Applicant/PHRC: ***Hetero Drugs South Africa (Pty) Ltd***

*Product proprietary name****: GACTAZEL 40 INJECTION***

Dosage form and strength: ***Each vial contains esomeprazole sodium 42,5 mg equivalent to 40 mg esomeprazole***

APPROVED PROFESSIONAL INFORMATION FOR GACTAZEL 40 INJECTION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

GACTAZEL 40 INJECTION (powder for solution for injection and infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

GACTAZEL: Each vial contains esomeprazole sodium 42,5 mg equivalent to 40 mg esomeprazole.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection and infusion.

A white to off-white lyophilised cake.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

GACTAZEL is indicated for:

Gastro-oesophageal reflux disease (GORD) as an alternative to oral therapy in patients when oral therapy is not appropriate and for the shortest possible time.

Gastro-oesophageal reflux disease (GORD):

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- treatment of severe symptoms of reflux disease.

GACTAZEL is indicated for short-term maintenance of haemostasis and prevention of rebleeding in patients

following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

4.2 Posology and method of administration

Posology

When oral therapy is possible or appropriate, intravenous therapy with GACTAZEL should be discontinued and the therapy should be continued orally.

For single use only.

Adults:

Gastro-oesophageal reflux disease (GORD):

Treatment with GACTAZEL can be given for up to 7 days as part of a full treatment period for the specified indications. When oral therapy is possible or appropriate, intravenous therapy with GACTAZEL should be discontinued and therapy should be continued orally.

Erosive reflux oesophagitis:

40 mg once daily.

The duration of treatment should be 4 weeks. An additional 4 week treatment is recommended for patients in whom the oesophagitis has not healed or who have persistent symptoms.

Long-term management of patients with healed oesophagitis to prevent relapse and treatment of severe symptoms of reflux disease:

20 mg once daily.

Maintenance of haemostasis and prevention of rebleeding of gastric or duodenal ulcers:

80 mg administered as bolus infusion over 30 minutes followed by a continuous IV infusion of 8 mg/hour given over 3 days.

The parenteral treatment period should be followed by acid-suppression therapy with 40 mg esomeprazole orally once daily for 4 weeks.

Special populations

Elderly:

Dose adjustment is not required in the elderly.

Renal impairment:

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.

Hepatic impairment:

Gastro-oesophageal reflux disease (GORD):

Dose adjustment is not required in patients with mild to moderate liver impairment (Child-Pugh class A, B). For patients with severe liver impairment (Child-Pugh class C), a maximum daily dose of 20 mg of GACTAZEL should not be exceeded see section 5.2).

Bleeding ulcers:

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, following an initial bolus dose of 80 mg of GACTAZEL, a continuous IV dose of 4 mg/hour may be sufficient to maintain adequate acid control.

Method of administration

For instructions on dilution of the product before administration, see section 6.6 Special precautions for disposal and other handling).

Injection:

40 mg dose

5 ml of the reconstituted solution (8 mg/ml) should be given as an intravenous injection over a period of at least 3 minutes.

20 mg dose

2.5 ml or half of the reconstituted solution (8 mg/ml) should be given as an intravenous injection over a period of at least 3 minutes. Any unused solution should be discarded.

Infusion:

40 mg dose

The reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes.

20 mg dose

Half of the reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes. Any unused solution should be discarded.

80 mg bolus dose:

The reconstituted solution containing 2 GACTAZEL vials (2 x 40 mg) should be given as a continuous IV infusion over 30 minutes.

8 mg/hour dose

The reconstituted solution should be given as a continuous intravenous infusion over a period of 71.5 hours (calculated rate of infusion of 8 mg/h. See section 6.3 Shelf-life for shelf-life of the reconstituted solution).

4.3 Contraindications

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

- Concomitant use with nelfinavir and atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

In the presence of any alarming 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 GACTAZEL may alleviate symptoms and thereby delay diagnosis.

Concomitant use with nelfinavir and atazanavir (see sections 4.3 and 4.5) is not recommended.

Therapeutic medicine monitoring is recommended during concomitant treatment with warfarin.

During treatment with GACTAZEL serum gastrin increases, in response to the decreased acid secretion.

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

Gastrointestinal infections:

Decreased gastric acidity due to any means including proton pump inhibitors such as GACTAZEL increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with GACTAZEL may lead to increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients (see section 5.1).

Absorption of vitamin B12:

GACTAZEL 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:

There have been reports of severe hypomagnesaemia in patients treated with proton pump inhibitors (PPIs) like

GACTAZEL 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 GACTAZEL.

