PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

VIMOVO® 500/20 (Film-coated Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For full list of excipients, see section 6.1.

3. PHARMACUETICAL FORM

Film-coated Tablets

A yellow, oval, film-coated tablet, printed with 500/20 in black ink on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic relief in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, in patients needing proton-pump inhibitors to reduce the risk of developing non-steroidal anti-inflammatory drugs (NSAIDs) associated gastric and/or duodenal ulcers.

4.2 Posology and method of administration

Posology

Dosage in adults:

The dose is 1 tablet twice daily.

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).

VIMOVO is not recommended 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 section 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 section 5.2).

VIMOVO is contraindicated in patients with severe hepatic impairment because these patients should not receive more than 20 mg esomeprazole per day (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 4.4 and 5.2).

Children (≤ 18 years):

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

Method of administration

VIMOVO tablets must be swallowed whole with water, and not split, chewed or crushed.

It is recommended that VIMOVO tablets are taken at least 30 minutes prior to food intake (see section 5.2).

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 and lactation (see section 4.6)
- Severe hepatic impairment (e.g. Childs-Pugh C)

4.4 Special warnings and 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 4.2 and 5.2)

Gastrointestinal effects:

Naproxen: Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time 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 5.1).

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 4.5).

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 4.8).

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: 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.

NSAIDs may be associated with an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction, and stroke. This risk may occur as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

Patients with established cardiovascular diseases (e.g. uncontrolled hypertension, congestive heart failure, ischaemic heart disease, risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking) should only be treated with naproxen after careful consideration.

Renal effects:

Naproxen: Long-term administration of NSAIDs e.g. naproxen 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 e.g. naproxen 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, ACE or angiotensin II receptor antagonists, inhibitors, and the elderly. Discontinuation of NSAID e.g. naproxen therapy is usually followed by recovery to the pre-treatment state (see also below, and sections 4.2 and 4.5).

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, ACE-inhibitors or angiotensin II receptor antagonist 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 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 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.

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.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking

NSAIDs such as VIMOVO. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue VIMOVO and evaluate the patient immediately.

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 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.

Combination with other medicinal products:

The combination of VIMOVO and non-aspirin NSAIDs including cyclo-oxygenase 2 selective inhibitors is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events.

Esomeprazole: Concomitant administration with esomeprazole and medicines such as atazanavir and nelfinavir is not recommended (see section 4.5).

Esomeprazole is a CYP2C19 inhibitor. 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.

Female fertility:

Naproxen: There is some evidence that drugs which inhibit cyclooxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of VIMOVO should be considered (see section 4.6).

General:

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

Some published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with a small increased risk for osteoporosis related fractures. However, in other similar observational studies no such increased risk was found.

In randomised, double-blind and controlled clinical studies on omeprazole and esomeprazole (including two open long-term studies of up to more than 12 years) there are no indications that PPIs are associated with osteoporotic fractures.

Although a causal relationship between omeprazole/esomeprazole and osteoporotic fractures has not been established, patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Laboratory test interactions:

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 medicine 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).

4.5 Interaction with other medicines and other forms of interaction

Concomitant use not recommended:

Antiretroviral agents:

Omeprazole, the racemate of esomeprazole, has been reported to interact with some antiretroviral medicines. 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 medicine. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral medicines, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Concomitant administration with omeprazole and medicines such as atazanavir is therefore not recommended. For other antiretroviral medicines, such as saquinavir, increased serum levels have been

reported. There are also some antiretroviral medicines 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 medicines such as atazanavir and nelfinavir is not recommended (see section 4.4).

Clopidogrel:

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40 % and resulting in decreased maximum inhibition of (adenosine diphosphate induced) platelet aggregation by an average of 14 %.

It is, however, uncertain to what extent this interaction is clinically important. One prospective, randomised (but incomplete) study (in over 3 760 patients comparing placebo with omeprazole 20 mg in patients treated with clopidogrel and acetylsalicylic acid) and non-randomised, post-hoc analyses of data from large, prospective, randomized clinical outcome studies (in over 47 000 patients) did not show any evidence of an increased risk for adverse cardiovascular outcome when clopidogrel and proton pump inhibitors, including esomeprazole, were given concomitantly.

