PROPOSED PROFESSIONAL INFORMATION FOR

ESOMEPRAZOLE UNICORN

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

ESOMEPRAZOLE 20 UNICORN film coated gastro-resistant tablets

ESOMEPRAZOLE 40 UNICORN film coated gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ESOMEPRAZOLE 20 UNICORN: Each film coated gastro-resistant tablet contains 22, 264 mg esomeprazole magnesium equivalent to 20 mg esomeprazole.

Contains sugar: Sucrose 62,016 mg

ESOMEPRAZOLE 40 UNICORN: Each film coated gastro-resistant tablet contains 44,528 mg esomeprazole magnesium equivalent to 40 mg esomeprazole.

Contains sugar: Sucrose 124,032 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated gastro-resistant tablets.

ESOMEPRAZOLE 20 UNICORN: A light pink coloured, oblong, biconvex, film coated gastro-resistant tablet, with “20” debossed on one side and “CE” on the other side.

ESOMEPRAZOLE 40 UNICORN: A pink coloured, oblong, biconvex, film coated gastro-resistant tablet, with “40” debossed on one side and “CE” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

ESOMEPRAZOLE UNICORN is indicated for the following (see sections 4.4 and 5.1):

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 NSAID therapy:

- prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug (NSAID) therapy in patients at risk.

In combination with appropriate antibacterial therapeutic regimen 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.

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

4.2. Posology and method of administration

Posology:

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.

  If gastroesophageal reflux disease (GORD) symptom control has not been achieved after four weeks of treatment with the prescribed daily dose, especially where differentiation of diagnosis of GORD with angina and congestive heart failure is present, further investigation is recommended.

- 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.

Patients requiring continued 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 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 ESOMEPRAZOLE UNICORN with 1 g amoxicillin and 500 mg clarithromycin, all twice daily for 7 days.

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

- The recommended initial dosage is 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 an on-demand regimen, taking 20 mg once daily, when needed.

Doses over 1 mg/kg/day have not been studied.

Special populations

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 ESOMEPRAZOLE UNICORN should be used.

Elderly:

Dose adjustment is not required in the elderly.

Paediatric population

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

Method of administration

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

4.3. Contraindications

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of ESOMEPRAZOLE UNICORN.
Concomitant administration of ESOMEPRAZOLE UNICORN with atazanavir or nelfinavir (see section 4.5).

4.4. Special warnings and precautions for use

ESOMEPRAZOLE UNICORN is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

Prior to treatment or 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, the possibility of malignancy of gastric ulcer or a malignant disease of the oesophagus should be excluded, as the treatment with ESOMEPRAZOLE UNICORN may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Concomitant administration of clopidogrel and esomeprazole resulted in decreased exposure to the active metabolite of clopidogrel by an average of 40 %. The maximum inhibition of (ADP induced) platelet aggregation decreased by an average of 14 %. Based on these data, concomitant use of ESOMEPRAZOLE UNICORN and clopidogrel should be avoided.

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. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference, the esomeprazole treatment should be temporarily stopped 5 days before CgA measurements.

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

Decreased gastric acidity due to any means including proton pump inhibitors such as ESOMEPRAZOLE UNICORN tablets, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with ESOMEPRAZOLE UNICORN 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.

There is an increased risk of subclinical acute interstitial nephritis (AIN), associated with proton pump inhibitors (PPIs), such as ESOMEPRAZOLE UNICORN, which may progress to acute kidney injury and/or chronic renal failure. Symptoms of interstitial nephritis may persist even when treatment with the PPI is terminated.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like ESOMEPRAZOLE UNICORN, 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 PPIs, including ESOMEPRAZOLE UNICORN, with digoxin or medicine that may cause hypomagnesaemia (e.g. diuretics), healthcare providers should consider measuring magnesium levels before starting ESOMEPRAZOLE UNICORN treatment and periodically during treatment.

Esomeprazole, as all acid-blocking medicines, 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.

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.