If patients are expected to be on prolonged GACTAZEL treatment or given GACTAZEL with digoxin or medicines that may cause hypomagnesaemia (e.g., diuretics), healthcare professionals should consider measuring magnesium levels before starting GACTAZEL treatment and periodically during treatment.

Subacute cutaneous lupus erythematosus (SCLE):

Proton pump inhibitors, such as GACTAZEL, are associated with rare 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 discontinuation of GACTAZEL treatment should be considered. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Risk of fracture:

GACTAZEL, especially if used in high doses and over long durations (> 1 year), increases the risk of hip, wrist and spine fracture, predominantly in the elderly or in the presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors increase the overall risk of fracture by 10 – 40 %. Patients at risk of developing osteoporosis should be appropriately managed and they should have an adequate intake of vitamin D and calcium.

Combination with other medicines

Co-administration of esomeprazole with atazanavir is not recommended (see sections 4.3 and 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir;

esomeprazole 20 mg should not be exceeded.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with medicinal products 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.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole 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.

Paediatric population:

GACTAZEL 40 mg IV should not be used in children, since no data are available.

Renal Failure:

Interstitial nephritis may progress to renal failure as it is not necessarily reversed when treatment is discontinued.

GACTAZEL contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’**.**

4.5 Interaction with other medicines and other forms of interaction

Effects of GACTAZEL on the pharmacokinetics of other medicines:

Protease inhibitors:

Omeprazole has been reported to interact with some antiretroviral medicines. 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 antiretroviral medicine. Other possible interaction mechanisms are

via

CYP2C19. For some antiretroviral medicines, e.g., atazanavir and nelfinavir, decreased serum levels have been reported when given together with esomeprazole and concomitant administration is not recommended.

For other antiretroviral medicines, e.g., saquinavir, increased serum levels have been reported. There are also some antiretroviral medicines for which unchanged serum levels have been reported when given with omeprazole. Due to similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with GACTAZEL and antiretroviral medicines, e.g., atazanavir and nelfinavir is contraindicated (see section 4.3).

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 GACTAZEL with tacrolimus 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 it may be necessary to adjust the dosage of tacrolimus.

Medicines with pH dependent absorption:

Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicines with a gastric pH dependent absorption. As with other medicines that decrease intragastric acidity, the absorption of

medicines such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with esomeprazole. Caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic

medicinal product monitoring of digoxin should then be reinforced.

Medicines metabolised by CYP2CY19:

GACTAZEL inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when GACTAZEL is combined with medicines metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine or phenytoin, the plasma concentrations of these medicines may be increased, and a dose reduction could be needed.

The effect of esomeprazole on medicines metabolised by CYP2C19 may be more pronounced during this regimen, and patients should be monitored closely for adverse effects, during the 3day intravenous treatment period.

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 and phenytoin resulted in a 13 % increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor plasma concentrations of phenytoin when treatment with GACTAZEL is introduced or withdrawn.

Voriconazole

When omeprazole is given with voriconazole, exposure to both drugs is increased. A dose adjustment of omeprazole is not routinely indicated, unless patients have severe hepatic impairment and long-term treatment is indicated. When patients already receiving omeprazole are started on voriconazole, the dose of omeprazole should be halved.

Cilostazol:

GACTAZEL acts as a CYP2C19 inhibitor and may increase AUC for cilostazol and one of its active metabolites.

Warfarin:

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketed use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending concomitant GACTAZEL treatment with warfarin or other coumarin derivatives.

Clopidogrel:

Clopidogrel given concomitantly with GACTAZEL has shown a pharmacokinetic (PK)/ pharmacodynamic (PD) interaction between clopidogrel and GACTAZEL. Concomitant use of GACTAZEL with clopidogrel should be discouraged, as inconsistent data is available with regards to the clinical implications of this PK/PD interaction on cardiovascular events (see section 4.4).

Effects of other medicines on the pharmacokinetics of GACTAZEL:

Medicines which inhibit CYP2C19 and/or CYP3A4:

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of GACTAZEL and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of GACTAZEL and a combined inhibitor of CYP2C19 and CYP3A4, e.g., voriconazole, may result in more than doubling of esomeprazole exposure. However, dose adjustment of GACTAZEL is not required in either of these situations. In patients with severe hepatic impairment, and if long-term treatment is indicated, dose adjustment should be considered.

Medicines which induce CYP2C19 and/or CYP3A4:

Medicines known to induce CYP2C19 or CYP3A4 or both, such as St John's wort and rifampicin, may lead to decreased serum levels of GACTAZEL by increasing the metabolism of GACTAZEL.

