SCHEDULING STATUS: S4

1. NAME OF MEDICINE

ESSIUM IV (Powder for solution for injection and infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ESSIUM IV: Each vial contains esomeprazole sodium 42,5 mg, equivalent to esomeprazole 40 mg and disodium edetate (EDTA) as chelating agent.

Sugar free

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection and infusion.

White to pale yellow coloured lyophilized powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ESSIUM IV is indicated for Gastro-oesophageal Reflux Disease as an alternative where oral therapy is not appropriate and for the shortest possible time.

Gastro-oesophageal reflux disease:

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

ESSIUM IV is indicated for the short-term maintenance of haemostasis and prevention of re-bleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

4.2 Posology and method of administration

Posology

Adults:

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

Gastro-oesophageal reflux disease (GORD):

Treatment with **ESSIUM IV** can be given for up to 7 days as part of a full treatment period for the specified indications.

Erosive reflux oesophagitis:

40 mg once daily.

The duration of treatment should be 4 weeks. An additional 4 weeks 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.

Severe liver impairment (Child-Pugh class C):

Maximum daily dose of 20 mg of **ESSIUM IV** should not be exceeded.

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 **ESSIUM IV**, a continuous IV dose of 4 mg/hour may be sufficient to maintain adequate acid control.

Paediatric population

ESSIUM IV should not be used in children since no data are available.

Method of administration

For instructions on reconstitution of the medicine before administration, see section 6.6.

Injection:

40 mg dose*:*

The reconstituted solution should be given as an intravenous injection over a period of at least 3 minutes (see section 6.6).

20 mg dose:

Half the reconstituted solution should be given as an intravenous injection over a period of approximately 3 minutes (see section 6.6).

Infusion:

40 mg dose:

The reconstituted solution should be given as an intravenous infusion over a period of 10 – 30 minutes (see section 6.6).

20 mg dose:

Half of the reconstituted solution should be given as an intravenous infusion over a period of 10 – 30 minutes (see section 6.6).

*Continuous infusion (*40 mg *vial):*

80 mg bolus dose:

The reconstituted solution containing 80 mg esomeprazole should be given as a continuous intravenous infusion over 30 minutes (see section 6.6).

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/hour).

4.3 Contraindications

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

ESSIUM IV should not be used concomitantly with nelfinavir and atazanavir (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, hematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with **Essium IV** may alleviate symptoms and delay diagnosis.

Concomitant administration of **ESSIUM IV** with medicines such as atazanavir and nelfinavir is contraindicated (see section 4.5 and 4.3).

Therapeutic medicine monitoring is recommended during concomitant treatment with warfarin.

During treatment with **ESSIUM IV** serum gastrin increases, in response to the decreased acid secretion.

Gastrointestinal infections

Treatment with proton pump inhibitors may lead to increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Absorption of vitamin B_{12}

ESSIUM IV may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypoorachlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} absorption on long-term therapy.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like **ESSIUM IV** 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 **ESSIUM IV**. For patients expected to be on prolonged treatment or who take **ESSIUM IV** with digoxin or medicinal products that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting **ESSIUM IV** treatment and periodically during treatment.

Risk of fracture

ESSIUM IV 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.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors such as **ESSIUM IV** 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 **Essium IV**. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Combination with other medicines

Co-administration of esomeprazole with atazanavir is not recommended (see section 4.5).

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, **ESSIUM IV** 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 as in **ESSIUM IV**.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicinal products on esomeprazole

Medicines which inhibit CYP2C19 and/or CYP3A4:

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of **ESSIUM IV** and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to esomeprazole.

Concomitant administration of **ESSIUM IV** and a combined inhibitor of CYP2C19 and CYP3A4, e.g. voriconazole, may result in more than doubling of esomeprazole exposure. However, dose adjustment of **ESSIUM IV** 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 esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of other medicinal products on esomeprazole

The decreased intragastric acidity during treatment with **ESSIUM IV**, might increase or decrease the absorption of medicines if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole, itraconazole and erlotinib can decrease while the absorption of medicines such as digoxin can increase during treatment with **ESSIUM IV**. 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 **ESSIUM IV** is given at high doses in elderly patients. Therapeutic monitoring of digoxin levels should be done.

ESSIUM IV inhibits CYP2C19, the major esomeprazole metabolising enzyme. Concomitant administration of 30 mg Esomperazole as in **ESSIUM IV** 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 as in **ESSIUM IV** resulted in

a 13 % increase in trough plasma levels of phenytoin in epileptic 157 patients; dose adjustment was not required in this study.

From post marketed use cases of elevated International Normalised Ratio (INR) of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when warfarin or other coumarine derivatives is co-administered with **ESSIUM IV** at initiation of treatment, during the treatment and ending the treatment.

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 26 164 % respectively, and one of its metabolites by 29 % and 69 % respectively.

In healthy volunteers, concomitant administration of 40 mg Esomeprazole as in **ESSIUM IV** resulted in a 32 % increase in area under the plasma concentration-time curve (AUC) and a 31 % prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. 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 by up to three fold. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

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. 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.

