock	
Metabolism and nutrition disorders		peripheral oedema	hyponatraemia	hypomagnesaemia
Psychiatric disorders		insomnia	agitation, confusion, depression	aggression, hallucinations

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

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 Special warnings and special precautions for use). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section Special warnings and special 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.

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, 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.

Management of overdose
Related to naproxen
Patients should be managed by symptomatic and supportive care following a NSAID overdose, particularly with respect to gastrointestinal effects and renal damage. There are no specific antidotes. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine or hemoperfusion may not be useful due to high protein binding.

Related to esomeprazole
No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group and ATC code: MO1AE52, naproxen and esomeprazole.

Mechanism of action
VIMOVO has been developed as a sequential-delivery tablet formulation combining an immediate release esomeprazole magnesium layer and an enteric coated 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.
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*-isomer 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^+K^+-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

Pharmacodynamic effects

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 drugs, serum gastrin increases in response to the decreased acid secretion. Also chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the esomeprazole treatment should be temporarily stopped five days before CgA measurements.

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* and, in hospitalised patients, possible also *Clostridium difficile*.

Clinical efficacy and safety
In two randomised, double-blind, active-controlled studies, VIMOVO given as 500 mg/20 mg twice daily was shown to significantly reduce the occurrence of gastric ulcers compared to enteric-coated naproxen 500 mg twice daily during a 6-month treatment period. The gastric ulcer incidences for VIMOVO were 7.1% and 4.1%, and for enteric-coated naproxen 24.3% and 23.1%, in the two studies. VIMOVO also significantly reduced the occurrence of pre-specified NSAID associated upper gastrointestinal adverse events compared to enteric-coated naproxen during these trials (52.3% vs 69.0% in one trial; 54.3% vs 71.9% in the other). The reduction in gastric ulcer occurrence was also evident in a subset of patients (pooled across both studies) who were receiving concomitant low-dose aspirin. In this group the gastric ulcer incidence was 3.9% for patients receiving VIMOVO and 28.4% for patients receiving enteric-coated naproxen ($p<0.001$).

In these studies, patients receiving VIMOVO had a mean duration of therapy of 152 days compared to 124 days in patients receiving naproxen alone. A significantly lower proportion of patients taking VIMOVO (4.0%) discontinued the studies due to pre-specified NSAID associated upper gastrointestinal adverse events (including duodenal ulcers) compared to patients in the naproxen groups (12.0%).

In two double-blind, placebo-controlled studies in patients with osteoarthritis of the knee VIMOVO was given as 500 mg/20 mg twice daily, and was compared to celecoxib 200 mg given once daily over 12 weeks for treatment of the signs and symptoms of osteoarthritis. Patients receiving VIMOVO had similar pain management results compared to patients receiving celecoxib, as measured by change from baseline WOMAC scores on domains of pain and physical function as well as on Patient Global Assessment Scores. VIMOVO and celecoxib had similar time to onset of pain relief following initiation of dosing. The discontinuation rate due to adverse events was similar in patients receiving VIMOVO (6.9%) and celecoxib (7.8%).

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_{max}) of naproxen, has been demonstrated for both doses, 375 mg and 500 mg.

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 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 Posology and method of administration).

Distribution

Naproxen

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

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

Naproxen is extensively metabolized in the liver by the cytochrome P450 system (CYP), primarily CYP2C9, 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 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%), 6-0-desmethyl naproxen (<1%) or their conjugates (66% to 92%). Small amounts, 3% or less of the administered dose, are excreted in the faeces. In patients with renal failure metabolites may accumulate (see section Special warnings and special precautions for use).

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 not recommended for use in patients with severe renal impairment (creatinine clearance <30 ml/min) (see section Special warnings and special precautions for use).

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.

Due to increase of risk of NSAID associated bleeding and/or renal failure in this subpopulation naproxen should not be used in patients with severe 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 Contraindications).

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. 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 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.

Preclinical safety data

No preclinical 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
Preclinical data reveal no special hazards 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 gastrointestinal 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 and has also been demonstrated in pregnant rats given aspirin or indometacin.

Esomeprazole
Preclinical 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.

List of excipients

The names of excipients may vary according to region.

Tablet core
Croscarmellose sodium
Magnesium stearate
Povidone
Silica, colloidal anhydrous

Coating
Carnauba wax

Glycerol monostearate 40-55
Hypromellose
Iron oxide (yellow, black)
Macrogols
Methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30 per cent
Methyl parahydroxybenzoate
Polydextrose
Polysorbate 80
Propyl parahydroxybenzoate
Propylene glycol
Titanium dioxide
Triethyl citrate

Shelf-life

Please refer to expiry date on the bottle or outer carton.

Special precautions for storage

Do not store above 30°C.

Nature and contents of container

HDPE bottles containing desiccant with either a childresistant or non-childresistant (dispensing pack) polypropylene closure with an induction seal.

Pack sizes: 6, 30 or 60 tablets

Not all presentations may be available locally.

Instructions for use, handling and disposal

Not applicable.

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