Investigated medicines with no clinically relevant interaction:

Amoxicillin or quinidine:

GACTAZEL has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or

quinidine.

Naproxen or rofecoxib:

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Limited clinical data on exposed pregnancies are available. A moderate amount of data on pregnant women (between 300 – 1 000 pregnancy outcomes) indicated no malformative or foetal/neonatal toxicity of GACTAZEL. However, caution should

be exercised when prescribing GACTAZEL to pregnant women.

Breastfeeding

It is not known whether GACTAZEL is excreted in human breast milk. No studies in lactating women have been performed. Therefore, GACTAZEL should not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

GACTAZEL has minor influence on the ability to drive and use machines. Adverse reactions such as dizziness (less frequent) and blurred vision (less frequent) have been reported (see section 4.8). If affected patients should not drive or use machines.

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. No dose-related adverse reactions have been identified.

b. Tabulated summary of adverse reactions

Blood and the lymphatic system disorders:	
Less frequent	Leucopenia, agranulocytosis, pancytopenia, thrombocytopenia,
Immune system disorders:	
Less frequent	Hypersensitivity reactions e.g., angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders:	
Less frequent	Peripheral oedema, hyponatraemia
Frequency not known	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, eye disorders
Ear and labyrinth disorders:	
Less frequent	Vertigo, tinnitus
Cardiac disorders:	

Frequency not known:	Angina, tachycardia, bradycardia
Respiratory, thoracic and mediastinal disorders:	
Less frequent	Bronchospasm, coughing
Gastrointestinal disorders:	
Frequent	Abdominal pain, diarrhoea, flatulence, nausea, vomiting, constipation
Less frequent	Dry mouth, stomatitis, gastrointestinal candidiasis, pancreatitis
Frequency not known:	Microscopic colitis
Hepato-biliary disorders:	
Less frequent	Increased liver enzymes, hepatitis with or without jaundice, hepatic failure, hepatic encephalopathy
Skin and subcutaneous tissue disorders:	
Frequent	Administration site reactions*
Less frequent	Dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, bullous eruption
Frequency not known	Subacute cutaneous lupus erythematosus
Musculoskeletal, connective tissue and bone disorders:	
Less frequent	Arthralgia, myalgia, muscular weakness, fractures of the hip, wrist or spine (see section 4.4), back pain
Renal and urinary disorders:	
Less frequent	Interstitial nephritis, urinary disorders
Reproductive system and breast disorders:	

Less frequent	Gynaecomastia
General disorders and administrative site conditions:	
Less frequent	Malaise, hyperhidrosis.

*Administration site reactions have mainly been observed in a study with high-dose exposure over 3 days (72 hours). In the non-clinical programme for esomeprazole intravenous formulation there was no evidence of vaso-irritation but a slight tissue inflammatory reaction at the injection site after subcutaneous (paravenous) injection was noted. The non-clinical findings somewhat indicated that the clinical tissue irritation was concentration related.

c. Description of selected adverse reactions

Other effects related to acid inhibition:

During treatment with GACTAZEL serum gastrin increases, in response to decreased acid secretion. During long-term oral treatment with GACTAZEL gastric glandular cysts occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign, and appear to be reversible.

Decreased gastric acidity due to any means including proton pump Inhibitors such as GACTAZEL, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with GACTAZEL may lead to increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Irreversible visual impairment has been reported in isolated cases of critically ill patients who have received omeprazole (the racemate) intravenous injection, especially at high doses, but no causal relationship has been established.

Paediatric population

Malabsorption

GACTAZEL may reduce cyanocobalamin (vitamin B_{12}) absorption probably related to the increase in gastric pH

and indicating a potential risk of vitamin deficiency with long-term therapy. It is recommended that vitamin B_{12} concentrations be monitored in severly ill children, who may have borderline body stores and require long-term therapy (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers **are asked to report any suspected adverse 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** or to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com.

4.9 Overdose

The symptoms described in connection with deliberate GACTAZEL overdose (limited experience of oral doses in excess of 240 mg/day) are transient. Single oral dose of 80 mg and intravenous doses of 308 mg GACTAZEL over 24 hours were uneventful. No specific antidote is known. GACTAZEL is extensively plasma protein bound and is therefore not readily dialysable. As is any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 11.4.3 Medicines acting on gastrointestinal tract. Other.

Pharmacotherapeutic group: Medicines for acid-related disorders,

proton pump inhibitor

ATC code: A02B C05

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through inhibitor of the enzyme H^+K^+-ATPase, 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. This effect on the final step of the gastric acid secretion is dose dependent and inhibitory for both basal and stimulated acid secretion. 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, after oral administration of esomeprazole.