Results from a number of observational studies are inconsistent with regard to increased risk or no increased risk for cardiovascular thromboembolic events when clopidogrel is given together with a proton pump inhibitor.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg and acetylsalicylic acid 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40 % of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (adenosine diphosphate induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel and the combined (esomeprazole and acetylsalicylic acid) product groups, likely due to

the concomitant administration of low dose acetylsalicylic acid).

No clinical studies on the interaction between clopidogrel and the fixed dose combination of naproxen and esomeprazole (VIMOVO) have been performed.

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 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).

Clinical pharmacodynamic data suggest that concomitant naproxen usage for more than one day consecutively may inhibit the effect of low-dose aspirin on platelet activity and this inhibition may persist for up to several days after stopping naproxen therapy. The clinical relevance of this interaction is not known.

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 post-marketing 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):

Epidemiological studies, both of the case-control and cohort design, have demonstrated an association

between use of psychotropic medicines that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In 2 studies, concurrent use of an 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 4 .4).

ACE-inhibitors/Angiotensin II receptor antagonists:

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors and angiotensin II receptor antagonists. NSAIDs may also increase the risk of renal impairment associated with the use of ACE-inhibitors or angiotensin II receptor antagonists. The combination of NSAIDs and ACE-inhibitors or angiotensin II receptor antagonists should be given with caution in patients who are elderly, volume-depleted, or with impaired renal function (see section 4.4).

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:

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Sulphonylureas, Hydantoins:

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

Warfarin:

The effects of warfarin and NSAIDs on gastrointestinal bleeding are synergistic, such that users of both medicines together have a risk of serious gastrointestinal bleeding higher than users of either medicine alone. No significant interactions have been observed in clinical studies with naproxen and coumarin-type anticoagulants. However, caution is advised since interactions have been seen with other non-steroidal agents of this class. The free fraction of warfarin may increase substantially in some subjects and naproxen interferes with platelet function (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 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.

Ciclosporin:

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

Tacrolimus:

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus. As

with all NSAIDs caution is advised when tacrolimus is co-administered because of the increased risk of nephrotoxicity.

Probenecid:

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

Medicines with gastric pH-dependent absorption:

The decreased intragastric acidity during treatment with esomeprazole might increase or decrease the absorption of medicines if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole.

Other information concerning interactions:

Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib (COX-2-selective NSAID) did not identify any clinically relevant interaction.

Concomitant administration of colestyramine can delay the absorption of naproxen.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolizing 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.

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and AUC for cilostazol by 18 % and 26 % respectively, and one of its active metabolites by 29 % and 69 % respectively.

4.6 Fertility, pregnancy and lactation

There are no data on the use of VIMOVO in pregnant women.

Pregnancy

Naproxen:

In humans, data from epidemiological studies suggest that there may be an increased risk of miscarriage after use of NSAIDs in early pregnancy. Congenital abnormalities have been reported in association with NSAID administration in humans. Use of naproxen in the last trimester of pregnancy is contraindicated (see section 4.3) because of possibility of early closure of the foetal ductus arteriosus and pulmonary hypertension. Use of NSAIDs may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. VIMOVO should not be used in women attempting to conceive or during the first 2 trimesters of pregnancy. If VIMOVO is used, the dose should be kept as low and the duration of treatment as short as possible.

VIMOVO is not recommended in labour and delivery because, through its prostaglandin synthesis inhibitory effect, VIMOVO may adversely affect foetal circulation and inhibit contractions with an increased bleeding

tendency in both mother and child.

Esomeprazole:

Safety during pregnancy has not been established.

Breastfeeding

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

Fertility

The use of NSAIDs like naproxen may impair female fertility. Animal studies indicate that NSAIDs like naproxen can suppress ovulation. Reports of women with infertility, who were taking NSAIDs such as naproxen, suggest reversal of the infertility upon discontinuation of the NSAID. A benefit-risk assessment should be performed before treatment with VIMOVO in women attempting to conceive (see also Pregnancy section above).

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 Undesirable effects

a) Summary of the safety profile

VIMOVO contains both naproxen and esomeprazole and the same pattern of undesirable effects as reported for both of these individual active substances may occur.

In placebo-controlled clinical studies, adverse events reported more frequently for VIMOVO (n = 490) compared to placebo (n = 246) were diarrhoea, upper abdominal pain, constipation, dizziness and peripheral

oedema.

b) 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).

