**PROFESSIONAL INFORMATION**

**ESOMEPRAZOLE 40 IV CIPLA 40 mg injection/infusion**

**SCHEDULING STATUS**

**S4**

## 1. NAME OF THE MEDICINE

ESOMEPRAZOLE 40 IV CIPLA

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains esomeprazole sodium 42,55 mg, equivalent to esomeprazole 40 mg

Sugar free.

For full list of excipients, see **section 6.1**.

## 3. PHARMACEUTICAL FORM

Powder for solution for injection and infusion

White to almost white cake in a colourless glass vial.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

ESOMEPRAZOLE 40 IV CIPLA is indicated for:

- The treatment of 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.
- The short-term maintenance of haemostasis.
- The prevention of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

## 4.2. Posology and method of administration

**Posology:**

**Adults:**

*Gastro-oesophageal Reflux Disease (GORD):*

Treatment with ESOMEPRAZOLE 40 IV CIPLA 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 ESOMEPRAZOLE 40 IV CIPLA should be discontinued and the therapy should be continued orally.

*Treatment of 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 intravenous infusion of 8 mg/hour given over 3 days.

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

**Method of administration:**

***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.

*40 mg dose:*

The reconstituted solution should be given as an intravenous injection over a period of at least 3 minutes.

*20 mg dose:*

Half of the reconstituted solution should be given as an intravenous injection over a period of approximately 3 minutes.

***Infusion (40 mg vial):***

A solution for infusion is prepared by dissolving the contents of 1 vial in up to 100 mℓ 0,9 % sodium chloride for intravenous use.

*40 mg dose:*

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

*20 mg dose:*

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

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

A solution for infusion is prepared by dissolving the content of 2 vials of esomeprazole 40 mg in up to 100 mℓ of 0,9 % sodium chloride for intravenous use.

*80 mg bolus dose:*

The reconstituted solution containing 80 mg esomeprazole should be given as an intravenous infusion over a period of 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/hour).

**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:**

*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 ESOMEPRAZOLE 40 IV CIPLA 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 ESOMEPRAZOLE 40 IV CIPLA, a continuous intravenous infusion dose of 4 mg/hour may be sufficient to maintain adequate acid control.

**Elderly:**

Dose adjustment is not required in the elderly.

## 4.3. Contraindications

ESOMEPRAZOLE 40 IV CIPLA is contraindicated in:

- Patients with known hypersensitivity to esomeprazole, substituted benzimidazoles or any other inactive ingredients of ESOMEPRAZOLE 40 IV CIPLA listed in section 6.1.
- Patients treated concomitantly with nelfinavir or atazanavir.

## 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 ESOMEPRAZOLE 40 IV CIPLA may alleviate symptoms and delay diagnosis.

There is an increased risk of subclinical acute interstitial nephritis (AIN), associated with proton pump inhibitors (PPIs), such as ESOMEPRAZOLE 40 IV CIPLA, 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.

**ESOMEPRAZOLE 40 IV CIPLA** should be used with caution in hepatic impairment and dose adjustment may be required (see **section 4.2**).

Concomitant administration with ESOMEPRAZOLE 40 IV CIPLA and medicines such as atazanavir and nelfinavir is not recommended (see **sections 4.3 and 4.5**).
Therapeutic medicine monitoring is recommended during concomitant treatment with warfarin (see **section 4.5**).

**Other effects related to acid inhibition:**

During treatment with ESOMEPRAZOLE 40 IV CIPLA serum gastrin increases, in response to decreased acid secretion.

During long-term oral treatment with esomeprazole 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 ESOMEPRAZOLE 40 IV CIPLA, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with ESOMEPRAZOLE 40 IV CIPLA may lead to increased risk of gastrointestinal infections, such as *Salmonella* and *Campylobacter, Shigella* and possibly also *Clostridium* difficile in hospitalised patients (see **section 4.8**).

ESOMEPRAZOLE 40 IV CIPLA, 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.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like ESOMEPRAZOLE 40 IV CIPLA, 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 40 IV CIPLA**,** with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting ESOMEPRAZOLE 40 IV CIPLA treatment and periodically during treatment.

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 40 IV CIPLA and clopidogrel should be avoided.

Proton pump inhibitors, including ESOMEPRAZOLE 40 IV CIPLA, especially if used in high doses and over long duration, 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 sub-acute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping ESOMEPRAZOLE 40 IV CIPLA. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

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.

**Children:**

ESOMEPRAZOLE 40 IV CIPLA should not be used in children since no data are available.

**Incompatibilities:**

The degradation of the reconstituted solution is highly pH dependent and the product must therefore only be reconstituted with 0,9 % sodium chloride for intravenous use according to the instructions below (see **section 4.2**). The reconstituted solution should not be mixed or co-administered in the same infusion set with any other medicine.

