HCR: LHC Pharmaceuticals (Pty) Ltd
Product Name: EMANERA 20 mg and EMANERA 40 mg
Dosage form and strength: Gastro-resistant capsules, Esomeprazole 20 mg and 40 mg
Date of Approval: 22 October 2024

APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

EMANERA 20 mg gastro-resistant capsules, hard

EMANERA 40 mg gastro-resistant capsules, hard

2. QUALITATIVE AND QUANTITAVE COMPOSITION

EMANERA 20 mg**:** Each gastro-resistant capsule, hard, contains 20 mg esomeprazole (as esomeprazole magnesium dihydrate).

EMANERA 40 mg: Each gastro-resistant capsule, hard, contains 40 mg esomeprazole (as esomeprazole magnesium dihydrate).

Contains sugar:

Sucrose: 28.46 – 32.56 mg (20 mg gastro-resistant capsule)

Sucrose: 56.93 – 65.11 mg (40 mg gastro-resistant capsule)

3. PHARMACEUTICAL FORM

Gastro-resistant capsule, hard

EMANERA 20 mg: The body and the cap are slightly pink in colour; the capsules contain white to almost white pellets. Capsule size: no. 3.

EMANERA 40 mg: The body and the cap are off-pink in colour; the capsules contain white to almost white pellets. Capsule size: no. 1.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

EMANERA 20 mg and 40 mg capsules are indicated in adults for:

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)

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.

Patients requiring continued NSAID therapy:

- healing of gastric ulcers associated with NSAID therapy.
- prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.

Treatment of Zollinger Ellison Syndrome

In combination with antibiotics in treatment of duodenal ulcer caused by *Helicobacter pylori*

4.2 Posology and method of administration

Gastro-oesophageal Reflux Disease (GORD):

- treatment of erosive reflux oesophagitis

40 mg once daily for 4 weeks

An additional 4 week 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 an on-demand regimen, taking 20 mg once daily, when needed.

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

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

20 mg **EMANERA** with 1 g amoxicillin and 500 mg clarithromycin (as per local protocol or guideline), all twice daily for 7 days.

Patients requiring continued NSAID therapy:

- healing of gastric ulcers associated with NSAID therapy the usual dose is 20 mg once daily. The treatment duration is 4 – 8 weeks.
- prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk

20 mg or 40 mg once daily.

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

The recommended initial dosage is **EMANERA** 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 40mg once daily for 4 weeks

  An additional 4 week 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.

Treatment of duodenal ulcer caused by *Helicobacter pylori*

When selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents. The treatment should be supervised by a specialist.

The posology recommendation is:

Weight Posology

30 - 40 kg Combination with two antibiotics: **EMANERA** 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered together twice daily for one week.

> 40 kg Combination with two antibiotics: **EMANERA** 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered together twice daily for one week.

Children:

EMANERA should not be used in children younger than 1 year since no data is available.

Impaired renal function:

Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution.

Impaired hepatic function:

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum daily dose of 20 mg **EMANERA** should be used.

Elderly:

Dose adjustment is not required in the elderly.

Method of administration

The capsules should be swallowed whole with some water. The capsules should not be chewed or crushed.

For patients who have difficulty in swallowing, the capsules can also be opened and the pellets mixed in half a glass of non-carbonated water. No other liquids should be used as the enteric coating may be dissolved. Drink the water 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 capsules can be opened and pellets mixed in non-carbonated water and administered through a gastric tube. It is important that the appropriateness of the selected syringe and tube is carefully tested before use (see section 6.6).

Do not eat the desiccant capsule provided in the container.

4.3 Contraindications

Hypersensitivity to esomeprazole, substituted benzimidazoles or to any of the excipients listed in section 6.1.

EMANERA should not be used concomitantly with atazanavir or nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use

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 **EMANERA** may alleviate symptoms and delay diagnosis.

Long term use

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

On demand treatment

Patients on on-demand treatment should be instructed to contact their medical doctor if their symptoms change in character.

***Helicobacter pylori* eradication**

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible active substance interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be

considered when the triple therapy is used in patients concurrently taking other medicinal products metabolised via CYP3A4 such as cisapride.

Gastrointestinal infections

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

Absorption of vitamin B12

Esomeprazole may reduce the absorption of vitamin B12 (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.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole 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 arrhythmia 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 PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Risk of fracture

Proton pump inhibitors, 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
10–40%. 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.