Naproxen:

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

Table 1

	Common	**Uncommon/ Rare**	**Not Known**
Investigations		Abnormal liver function tests, increased bleeding time, raised serum creatinine	
Cardiac disorders	Palpitations	Dysrhythmia, congestive heart failure, myocardial infarction, tachycardia	
Blood and lymphatic system disorders		Agranulocytosis, aplastic anaemia, eosinophilia, granulocytopenia, haemolytic anaemia, leucopenia, lymphadenopathy, pancytopenia, thrombocytopenia	
Nervous system disorders	Dizziness, drowsiness,	Cognitive dysfunction, coma, convulsions, inability to	

	headache, light-headedness, vertigo	concentrate, optic neuritis, paraesthesia, syncope, tremor	
Eye disorders	Visual disturbances	Blurred vision, conjunctivitis, corneal opacity, papilloedema	
Ear and labyrinth disorders	Tinnitus, hearing disturbances	Hearing impairment	
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Asthma, bronchospasm, eosinophilic pneumonitis, pneumonia, pulmonary oedema, respiratory depression	
Gastrointestinal disorders	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), non-peptic gastrointestinal ulceration, rectal bleeding, ulcerative stomatitis	
Renal and urinary disorders		Glomerulonephritis, haematuria, interstitial nephritis, nephrotic syndrome, oliguria/polyuria, proteinuria, renal failure, renal papillary necrosis, tubular necrosis	

Skin and subcutaneous tissue disorders	Pruritus, ecchymoses, purpura, skin rashes	Alopecia, exanthema, urticaria, toxic epidermal necrolysis, erythema multiforme, erythema nodosum, fixed drug eruption, lichen planus, systemic lupus erythematoses, Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including cases resembling porphyria cutanea tarda (pseudoporphyria), exfoliative dermatitis, angioneurotic oedema	
Musculoskeletal and connective tissue disorders		Muscle weakness, myalgia	
Metabolism and nutrition disorders		Appetite disorder, fluid retention, hyperglycaemia, hyperkalaemia, hyperuricaemia, hypoglycaemia, weight changes	
Infections and infestations	Diverticulitis	Aseptic meningitis, infection, sepsis	
Vascular disorders		Hypertension, hypotension, vasculitis	Stroke
General disorders and administration site disorders	Fatigue, oedema, sweating, thirst	Asthenia, malaise, pyrexia	

Immune system disorders		Anaphylactic reactions, anaphylactoid reactions, hypersensitivity reactions	
Hepatobiliary disorders		Cholestasis, hepatitis, jaundice, liver failure	
Reproductive system and breast disorders		Infertility, menstrual disorder	
Psychiatric disorders	Depression, insomnia	Agitation, anxiety, confusion, dream abnormalities, hallucinations, nervousness	

Esomeprazole:

The following adverse reactions have been identified or suspected in the clinical trials programme for enteric-coated esomeprazole. None were found to be dose-related.

Table 2

	Common	**Uncommon**	**Rare**	**Very Rare**
Blood and lymphatic system disorders			Leukopenia, thrombocytopenia	
Nervous system disorders	Headache	Dizziness, paraesthesia, somnolence	Taste disturbance	
Eye disorders			Blurred vision	
Ear and labyrinth		Vertigo		

disorders				
Respiratory, thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Abdominal pain, diarrhoea, flatulence, nausea/ vomiting, constipation	Dry mouth	Stomatitis, gastrointestinal candidiasis	
Skin and subcutaneous tissue disorders		Dermatitis, pruritus, urticaria, rash	Alopecia, photosensitivity	
Musculoskeletal and connective tissue disorders			Arthralgia, myalgia	
Metabolism and nutrition disorders		Peripheral oedema	Hyponatraemia	Severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesamia may also result in hypokalaemia.
General disorders and			Malaise, hyperhidrosis	

administration site disorders				
Immune system disorders			Hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock	
Hepatobiliary disorders		Increased liver enzymes	Hepatitis with or without jaundice	Hepatic encephalopathy
Reproductive system and breast disorders				Gynaecomastia
Psychiatric disorders		Insomnia	Agitation, confusion, depression	Aggression, hallucination

Post-marketing experience:

The events listed above for clinical trials have also been reported from marketing experience for enteric-coated esomeprazole. In addition, the following adverse events have been reported during post marketed use.

