APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PEPTIMEP 20 gastro-resistant tablets

PEPTIMEP 40 gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITON

PEPTIMEP 20: Each gastro-resistant tablet contains esomeprazole magnesium equivalent to 20 mg esomeprazole.

PEPTIMEP 40: Each gastro-resistant tablet contains esomeprazole magnesium equivalent to 40 mg esomeprazole.

PEPTIMEP 20 contains sugar (lactose monohydrate, 31,88 mg and sucrose, no more than 14,63 mg per tablet)

PEPTIMEP 40 contains sugar (lactose monohydrate, 63,75 mg and sucrose, no more than 29,26 mg per tablet)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

PEPTIMEP 20: Brick red coloured, round shaped, biconvex, film coated tablet, imprinted with “20” on one side with black ink and plain on the other side.

PEPTIMEP 40: Brick red coloured, round shaped, bevel edged, biconvex, film coated tablet, imprinted with “40” on one side with black ink and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gastro-oesophageal reflux disease (GORD):

- Treatment of erosive reflux oesophagitis.
- Long-term management of patients with healed oesophagitis to prevent relapse.
- Symptomatic treatment of gastro-oesophageal reflux disease (GORD).

Patients requiring continued nonsteroidal anti-inflammatory drug (NSAID) therapy:

- Prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk.

In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori*:

- Healing of *Helicobacter pylori* associated duodenal ulcer.
- Prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcer disease.

PEPTIMEP has been used in pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion.

4.2 Posology and method of administration

Posology

Adults

Gastro-oesophageal reflux disease (GORD):

Treatment of erosive reflux oesophagitis:

40 mg once daily for 4 weeks. An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed, or who have persistent symptoms.

Long-term management of patients with healed oesophagitis to prevent relapse:

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD):

20 mg once daily in patients without oesophagitis. If symptom control has not been achieved after 4 weeks, the patients should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen, taking 20 mg once daily, when needed.

Patients requiring continued nonsteroidal anti-inflammatory drug (NSAID) therapy:

Prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk:

20 mg or 40 mg once daily.

In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori:*

Healing of Helicobacter pylori *associated duodenal ulcer and prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcer disease:*

20 mg PEPTIMEP with 1 g amoxicillin and 500 mg clarithromycin, twice daily for 7 days.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion:

The recommended initial dose is PEPTIMEP 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated.

Doses up to 120 mg twice daily have been administered.

Adolescents 12 – 18 years

Gastro-oesophageal reflux disease (GORD):

Treatment of erosive reflux oesophagitis:

40 mg once daily for 4 weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed, or who have persistent symptoms.

Long-term management of patients with healed oesophagitis to prevent relapse:

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD):

20 mg once daily in patients without oesophagitis. If symptom control has

not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Impaired renal function:

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience, caution is advised in patients with severe renal insufficiency.

Impaired hepatic function:

Dosage adjustment is not required in patients with mild to moderate liver impairment. A maximum daily dose of 20 mg **PEPTIMEP** should be used for patients with severe liver impairment.

Elderly:

Dosage adjustment is not required in the elderly.

Children:

The safety and efficacy of TRUSTAN in children younger than 12 years of age has not been established.

No data is available.

Method of administration

PEPTIMEP tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed.

The tablets can also be dispersed in half a glass of non-carbonated water. No other liquids may be used. Stir until the tablets disintegrate and drink the liquid with the

with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink.

The pellets must not be chewed or crushed.

For patients who cannot swallow the tablets, the tablets can be dispersed in non-carbonated water and administered through a gastric tube.

4.3 Contraindications

Hypersensitivity to esomeprazole, substituted benzimidazoles or any other ingredients of PEPTIMEP (see section 2 and 6.1).