During intravenous administration of 80 mg esomeprazole as a bolus infusion over 30 minutes followed by a continuous intravenous infusion of 8 mg/h for 23,5 hours, intragastric pH above 4, and pH above 6 was maintained for a mean time of 21 hours, and 11 – 13 hours, respectively, over 24 hours.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also, CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin levels, in both children and adults during long-term treatment with esomeprazole.
During long-term oral treatment with antisecretory medicines, gastric glandular cysts occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile (*see section 4.8).

5.2 Pharmacokinetic properties:

Distribution:

The apparent volume of distribution at steady-state in healthy subjects is approximately 0,22 l/kg body weight. Esomeprazole is 97 % plasma protein bound.

Biotransformation:

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 following parameters reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, i.e., extensive metabolisers. Total plasma clearance is about 17 litres/hour after a single dose and about 9 litres/hour after repeated administration. The plasma elimination $t_{½}$ is about 1,3 hours after repeated once-daily dosing. 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 medicinal product is found in urine.

.

Linearity/ non-linearity:

Total exposure (AUC) 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 inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Following repeated doses of 40 mg administered as intravenous injections, the mean peak plasma concentration is approx. 13.6 micromol/L. The mean peak plasma concentration after corresponding oral doses is approx. 4.6 micromol/L. A smaller increase (of approx. 30 %) can be seen in total exposure after intravenous administration compared to oral administration.

There is a dose-linear increase in total exposure following intravenous administration of esomeprazole as a 30-minute infusion (40 mg, 80 mg or 120 mg) followed by a continuous infusion (4 mg/h or 8 mg/h) over 23.5 hours.

Special patient populations:

Elderly:

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

Gender:

Following a single oral dose of esomeprazole 40 mg, 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. Similar differences have been seen for IV administration of esomeprazole. These findings have no implications for the dosage of esomeprazole.

Renal impairment:

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

Hepatic impairment:

The 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 (Child-Pugh C) 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 hepatic dysfunction. For patients with bleeding ulcers and severe liver dysfunction, following an initial bolus dose of 80 mg, a maximum continuous IV infusion dose of 4 mg/hour may be sufficient in patients with bleeding ulcers. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate, Sodium hydroxide and Water for injection.

6.2 Incompatibilities

The degradation of the reconstituted solution is highly pH dependent and GACTAZEL must therefore only be reconstituted with either 0,9 % sodium chloride for intravenous use, Ringer's lactate solution or 5 % dextrose injection according to the instructions below (see section 6.6 Special precautions for disposal and other handling).

The reconstituted solution should not be mixed or co-administered in the same infusion set with any other medicine.

6.3 Shelf life

24 months for powder for solution for injection

After reconstitution:

The reconstituted solution should be administered within12 hours after reconstitution with either 0,9 % sodium chloride injection or ringer's lactate solution. Administer within 6 hours if 5 % dextrose injection is used for reconstitution.

6.4 Special precautions for storage

Before reconstitution: Store at or below 25 °C. Protect from light.

Keep vial in outer carton until required for use.

The reconstituted solution should be stored at or below 25 °C.

No refrigeration is required.

6.5 Nature and contents of container

GACTAZEL: 5 ml clear, colourless type I tubular glass vial with 13 mm neck with grey bromobutyl double slotted

rubber stopper with a white flip-off seal.

Pack size: 5 or 10 vials.

6.6 Special precautions for disposal and other handling

The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. Only clear solution should be used.

For single use only.

If the entire reconstituted content of the vial is not required, any unused solution should be disposed of in accordance with local requirements.

Injection 40 mg

A solution for injection (8 mg/ml) is prepared by adding 5ml of 0.9% sodium chloride for intravenous use to the esomeprazole 40 mg vial.

The reconstituted solution for injection is clear and colourless to very slightly yellow.

Infusion 40 mg

A solution for infusion is prepared by dissolving the content of one vial with esomeprazole 40 mg in up to 100 ml of 0.9% sodium chloride for intravenous use.

Infusion 80 mg

A solution for infusion is prepared by dissolving the contents of two vials of esomeprazole 40 mg in up to 100 ml of 0.9% sodium chloride for intravenous use.

The reconstituted solution for infusion is clear and colourless to very slightly yellow.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

Waterfall Corporate

Campus, Building No.2,

First Floor, 74 Waterfall Drive, Midrand, 2066

Telephone number: 012 644 1220

e-mail address: nokuthula.n@hetero.com

8 REGISTRATION NUMBER(S)

54/11.4.3/0283

9 DATE OF FIRST AUTHORISATION

22 October 2024

10 DATE OF REVISION OF THE TEXT