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 healthcare provider should consider stopping ESOMEPRAZOLE UNICORN. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors

Sugar

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

4.5. Interaction with other medicines and other forms of interaction

Effects of ESOMEPRAZOLE UNICORN on the pharmacokinetics of other medicines:

The gastric acid suppression during treatment with ESOMEPRAZOLE UNICORN, might decrease or increase the absorption of medicines with a gastric pH dependent absorption. The absorption of medicines such as ketoconazole, itraconazole and erlotinib can decrease while the absorption of medicines such as digoxin can increase during treatment with ESOMEPRAZOLE UNICORN.

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 ESOMEPRAZOLE UNICORN is given at high doses in elderly patients. Therapeutic monitoring of digoxin levels should be done.

ESOMEPRAZOLE UNICORN inhibits CYP2C19, the major ESOMEPRAZOLE UNICORN metabolising enzyme. Concomitant administration of 30 mg ESOMEPRAZOLE UNICORN 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 UNICORN resulted in a 13 % increase in trough plasma levels of phenytoin in epileptic patients.

Concomitant administration of 40 mg ESOMEPRAZOLE UNICORN 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.

From post marketed use, cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when warfarin is co-administered with ESOMEPRAZOLE UNICORN at initiation of treatment, during the treatment and at ending treatment.

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 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 %. Based on these data, concomitant use of ESOMEPRAZOLE UNICORN and clopidogrel should be avoided.

Omeprazole as well as esomeprazole act as inhibitors of CYP 2C19. Omeprazole given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and AUC for cilostazol by 18 % and 26 % respectively, and one of its metabolites by 29 % and 69 % respectively. ESOMEPRAZOLE UNICORN can be suspected to have a similar effect.

In concomitant administration of 40 mg ESOMEPRAZOLE UNICORN resulted in a 32 % increase in area under the plasma concentration-time curve (AUC) and a 31 % prolongation of elimination half-life (t½) but no significant increase in peak plasma levels of cisapride. This interaction did not alter the influence of cisapride on cardiac electrophysiology.

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

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

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

Concomitant administration of ESOMEPRAZOLE UNICORN may significantly reduce the plasma levels of atazanavir.

Omeprazole has been reported to interact with some antiretroviral medicines. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral medicines. 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 and concomitant administration is not recommended. Co-administration of esomeprazole (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 %. ESOMEPRAZOLE UNICORN substantially decreases

the concentration of nelfinavir. Concomitant administration with esomeprazole and antiretroviral medicines such as atazanavir and nelfinavir is not recommended.
For other antiretroviral medicines, such as saquinavir, increased serum levels have been reported of 80 - 100 %. 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 ESOMEPRAZOLE UNICORN. Co-administration is not recommended. However, if used concurrently, the dose of ESOMEPRAZOLE UNICORN should be increased.

Effects of other medicines on the pharmacokinetics of ESOMEPRAZOLE UNICORN:
ESOMEPRAZOLE UNICORN is metabolised by CYP2C19 and CYP3A4. Concomitant administration of ESOMEPRAZOLE UNICORN and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to ESOMEPRAZOLE UNICORN. Concomitant administration of ESOMEPRAZOLE UNICORN and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than tripling of the ESOMEPRAZOLE UNICORN exposure.
Dose adjustment of ESOMEPRAZOLE UNICORN is not required.

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.

4.6. Fertility, pregnancy and lactation

Pregnancy

Safety during pregnancy has not been established

Breastfeeding

Safety during lactation has not been established

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

a) 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.

b) Tabulated summary of adverse reactions

Blood and lymphatic system disorders

Less Frequent: Leukopenia, thrombocytopenia

Immune system disorders

Less Frequent: Hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Less Frequent: Peripheral oedema, hyponatraemia, hypomagnesaemia

Frequency Unknown: Severe hypermagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.

Psychiatric disorders

Less Frequent: Insomnia, agitation, confusion, depression, aggression, hallucination

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, diarrhoea, flatulence, nausea/vomiting, constipation, fundic gland polyps (benign)

Less Frequent: Dry mouth, stomatitis, gastrointestinal candidiasis, gastrointestinal infections, microscopic colitis

Hepatobiliary disorders

Less Frequent: Increased liver enzymes, hepatitis with or without jaundice, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Less Frequent: Dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity

Frequency Unknown: Subacute cutaneous lupus erythematosus

Musculoskeletal and connective tissue disorders

Less Frequent: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Less Frequent: Interstitial nephritis, may progress to acute kidney injury and/or chronic

renal failure. In some patient's renal failure has been reported concomitantly.