Combination with other medicines

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

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

When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered. (see section 4.5).

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, **EMANERA** treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of 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 health care professional should consider stopping **EMANERA**. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Tubulointerstitial nephritis

Increased risk of subclinical acute or chronic interstitial nephritis associated with protein pump inhibitors (PPI's) leading to chronic renal inflammation and reduced renal function. The preferred term to describe the histological findings of tubular injury being "tubulointerstitial nephritis".

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. 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 **EMANERA** , is a class effect.

Special information about some of the ingredients

EMANERA contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltose insufficiency should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Effects of **EMANERA** on the pharmacokinetics of other medicines

Protease inhibitors

Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP 2C19.

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max} and C_{min}). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg once daily without omeprazole 20 mg once daily. Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir AUC, C_{max} and C_{min} by 36-39 % and mean AUC, C_{max} and C_{min} for the pharmacologically active metabolite M8 was reduced by 75-92%. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir or nelfinavir is contraindicated (see section 4.3).

For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg once daily). Treatment with omeprazole 20 mg once daily had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg once daily had no effect on the exposure of amprenavir

(with and without concomitant ritonavir). Treatment with omeprazole 40 mg once daily had no effect on the exposure of lopinavir (with concomitant ritonavir).

Methotrexate

When given together with PPIs, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

Medicines with pH dependent absorption

Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal products such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of 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). Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

Medicines metabolised by CYP2C19

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with active substances metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these active substances may be increased, and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Diazepam

Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Voriconazole

Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC_{τ} by 15% and 41%, respectively.

Cilostazol

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

Cisapride

In healthy volunteers, concomitant administration of 40 mg esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half- life ($t_{½}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see also section 4.4).

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

Clopidogrel

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

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 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 (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution concomitant use of clopidogrel should be discouraged.

Investigated medicines with no clinically relevant interaction

Amoxicillin and quinidine

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

Naproxen or rofecoxib

Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.

Effects of other medicines on the pharmacokinetics of EMANERA

Medicines which inhibit CYP2C19 and/or CYP3A4

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP 3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC_{τ} by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment 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 esomeprazole serum levels by increasing the esomeprazole metabolism.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been established.

4.7 Effects on ability to drive and use machines

EMANERA may cause dizziness and blurred vision, thereby affecting the ability to drive or use machinery.

4.8 Undesirable effects

Summary of the safety profile

Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported in clinical trials (and also from post-marketing use). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.

Tabulated summary of adverse reactions

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

System Organ Class	**Frequency**	**Undesirable Effect**
Blood and lymphatic system disorders	Less frequent	Leukopenia, thrombocytopenia agranulocytosis, pancytopenia
Immune system disorders	Less frequent	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders	Less frequent	Peripheral oedema, hyponatraemia
	Frequency unknown	Hypomagnesaemia (see section 4.4); severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.
Psychiatric disorders	Less frequent	Insomnia, agitation, confusion, depression aggression, hallucinations
Nervous system disorders	Frequent	Headache
	Less frequent	Dizziness, paraesthesia, somnolence**,**

		taste disturbance
Eye disorders	Less frequent	Blurred vision
Ear and labyrinth disorders	Less frequent	Vertigo
Respiratory, thoracic and mediastinal disorders	Less frequent	Bronchospasm
Gastrointestinal disorders	Frequent	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)
	Less frequent	Dry mouth**, s**tomatitis, gastrointestinal candidiasis, gastrointestinal infections, microscopic colitis
Hepato-biliary disorders	Less frequent	Increased liver enzymes, hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease
Skin and subcutaneous tissue disorders	Less frequent	Dermatitis, pruritus, rash, urticaria**,** alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
	Frequency unknown	Subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal and connective tissue disorders	Less frequent	Fracture of the hip, wrist or spine (see section 4.4), arthralgia, myalgia, muscular weakness
Renal and urinary disorders	Less frequent	Interstitial nephritis; in some patients renal failure has been reported concomitantly.
Reproductive system and breast disorders	Less frequent	Gynaecomastia
General disorders and administration site conditions	Less frequent	Malaise, increased sweating

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X

SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

No specific antidote is known. **EMANERA** is extensively plasma protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 11.4.3 Medicines acting on gastro-intestinal tract. Other.