## 4.5. Interaction with other medicines and other forms of interaction

The absorption of ketoconazole and itraconazole can decrease and the absorption of digoxin can increase during treatment with ESOMEPRAZOLE 40 IV CIPLA.

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 reported infrequently. However, caution should be exercised when ESOMEPRAZOLE 40 IV CIPLA is given at high doses in elderly patients. Therapeutic monitoring of digoxin should then be reinforced.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Concomitant oral administration of 30 mg esomeprazole resulted in a 45 % decrease in clearance of the CYP2C19 substrate diazepam. The interaction is unlikely to be of clinical relevance. Concomitant oral administration of 40 mg esomeprazole resulted in a 13 % increase in trough plasma levels of phenytoin in epileptic patients; dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with ESOMEPRAZOLE 40 IV CIPLA is introduced or withdrawn.

Concomitant oral administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentrations of 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 treatment with warfarin or other coumarin derivatives (see **section 4.4**).

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamics interaction between clopidogrel (300 mg loading dose / 75 mg daily maintenance dose) and esomeprazole (40 mg orally 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 %.

Inconsistent data on the clinical implications of a pharmacokinetic/pharmacodynamic interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. The use of ESOMEPRAZOLE 40 IV CIPLA with clopidogrel should be discouraged.

When given together with proton pump inhibitors, including ESOMEPRAZOLE 40 IV CIPLA, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of ESOMEPRAZOLE 40 IV CIPLA may need to be considered.

Concomitant administration of ESOMEPRAZOLE 40 IV CIPLA 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.

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 metabolites by 29 % and 69 % respectively.

In healthy volunteers, concomitant oral 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 ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride.

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, 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. There are also some antiretroviral medicines for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with ESOMEPRAZOLE 40 IV CIPLA and antiretroviral medicines such as atazanavir and nelfinavir is not recommended (see sections **4.3** and **4.4**).

ESOMEPRAZOLE 40 IV CIPLA has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

**Effects of other medicines on the pharmacokinetics of ESOMEPRAZOLE 40 IV CIPLA:**

Esomeprazole is metabolised by CYP2C19 and CYP3A4.

Concomitant oral administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily) resulted in a doubling of exposure (AUC) to esomeprazole. Concomitant administration of ESOMEPRAZOLE 40 IV CIPLA and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of ESOMEPRAZOLE 40 IV CIPLA is not required in either of these situations. A dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Medicines known to induce CYP2C19 or CYP34A 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**

Limited clinical data on exposed pregnancies are available for esomeprazole.

**Breast-feeding**

It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore ESOMEPRAZOLE 40 IV CIPLA should not be used during breastfeeding.

**Fertility**

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

### 4.7. Effects on ability to drive and use machines

**ESOMEPRAZOLE 40 IV CIPLA** has minor influence on the ability to drive or use machines. Adverse reactions such as dizziness and blurred vision have been reported less frequently (see **section 4.8**). If affected, patients should not drive or use machines.

This medicine contains less than 1 mmol sodium (23 mg) per tablet. ESOMEPRAZOLE 40 IV CIPLA is essentially 'sodium-free'.

### 4.8. Undesirable effects

The following adverse reactions have been reported:

**Infections and infestations:**

| | |
|---|---|
| *Less frequent:* | Gastrointestinal candidiasis. |
| *Frequency unknown:* | Enteric infections. |

**Blood and lymphatic system disorders:**

| | |
|---|---|
| *Less frequent:* | Leucopenia, thrombocytopenia, agranulocytosis, pancytopenia. |

**Immune system disorders:**

| | |
|---|---|
| *Less frequent:* | Hypersensitivity reactions e.g. angioedema, anaphylactic reaction or shock. |

**Metabolism and nutrition disorders:**

| | |
|---|---|
| *Less frequent:* | Hyponatraemia. |
| *Frequency unknown:* | Hypomagnesaemia, hypocalcaemia, hypokalaemia, malabsorption (cyanocobalamine, vitamin C and calcium). |

**Psychiatric disorders:**

| | |
|---|---|
| *Less frequent:* | Insomnia, agitation, confusion, depression, aggression, hallucination. |

**Nervous system disorders:**

| | |
|---|---|
| *Frequent:* | Headache. |
| *Less frequent:* | Dizziness, paraesthesia, somnolence, taste disturbance. |
| *Frequency unknown:* | Ataxia, anxiety with panic attacks, episodic night terrors attention deficit. |

**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 or vomiting, constipation. |
| *Less frequent:* | Dry mouth, stomatitis. |
| *Frequency unknown:* | Microscopic colitis. |

**Hepato-biliary disorders:**

| | |
|---|---|
| *Less frequent:* | Increased liver enzymes, hepatitis with or without jaundice, hepatic failure, hepatic encephalopathy. |

**Skin and subcutaneous tissue disorders:**

| | |
|---|---|
| *Less frequent:* | Dermatitis, pruritus, |

| | |
|---|---|
| | urticaria, rash, alopecia, photosensitivity, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, bullous eruption. |
| *Frequency unknown:* | Sub-acute cutaneous lupus erythematosus. |