Concomitant administration of PEPTIMEP with atazanavir and nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use

- PEPTIMEP is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.
- In the presence of any alarm symptom (such as 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 PEPTIMEP may alleviate symptoms and delay diagnosis.
- Regular monitoring of patients on long-term treatment (particularly those treated for more than a year) is recommended.
- Caution is advised in patients with hepatic impairment and dosage reductions may be required.
- Acute interstitial nephritis (AIN)/acute tubulointerstitial nephritis has been observed in patients taking PPIs, such as PEPTIMEP, and may occur at any point during PPI therapy. Acute tubulointerstitial nephritis is

characterised by an inflammatory reaction within the tubulointerstitial space of the kidney. Acute interstitial inflammatory reactions are associated with damage to the tubulointerstitium, leading to acute kidney
injury (acute renal failure).
Tubulointerstitial nephritis may be medicine-related, infectious, systemic, autoimmune, genetic, and idiopathic with the most common cause being related to a medication or medicine exposure. The risk of tubulointerstitial nephritis leading to chronic inflammation and reduced renal function associated with the use of protein pump inhibitors such as PEPTIMEP, is a class effect. Patients may present with non- specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). A delay in diagnosis and continued use of PEPTIMEP could lead to chronic kidney failure. Healthcare professionals should frequently monitor renal function and check urine for haematuria and/or proteinuria. Patients should be advised to report any decrease in urine volumes or suspect that there is blood in their urine. Treatment with PEPTIMEP should be discontinued in patients with acute interstitial nephritis.

- PEPTIMEP reduces gastric acidity which may increase gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with PEPTIMEP may lead to increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and also *Clostridium difficile* in hospitalised patients.

- *Clostridium difficile* is a bacterium that can cause severe debilitating diarrhoea that does not improve. Symptoms may include watery stools, abdominal pain, fever, and patients may develop more serious intestinal conditions.

- Hypergastrinaemia may occur during treatment with PEPTIMEP**.**

- PEPTIMEP may reduce the absorption of some vitamins such as vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.
- Proton pump inhibitors such as PEPTIMEP, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10 to 40 %. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical
  guidelines and they should have an adequate intake of vitamin D and calcium.

- Treatment with PEPTIMEP may cause false-negative results in the urea breath test for *Helicobacter pylori* infection.
- Prothrombin time and international normalised ratio (INR) should be monitored for increases in patients receiving PEPTIMEP and warfarin concurrently (see section 4.5).
- Patients on on-demand treatment should be instructed to contact their healthcare provider if their symptoms change in character. When prescribing PEPTIMEP for on- demand therapy, the implications for interactions with other medicines, due to fluctuating plasma concentrations of PEPTIMEP, should be considered.

- Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like PEPTIMEP for at least three months, and

in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular dysrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PEPTIMEP with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare providers should consider measuring magnesium levels before starting PEPTIMEP treatment and periodically during treatment.

- PEPTIMEP is a CYP2C19 inhibitor. When starting or ending treatment with PEPTIMEP, the potential for interactions with medicines metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and PEPTIMEP (see section 4.5). Concomitant administration of clopidogrel and esomeprazole resulted in decreased exposure of the active metabolite of clopidogrel by an average of 40 %.
  The maximum inhibition of (ADP induced) platelet aggregation decreased by an average of 14 %. As a precaution, concomitant use of PEPTIMEP and clopidogrel should be discouraged.
- Proton pump inhibitors, such as PEPTIMEP, are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the healthcare provider should consider stopping PEPTIMEP. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

- During treatment with antisecretory medicines, serum gastrin increases in response to the decreased acid secretion. Also chromogranin A (CgA) increase due to decreased gastric acidity. Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, PEPTIMEP treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated14 days after cessation of PEPTIMEP treatment.

Paediatric population

The safety and efficacy of PEPTIMEP in children younger than 12 years of age has not been established.

Excipient warnings

PEPTIMEP contains sucrose and lactose. Patients with rare hereditary conditions such as fructose and/or galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose- galactose malabsorption or sucrase-isomaltase insufficiency should not take PEPTIMEP.

4.5 Interaction with other medicines and other forms of interaction

Effects of PEPTIMEP on the pharmacokinetics of other medicines:

- Omeprazole has been reported to interact with some antiretroviral medicines. Increased gastric pH during omeprazole treatment may change the absorption of the anti-retroviral medicines. Other possible interaction mechanisms are via CYP2C19.