Table 3

Blood and lymphatic system disorders	Agranulocytosis, pancytopenia
Renal and urinary disorders	Interstitial nephritis
Skin and subcutaneous tissue disorders	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic

	symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Muscular weakness
Hepatobiliary disorders	Hepatic failure

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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 characterised 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 medicine-related. It is not known what dose of the medicine 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. Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Emesis and/or activated charcoal (60-100 g in adults, 1-2 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 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: naproxen and esomeprazole ATC code: M01AE52

Pharmacological classification:

Esomeprazole - A 11.4.3 Medicines acting on the gastrointestinal tract. Other

Naproxen: A. 3.1 Antirheumatics (anti-inflammatory agents).

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.

Naproxen is a NSAID with analgesic and antipyretic properties. The mechanism of action of the naproxen anion 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 a combination of naproxen 500 mg and 20 mg esomeprazole, intragastric pH above 4 was maintained for a mean time of 17,1 hours over 24 hours in healthy volunteers. The inter-individual variability in time with intragastric pH above 4, expressed as coefficient of variation (CV) was 18 %.

Other effects related to acid inhibition:

During treatment with anti-secretory medicines, serum gastrin increases in response to the decreased acid secretion.

An increased number of enterochromaffin-like 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 anti-secretory medicines, including esomeprazole, gastric glandular cysts have been reported to occur with an 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 esomeprazole, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors including esomeprazole may lead to increased risk of gastrointestinal infections such as Salmonella and Campylobacter and possibly also Clostridium difficile in hospitalized patients.

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 (Cmax) of naproxen, has been demonstrated for 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 4-5 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 *("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 4.2).

Distribution:

Naproxen:

Naproxen has a volume of distribution of 0,16 litres/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/litre with 500, 1 000 and 1 500 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 litres/kg body weight. Esomeprazole is 97 % plasma protein bound.

Metabolism:

Naproxen:

Naproxen is extensively metabolised in the liver by the cytochrome P450 system (CYP), primarily CYP2C9, to 6-0-desmethyl naproxen. Neither the parent drug nor the metabolites induce metabolising enzymes. Both naproxen and 6-0-desmethyl naproxen are further metabolised 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 ("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 ("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 (66-92 %). 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 litres/hour after a single dose and about 9 litres/hour 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 4.4).

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. Therefore, a maximum of 20 mg daily should not be exceeded in patients with severe hepatic impairment.

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

Elderly:

There are no specific data on the pharmacokinetics of VIMOVO in patients over the age of 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 0,12-0,19 % of total naproxen concentration, compared with 0,05-0,075 % 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Croscarmellose sodium

Magnesium stearate

Povidone

Silica colloidal anhydrous

Coating:

Carnauba wax

Glycerol monostearate

Hypromellose

Iron oxide yellow, CI [77492]

Iron oxide black, CI [77268]

Macrogols

Methacrylic acid-ethyl acrylate copolymer

Methyl parahydroxybenzoate

Polydextrose

Polysorbate 80

Propyl parahydroxybenzoate

Propylene glycol

Titanium dioxide, CI [77891]

Triethyl citrate

Preservatives:

Approximately 0,02 mg methyl parahydroxybenzoate and 0,01 mg propyl parahydroxybenzoate per tablet.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

HDPE bottle: 36 Months

Blister: 24 Months

6.4 Special precautions for storage

Keep out of reach of children

Store at or below 25 °C.

Bottle: Store in original package and keep the bottle tightly closed.

Blister: Do not remove the blisters from the outer carton until required for use.

6.5 Nature and contents of container

White, round, HDPE bottles containing desiccant integrated in a child resistant polypropylene screw closure without an induction seal, in pack sizes of 6, 30, 60 or 100 tablets.

White, square shaped HDPE bottle containing a desiccant, with a child resistant polypropylene white screw closure, in pack sizes of 6, 30, 60 or 100 tablets.

White, rectangular-shaped HDPE bottle containing a desiccant, with a non-child resistant polypropylene white screw closure, in a pack size of 500 tablets.

Cold formed silver aluminium foil blister packages in pack sizes of 10, 30, 60 or 100 tablets.

The bottles and blister packs are packed into a cardboard carton.

Not all pack sizes presentation are marketed.

6.6 Special precautions for disposal and other handling

Not applicable

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road,

Erand Gardens,

Midrand, 1685

Customer Care: 0860 ADCOCK/ 232625

8. REGISTRATION NUMBER

45/3.1/0179

9. DATE OF FIRST AUTHORISATION

19 April 2013

10. DATE OF REVISION OF THE TEXT

21 July 2022

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