ATC Code: A02BC05

Esomeprazole, the S-isomer of omeprazole, reduces gastric acid secretion through specific inhibition of the acid pump in the parietal cell, where it is concentrated and converted to the active form in the acidic environment of the secretory canaliculi and inhibits the enzyme H^+K^+-ATPase – the acid pump. This effect on the final step of the gastric acid secretion is dose-dependent and provides for effective inhibition of both basal and stimulated 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 6-7 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 AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

Food intake had no significant influence on the effect of esomeprazole on intragastric acidity.

Other effects related to acid inhibition:

During long-term treatment with antisecretory medicines, gastric glandular cysts occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

5.2 Pharmacokinetic properties

Absorption and distribution:

Esomeprazole is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 89 % after repeated once-daily administration. 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 and excretion:

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). 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 parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme (extensive metabolisers).

Total plasma clearance is about 17 litres per hour after a single dose and about 9 litres per hour after repeated administration. The plasma elimination half-life is about 1,3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear 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 the 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 metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80 % of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1 % of the parent compound is found in urine.

Special patient populations:

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 %.

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years of age).

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

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

No studies have been performed 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.

Following repeated dose administration of 20 mg and 40 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma concentration (t_{max}) in 12–18-year-olds was similar to that in adults for both esomeprazole doses.

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma concentration (t_{max}) for the 10 mg dose was similar across the 1-11 year-olds and similar to the total exposure seen with the 20 mg dose in 12-18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6-11 year-olds compared to 12-18 year-olds and adults.

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1- 5 year-olds.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pellets in the capsule core:

Sugar spheres (sucrose and maize starch)

Povidone K30

Sodium lauryl sulphate

Polyvinyl alcohol

Titanium dioxide (E171)

Macrogol 6000

Macrogol 3000

Talc (E553b)

Magnesium carbonate, heavy

Polysorbate 80 (E433)

Methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30 per cent

Capsule shell:

Gelatin (E441)

Titanium dioxide (E171)

Red iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Blister pack/HDPE container: 24 months.

HDPE container: after first opening of the container, the product should be used within 6months.

6.4 Special precautions for storage

Blister pack consisting of OPA/Alu/PE + DES film/Alu foil

Store at or below 30 ºC. Store in the original package in order to protect from moisture.

Blister pack consisting of OPA/Alu/PVC/Alu foil

Store at or below 30 ºC. Store in the original package in order to protect from moisture.

HDPE container

Store at or below 30 ºC. Store in the original package in order to protect from moisture.

6.5 Nature of contents of container

Blister packs consisting of cold formed OPA/Alu/PE + DES film/Alu foil:

7, 10, 14, 15, 28, 30, 50, 56, 60, 90, 98 and 100 gastro-resistant capsules, hard, in a box.

Blister packs consisting of OPA/Alu/PVC/Alu foil:

7, 10, 14, 15, 28, 30, 50, 56, 60, 90, 98 and 100 gastro-resistant capsules, hard, in a box.

HDPE container, PP closure with a desiccant: 98 gastro-resistant capsules, hard, and a desiccant capsule, in a box.

Do not eat the desiccant capsule provided in the container.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Administration through gastric tube

1. Open the capsule and empty the pellets into an appropriate syringe and fill the syringe with approximately 25 ml water and approximately 5 ml air.

For some tubes, dispersion in 50 ml water is needed to prevent the pellets from clogging the tube.

2. Immediately shake the syringe to evenly distribute the granules throughout the suspension.
3. Hold the syringe with the tip up and check that the tip has not clogged.
4. Attach the syringe to the tube whilst maintaining the above position.
5. Shake the syringe and position it with the tip pointing down. Immediately inject 5 – 10 ml into the tube. Invert the syringe after injection and shake (the syringe must be held with the tip pointing up to avoid clogging of the tip)
6. Turn the syringe with the tip down and immediately inject another 5 – 10 ml into the tube. Repeat this procedure until the syringe is empty.
7. Fill the syringe with 25 ml of water and 5 ml of air and repeat step 5 if necessary to wash down any sediment left in the syringe. For some tubes, 50 ml water is needed.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LHC Pharmaceuticals (Pty) Ltd
N4 Gate Way Industrial Park
553 Willow Park Manor
33 Ghaap Street
PRETORIA

8. REGISTRATION NUMBER (S)

EMANERA 20 – 55/11.4.3/0910

EMANERA 40 – 55/11.4.3/0911

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 October 2024

10 DATE OF REVISION OF THE TEXT