Reproductive system and breast disorders

Less Frequent: Gynaecomastia

General disorders and administration site conditions

Less Frequent: Malaise, hyperhidrosis.

Post marketing experience

Blood and lymphatic system disorders:

Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders:

Hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock.

Metabolism and nutrition disorders:

Peripheral oedema, hyponatraemia

Psychiatric disorders:

Insomnia, agitation, confusion, depression, aggression, hallucination

Nervous system disorders:

Headache, dizziness, paraesthesia, somnolence, taste disturbance

Eye disorders:

Blurred vision

Ear and labyrinth disorders:

Vertigo

Respiratory, thoracic and mediastinal disorders:

Bronchospasm

Gastrointestinal disorders:

Abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation, dry mouth, stomatitis, gastrointestinal candidiasis

Hepatobiliary disorders:

Increased liver enzymes, hepatitis with or without jaundice, hepatic encephalopathy, hepatic failure

Skin and subcutaneous tissue disorders:

Dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders:

Arthralgia, myalgia, muscular weakness

Renal and urinary disorders:

Interstitial nephritis

Reproductive system and breast disorders:

Gynaecomastia

General disorders and administration site conditions:

Malaise, hyperhidrosis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ESOMEPRAZOLE UNICORN is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Healthcare 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.

Adverse reactions must also be reported to Unicorn Pharmaceuticals (Pty) Ltd to vigilance@unicornpharma.co.za.

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 11.4.3 Medicines acting on gastrointestinal tract. Other.

Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitor.

ATC code: A02B C05

Mechanism of Action:

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

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.

For 20 mg esomeprazole the corresponding values are 50 % and 68 % respectively. Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

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

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.

Elimination

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 Populations

Poor Metabolisers

Approximately 2,9 ± 1,5 % 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 %. These findings have no implications for the posology of esomeprazole.

Hepatic Insufficiency

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.

Renal Insufficiency:

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.

Gender

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.

Elderly:

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

Paediatric population:

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Crospovidone

Glycerol monostearate

Hydroxypropylcellulose

Hypromellose phthalate

Iron oxide red

Magnesium oxide light

Macrogol 400

Macrogol 6000

Methacrylic acid ethyl acrylate copolymer

Microcrystalline cellulose

Polysorbate 80

Povidone

Pregelatinised starch

Silica colloidal hydrated

Confectioner's sugar (containing sucrose and corn starch)

Sugar spheres (containing sucrose and maize starch)

Talc.

ESOMEPRAZOLE 20 UNICORN contains Opadry Pink 03B84893 containing hypromellose, iron oxide red, iron oxide yellow, macrogol, titanium dioxide.

ESOMEPRAZOLE 40 UNICORN contains Opadry Pink 03B54193 containing hypromellose, iron oxide red, macrogol, 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.

Protect from light and moisture.

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

6.5. Nature and contents of container

Aluminium/aluminium blister strips (PVC/OPA/Al/PVC blister with paper/PET/Al lidding foil) packed in an outer carton.

Pack size:

ESOMEPRAZOLE 20 UNICORN (14 tablets - 2 blister strips of 7 tablets each)

ESOMEPRAZOLE 20 UNICORN (28 tablets - 4 blister strips of 7 tablets each)

ESOMEPRAZOLE 40 UNICORN (28 tablets - 4 blister strips of 7 tablets each)

6.6. Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Corner of Searle & Pontac Streets

Cape Town

South Africa

8001

8. REGISTRATION NUMBER(S)

ESOMEPRAZOLE 20 UNICORN: A47/11.4.3/0200

ESOMEPRAZOLE 40 UNICORN: A47/11.4.3/0201

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 August 2022

10. DATE OF REVISION OF THE TEXT

Not applicable