Concomitant administration with esomeprazole and antiretroviral medicines such as atazanavir and nelfinavir is not recommended. ESSIUM IV substantially decreases the concentration of atazanavir and nelfinavir.

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 %.

Tipranavir may decrease the concentration of **ESSIUM IV.** Co-administration is not recommended. However, if used concurrently, the dose of **ESSIUM IV** should be increased.

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

Studies evaluating concomitant administration of Esomeprazole as in **ESSIUM IV** and either naproxen (non-selective NSAID) or rofecoxib (COX-2-selective NSAID) did not identify any clinically relevant interaction.

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 – 1000 pregnancy outcomes) indicated no malformative or foeto/neonatal toxicity of Esomeprazole as in **ESSIUM IV**. However, caution should be exercised when prescribing **ESSIUM IV** to pregnant women.

Breastfeeding

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

4.7 Effects on ability to drive and use machines

ESSIUM IV 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 frequently reported.

Tabulated list of adverse reactions

The following adverse drug reactions have been identified.

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. 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, tinnitus
Cardiac disorders	Frequency unknown	Angina, tachycardia, bradycardia
Respiratory, thoracic and mediastinal disorders	Less frequent	Bronchospasm, coughing
Gastrointestinal disorders	Frequent	Abdominal pain, constipation, diarrhoea, flatulence, nausea, vomiting, fundic gland polyps (benign)
	Less frequent	Dry mouth, stomatitis, gastrointestinal candidiasis
	Frequency unknown	Microscopic colitis
Hepatobiliary disorders	Less frequent	Increased liver enzymes, hepatitis with or without jaundice
	Frequency unknown	Hepatic failure, hepatic encephalopathy
Skin and subcutaneous tissue disorders	Less frequent	Dermatitis, pruritus, rash, urticarial, alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), bullous eruption
	Frequency unknown	Subacute cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Less frequent	Arthralgia, myalgia, fractures of the hip, wrist or spine, muscular weakness

Renal and urinary disorders	Less frequent	Interstitial nephritis, urinary disorders, renal failure
Reproductive system and breast disorders	Less frequent	Gynaecomastia, impotence
General disorders and administration site conditions	Frequent	Administration site reactions
	Less frequent	Malaise, increased sweating, fatigue

Reporting of suspected adverse reactions

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

4.9 Overdose

No specific antidote is known. **ESSIUM IV** 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

A 11.4.3 Medicines acting on gastrointestinal tract. Other.

Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02B C05

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.

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/hr 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 in healthy subjects.

Therapeutic effects of acid inhibition: In a study, patients with bleeding gastric or duodenal ulcers were randomised to receive esomeprazole IV for injection or placebo. Following endoscopic haemostasis, patients received either 80 mg esomeprazole IV administered as bolus infusion over 30 minutes followed by a continuous infusion of 8 mg/hour or placebo for 72 hours. After the initial 72 hour period, all patients received oral esomeprazole 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5,9 % in the treatment group compared to 10,3 % for the placebo group. At 7 and 30 days post-treatment, the occurrence was 7,2 % vs 12,9 % and 7,7 % vs 13,6 %, respectively.

5.2 Pharmacokinetic properties

Distribution:

The apparent volume of distribution at steady state in healthy subjects is approximately 0,22 litres/kg.

Plasma protein binding:

Esomeprazole is 97 % plasma protein bound.

Metabolism and excretion:

Esomeprazole is 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, 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 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 drug is found in urine.

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. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Hepatic impairment:

In patients with severe liver impairment (Child-Pugh C) there is a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in GORD patients with severe impairment. 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 (for pH adjustment)

6.2 Incompatibilities

The degradation of the reconstituted solution is largely dependent on pH and therefore the product should only be prepared with 0,9 % sodium chloride as specified for intravenous use in Section 4.2. Reconstituted solution should not be mixed with another medicine and should not be given with another medicine in the same infusion set.

6.3 Shelf life

24 months

Shelf life after reconstitution

Chemical and physical stability of reconstituted solution has been demonstrated for 12 hours at 25 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 – 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

For single use only.

Discard any unused portions.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep **ESSİUM IV** vial in outer carton, in order to protect from light.

6.5 Nature and contents of container

Type I colourless glass vial with a grey bromobutyl rubber stopper and a transparent flip-off transparent cap, in a unit carton.

1 or 5 or 10 vials per carton.

Not all pack sizes may be marketed.

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 vial):

A solution for injection is prepared by adding 5 ml of 0,9 % sodium chloride (for intravenous use) to the vial.

Infusion (40 mg vial):

A solution for infusion is prepared by dissolving the contents of one vial in up to 100 ml 0,9 % sodium chloride (for intravenous use).

Continuous infusion (40 mg vial):

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).

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (Pty) Ltd

Unit 1, 96 Hartley Road

Durban, 4091

8 REGISTRATION NUMBER(S)

55/11.4.3/0476

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 July 2023

10 DATE OF REVISION OF THE TEXT