**Musculoskeletal, connective tissue and bone disorders:**

| | |
|---|---|
| *Less frequent:* | Arthralgia, myalgia, muscular weakness, fracture of the hip, wrist or spine. |
| *Frequency unknown:* | Myopathy. |

**Renal and urinary disorders:**

| | |
|---|---|
| *Less frequent:* | Interstitial nephritis, renal failure. |

**Reproductive system and breast disorders:**

| | |
|---|---|
| *Less frequent:* | Gynaecomastia, impotence. |

**General disorders and administration site conditions:**

| | |
|---|---|
| *Frequent:* | Administration site reactions.* |
| *Less frequent:* | Malaise, hyperhidrosis, peripheral oedema. |
| *Frequency unknown:* | Fatigue, fever. |

* 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.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of [PRODU CT NAME] is important. It allows continued monitoring of the benefit/risk balance of ESOMEPRAZOLE 40 IV CIPLA. 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 or to Cipla Medpro (Pty) Ltd. (by e-mail: drugsafetysa@cipla.com).

### 4.9. Overdose

The symptoms described in connection with deliberate esomeprazole, as in ESOMEPRAZOLE 40 IV CIPLA, overdose (limited experience of oral doses in excess of 240 mg/day) are transient. Single oral doses of 80 mg and intravenous doses of 308 mg ESOMEPRAZOLE 40 IV CIPLA over 24 hours were uneventful. No specific antidote is known. Esomeprazole 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: drugs for acid-related disorders, proton pump inhibitor
ATC code: A02B C05.

Esomeprazole, the S-isomer of omeprazole, reduces gastric acid secretion through inhibition 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. Here, it is activated by proton-catalysed formation of a tetracyclic sulfenamide, trapping the medicine so that it cannot diffuse back across the canalicular membrane. The activated form then binds covalently with sulfhydryl groups of cysteines in the $H^+K^+$-ATPase, irreversibly inactivating the pump molecule. This effect on the final step of the gastric acid secretion is dose-dependent and inhibitory for both basal and stimulated acid secretion.

Acid secretion resumes only after new pump molecules are synthesised and inserted into the luminal membrane, providing a prolonged suppression of acid secretion, despite the much shorter plasma half-life of the parent compound.

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/hour 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.

In a clinical study, following endoscopic haemostasis, patients with bleeding gastric or duodenal ulcers 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.

The 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in symptomatic GORD (gastro-oesophageal reflux disorder) patients. On day 5, intragastric pH was maintained above 4,0 for a mean of 15,3 hours with esomeprazole, 13,3 hours with rabeprazole, 12,9 hours with omeprazole, 12,7 hours with lansoprazole and 11,2 hours with pantoprazole. Esomeprazole also provided a significantly higher percentage of patients with an intragastric pH greater than 4,0 for more than 12 hours relative to the other proton pump inhibitors.

## 5.2. Pharmacokinetic properties

*Distribution:*

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

*Plasma protein binding:*

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 parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, i.e. extensive metabolisers.

Total plasma clearance is about 17 ℓ/hour after a single dose and about 9 ℓ/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 in a non-linear fashion with repeated administration of esomeprazole. Esomeprazole is completely eliminated from plasma between doses, with no tendency for accumulation during once-daily administration. [(2B.3)] 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 population:**

These findings have no implications for the dosing of esomeprazole.

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

Following a single oral 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. Similar differences have been seen for intravenous administration of esomeprazole. These findings have no implications for the dosage of esomeprazole.

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.

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 impairment, following an initial bolus dose of 80 mg, a maximum continuous intravenous 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

Inactive ingredients are disodium edetate and sodium hydroxide.

### 6.2. Incompatibilities

This medicinal product must not be used with other medicinal products except those mentioned in **section 6.6**.

### 6.3. Shelf Life

24 months

### 6.4. Special precautions for storage

Store at or below 30 °C in the outer container.

Protect the vial from light. Vials can be stored exposed to normal in-door light, for up to 24 hours outside the box.

*Reconstituted solution for injection and infusion:*

Chemical in use stability of the reconstituted solution has been demonstrated for 12 hours in 0,9 % sodium chloride solution for intravenous use at 30 °C, however reconstituted solution should be used immediately and any unused portion discarded. 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 fridge (2 – 8 °C).

### 6.5. Nature and contents of container

Type I clear glass vial of 5 mℓ sealed with a dark grey rubber stopper and an aluminium cap with plastic flip-off seal, packaged in a cardboard box, or 10 vials of 5 mℓ in a cardboard box.

### 6.6. Special precautions for disposal and other handling

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

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

## 8. REGISTRATION NUMBER(S)

51/11.4.3/0442

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 July 2022

## 10. DATE OF REVISION OF THE TEXT

28 August 2024