Co-administration of PEPTIMEP and medicines such as atazanavir and nelfinavir is contraindicated, as it may significantly reduce plasma levels of the HIV-protease inhibitor and concomitant administration is not recommended (see section 4.3). Co -administration of PEPTIMEP (40 mg once daily) reduced mean nelfinavir exposure by approximately 40 % and the mean exposure of the pharmacological active metabolite was reduced by approximately 75 – 90 %. Concomitant use of PEPTIMEP and saquinavir resulted in increased serum levels of saquinavir. Treatment with PEPTIMEP had no effect on the exposure of darunavir (with ritonavir) or lopinavir (with ritonavir). There are also some antiretroviral medicines for which unchanged serum levels have been reported when given with omeprazole. Close monitoring or dose alteration is recommended. Tipranavir may decrease the concentration of PEPTIMEP. Co-administration is not recommended. However, if used concurrently, the dose of PEPTIMEP should be increased.

- The decreased intragastric acidity during treatment with PEPTIMEP might increase or decrease the absorption of medicines if the mechanism of absorption is influenced by gastric acidity. As with other inhibitors of acid secretion or antacids, the absorption of ketoconazole, itraconazole and erlotinib can decrease during treatment with PEPTIMEP while the absorption of digoxin can increase. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10 % (up to 30 % in 2 out of 10 subjects). Digoxin toxicity has been reported. Caution should be exercised when PEPTIMEP is given at high doses in elderly patients. Therapeutic monitoring of digoxin should then be reinforced.

- PEPTIMEP inhibits CYP2C19, the major PEPTIMEP metabolising enzyme. Concomitant administration of 30 mg PEPTIMEP resulted in a 45 % decrease in clearance of the CYP2C19 substrate diazepam. The interaction is unlikely to be of clinical relevance. When PEPTIMEP is combined with medicines metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these medicines may be increased and a dose reduction could be needed. This should be considered especially when prescribing PEPTIMEP for on-demand therapy.

- In epileptic patients, concomitant administration of 40 mg esomeprazole, as in PEPTIMEP, resulted in a 13 % increase in trough plasma levels of phenytoin, however, dose adjustment was not required. It is recommended that the plasma concentrations of phenytoin be monitored when treatment with PEPTIMEP is introduced or withdrawn.
- Concomitant administration of 40 mg PEPTIMEP to warfarin treated patients showed that, despite elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range.
- Cases of elevated INR of clinical significance have been reported during concomitant treatment of esomeprazole, as in PEPTIMEP, with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.
- Concomitant administration of 40 mg PEPTIMEP and cisapride resulted in a 32 % increase in area under the plasma concentration-time curve (AUC) and a 31 % prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc

interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with PEPTIMEP. This interaction did not alter the influence of cisapride on cardiac electrophysiology.

- PEPTIMEP has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.
- Co-administration of PEPTIMEP and naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify in any clinically relevant interaction.
- When given together with proton pump inhibitors (PPIs), methotrexate levels have been shown to increase in some patients by up to three-fold. In high-dose methotrexate administration a temporary withdrawal of PEPTIMEP should be considered.
- Co-administration of PEPTIMEP has been reported to increase serum levels of tacrolimus. Monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.
- A pharmacokinetic (PK)/pharmacodynamic (PD) interaction is observed between clopidogrel and PEPTIMEP resulting in decreased exposure to the active metabolite of clopidogrel and decreased maximum inhibition of (ADP induced) platelet aggregation. Inconsistent data on the clinical implications of a PK/PD interaction of PEPTIMEP in terms of major cardiovascular events have been reported. As a precaution concomitant use of clopidogrel should be discouraged.

- Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole given in doses of 40 mg to healthy subjects in a cross-over

subjects in a cross-over study, increased Cmax and AUC for cilostazol by 18 % and 26 % respectively, and one of its metabolites by 29 % and 69 % respectively. PEPTIMEP can be suspected to have a similar effect.

Effects of other medicines on the pharmacokinetics of PEPTIMEP:

Medicines which inhibit CYP2C19 and/or CYP3A4

- PEPTIMEP is metabolised by CYP2C19 and CYP3A4. Co-administration of PEPTIMEP and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.). resulted in a doubling of the exposure (AUC) to PEPTIMEP.
- Concomitant administration of PEPTIMEP and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than tripling of the PEPTIMEP exposure. Dose adjustment of PEPTIMEP is not regularly required, however, should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Medicines which induce CYP2C19 and/or CYP3A4

- Medicines known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased PEPTIMEP serum levels by increasing the PEPTIMEP metabolism.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

Clinical data on exposed pregnancies with PEPTIMEP are insufficient. With the racemic mixture omeprazole data on a larger number of exposed pregnancies from epidemiological studies indicate no malformative nor foetotoxic effect. 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. Caution should be exercised when prescribing to pregnant women. A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of esomeprazole. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Breastfeeding

It is not known whether PEPTIMEP is excreted in human breast milk. There is insufficient information on the effects of esomeprazole in newborns/infants. PEPTIMEP should not be used during breast-feeding.

Fertility

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

4.7 Effects on ability to drive and use machines

PEPTIMEP can cause side effects, such as blurred vision and dizziness. Caution is advised before driving a vehicle or operating machinery or performing any tasks that require concentration, until the effects of PEPTIMEP are known.

4.8 Undesirable effects

Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent	Agranulocytosis, leukopenia, thrombocytopenia, pancytopenia
Immune system disorders	Less frequent	Anaphylactic reaction, angioedema, bronchospasm
Metabolism and nutrition disorders	Less frequent	Hyponatraemia, hypomagnesaemia, severe hypomagnesaemia may result in hypocalcaemia, hypomagnesaemia may also result in hypokalaemia.
Psychiatric disorders	Less frequent	Insomnia, somnolence, aggression, confusional states, agitation, depression, hallucinations
Nervous system disorders	Frequent Less frequent	Headache Dizziness, paraesthesia
Eye disorders	Less frequent	Blurred vision, eye disorders
Ear and labyrinth disorder	Less frequent	Vertigo, tinnitus
Cardiac disorders	Less frequent	Angina, tachycardia, bradycardia
Respiratory, thoracic and mediastinal disorders	Less frequent	Respiratory infection, sinusitis, cough
Gastrointestinal disorders	Frequent Less frequent	Abdominal pain, diarrhoea, flatulence, nausea, vomiting, constipation, dyspepsia Dry mouth, taste disturbances, stomatitis, gastrointestinal candidiasis, pancreatitis, fundic gland polyps (benign)

	Frequency unknown	Microscopic colitis
Hepato-biliary disorders	Less frequent	Hepatitis, jaundice, hepatic encephalopathy, raised liver enzymes
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Rash Dermatitis, pruritus, urticaria, photosensitivity, bullous eruption, increased sweating, alopecia Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), subacute cutaneous lupus erythematosus (SCLE)
Musculoskeletal, and connective tissue disorders	Less frequent	Back pain, arthralgia, myalgia, muscular weakness, myopathy, fracture of hip, wrist or spine
Renal and urinary disorders	Less frequent	Acute interstitial nephritis/acute tubulointerstitial nephritis (which could lead to acute kidney injury and/or chronic renal failure), urinary disorders
Reproductive system and breast disorders	Less frequent	Gynaecomastia, impotence
General disorders and administration site conditions	Less frequent	Fever, peripheral oedema, malaise, fatigue

Reporting of suspected adverse reactions:

Reporting of 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

The symptoms described in connection with deliberate PEPTIMEP overdose (limited experience of doses in excess of 240 mg/day) are transient. Single oral doses of 80 mg were uneventful. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8). No specific antidote is known. PEPTIMEP is extensively plasma protein bound and is therefore not readily cleared by dialysis. Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Drugs for acid-related disorders, Proton pump inhibitors

ATC Code: A02B C05

A 11.4.3 Medicines acting on gastrointestinal tract. Other.

Mechanism of Action:

Esomeprazole is the S-isomer of omeprazole. Omeprazole consists of both R-and S-isomers which have similar pharmacodynamic activities. Esomeprazole reduces gastric acid secretion through the specific inhibition of the enzyme H^+,K^+-ATPase, which is the

acid pump in the parietal cells of the stomach. It accumulates in the acidic secretory canaliculi where it is concentrated, converted into the active form and inhibits both basal and stimulated acid secretion. The activated form irreversibly inactivates the pump molecule, and acid secretion only resumes after new pump molecules are synthesised, which provides prolonged suppression of acid secretion.

Effect on gastric acid secretion:

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within 1 hour. After repeated administration with 20 mg esomeprazole once daily for 5 days, mean peak acid output after pentagastrin stimulation is decreased by 90 % when measured 6 to 7 hours after dosing on day 5.

After 5 days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic Gastro-oesophageal Reflux Disease (GORD) patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours were 76 %, 54 % and 24 % respectively for esomeprazole 20 mg. Corresponding proportions for esomeprazole 40 mg were 97 %, 92 % and 56 % respectively.

Using area under the curve (AUC) as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown. Food intake has no significant influence on the effect of effect of esomeprazole on intragastric acidity.

Other effects related to acid inhibition:

Serum gastrin increases as a result of the decreased acid secretion during treatment with

esomeprazole. Long term treatment may lead to the formation of glandular cysts. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

5.2 Pharmacokinetic Properties

Absorption:

Esomeprazole is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the R-isomer is negligible. Esomeprazole is well absorbed and peak plasma concentrations are reached approximately 1 - 2 hours after oral dose.

Distribution:

The volume of distribution at steady-state in healthy patients, is approximately 0,22 L/kg body weight. The bioavailability of esomeprazole is 89 % after repeated once daily administration.

Plasma protein binding

Esomeprazole is 97 % bound to plasma proteins.

Metabolism and excretion:

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of esomeprazole metabolism 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 isoform, CYP3A4, which is responsible for the formation of the main metabolite in plasma, esomeprazole sulphone.

The following parameters reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, e.g., extensive metabolisers: Total plasma clearance of esomeprazole is approximately 17 L/h after a single dose and approximately 9 L/h after repeated dosing. The plasma elimination half-life of esomeprazole is approximately 1,3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases in a nonlinear fashion with repeated administration of esomeprazole. This increase is dose-dependent and results in a nonlinear dose-AUC relationship after repeated administration. This time- and dose- dependency is due to a decrease of first-pass metabolism and systemic clearance, probably caused by an inhibition of CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

The major esomeprazole metabolites have no effect on gastric acid secretion. Approximately 80 % of the metabolites are excreted in the urine after an oral dose, while < 1 % of esomeprazole is found in the urine. The remaining metabolites are excreted in the faeces.

Special patient groups:

Approximately 1-2 % 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 increased by about 60 %.

Elderly:

The metabolism of esomeprazole is not significantly changed in elderly patients (71 – 80 years).

Gender:

No gender differences have been noted after repeated once-daily administration. The mean area under the plasma concentration-time curve is approximately 30 % higher in females than in males following a single oral dose of esomeprazole 40 mg. These findings of esomeprazole 40 mg. These findings have no implications for the dosage of esomeprazole.

Renal impairment:

No studies have been performed in patients with decreased renal function. The metabolism of esomeprazole is not expected to be changed in patients with impaired renal function. The kidneys are responsible for the excretion of esomeprazole metabolites, but not for the elimination of esomeprazole.

Hepatic impairment:

The metabolism of esomeprazole in patients with mild to moderate hepatic dysfunction may be impaired. The metabolic rate is decreased in patients with severe hepatic dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Hepatic disease reduces the clearance of esomeprazole and dose reduction is recommended. A maximum of 20 mg should not be exceeded in patients with severe hepatic dysfunction. Once daily dosing does not show any tendency of esomeprazole or any of the major metabolites to accumulate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Co-povidone

Crospovidone

Diethyl phthalate

Ethyl cellulose

Ferric oxide red

Hypromellose

Light magnesium oxide

Macrogol

Magnesium stearate

Methacrylic acid ethyl acrylate copolymer

Opacode Black (containing shellac glaze and iron oxide black)

Povidone

Silicified microcrystalline cellulose (containing colloidal anhydrous silica and microcrystalline cellulose)

Starlac® (containing maize starch and lactose monohydrate), sugar spheres (containing maize starch and sucrose)

Talc

Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package in order to protect from light and moisture.

Keep the blister strips in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

Do not use after the expiry date printed on the label or the carton.

Return all unused tablets to your pharmacist.

Do not dispose of unused medicine in drains and sewerage systems.

6.5 Nature and contents of container

Silver aluminium/aluminium blister strips packed in an outer carton. Each blister strip contains 10 tablets.

Pack size: 10, 30, 60 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road & Bluegum Avenue

Anchorville

Lenasia, 1827

South Africa

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8. REGISTRATION NUMBERS

PEPTIMEP 20: 50/11.4.3/0031

PEPTIMEP 40: 50/11.4.3/0032

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 31 January 2020

10. DATE OF REVISION OF THE TEXT

17 February 2026