APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TRULOC IV 40 mg, powder for solution for injection/infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One mL provides 8 mg of esomeprazole after reconstitution with 5 mL of 0,9 % sodium chloride for intravenous use.

Sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion.

A white to almost white cake or powder in a colourless glass vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRULOC IV 40 mg 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 TRULOC IV 40 mg 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 TRULOC IV 40 mg 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.

Symptomatic gastro-oesophageal reflux disease (GORD)

If gastro-oesophageal 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 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.

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

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 TRULOC IV 40 mg 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 TRULOC IV 40 mg, 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.

Paediatric population

TRULOC IV 40 mg 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 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)

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)

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).

4.3 Contraindications

TRULOC IV 40 mg is contraindicated in:

- hypersensitivity to esomeprazole, substituted benzimidazoles or to any of the ingredients of TRULOC IV 40 mg (see section 6.1)
- patients treated concomitantly with nelfinavir or 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, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with TRULOC IV 40 mg may alleviate symptoms and delay diagnosis.

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

Concomitant administration with TRULOC IV 40 mg and medicines such as atazanavir and nelfinavir is contraindicated (see sections 4.3 and 4.5).

Therapeutic medicine monitoring is recommended during concomitant treatment with warfarin (see section 4.5).

Occurrence of acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including TRULOC IV

40 mg. Acute interstitial nephritis may occur at any point during therapy, which may progress to acute kidney injury and/or chronic renal failure. Discontinue TRULOC IV 40 mg if acute interstitial nephritis develops.

Other effects related to acid inhibition

During treatment with TRULOC IV 40 mg 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.

Gastrointestinal infections

Decreased gastric acidity due to any means, including proton pump inhibitors such as TRULOC IV 40 mg, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with TRULOC IV 40 mg 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).

Absorption of vitamin B_{12}

TRULOC IV 40 mg, as all acid-blocking medicines, may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. 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 TRULOC IV 40 mg, 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 TRULOC IV 40 mg, with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting TRULOC IV 40 mg treatment and periodically during treatment.

Risk of fractures

Proton pump inhibitors, including TRULOC IV 40 mg, 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.

Subacute cutaneous lupus erythematosus (SCLE)

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 healthcare professional should consider stopping TRULOC IV 40 mg. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Combination with other medicines

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 TRULOC IV 40 mg and clopidogrel should be avoided.

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 medicines 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

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.

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 TRULOC IV 40 mg.

Paediatric population

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

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on the pharmacokinetics of TRULOC IV 40 mg:

Protease inhibitors

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

Antiretroviral medicines

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, including darunavir (with concomitant ritonavir), amprenavir (with concomitant ritonavir) and lopinavir (with concomitant ritonavir). Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with TRULOC IV 40 mg and antiretroviral medicines such as atazanavir and nelfinavir is not recommended (see sections 4.3 and 4.4). Tipranavir may decrease the concentration of TRULOC IV 40 mg. Co-administration is not recommended. However, if used concurrently, the dose of TRULOC IV 40 mg should be increased.

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 TRULOC IV 40 mg.

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 TRULOC
IV 40 mg is given at high doses in elderly patients. Therapeutic monitoring of digoxin should then be reinforced.

Medicines metabolised by CYP2C19

Esomeprazole inhibits CYP2C19, the major esomeprazole-metabolising enzyme. Thus, when esomeprazole is combined with medicines metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these medicines may be increased and a dose reduction could be needed. No *in vivo* interaction studies have been performed with the high dose intravenous regimen (80 mg+8 mg/h). 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 3 day intravenous treatment period.

Diazepam

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.

Phenytoin

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 TRULOC IV 40 mg is introduced or withdrawn.

Warfarin

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).

Clopidogrel

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 TRULOC IV 40 mg with clopidogrel should be discouraged.

Methotrexate

When given together with proton pump inhibitors, including TRULOC IV 40 mg, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate

administration a temporary withdrawal of TRULOC IV 40 mg may need to be considered.

Tacrolimus

Concomitant administration of TRULOC IV 40 mg 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.

Cilostazol

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

Cisapride

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.

This interaction did not alter the influence of cisapride on cardiac electrophysiology.

Medicines which inhibit CYP2C19 and/or CYP3A4

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 TRULOC IV 40 mg 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 TRULOC IV 40 mg 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 which induce CYP2C19 and/or CYP3A4

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.

Medicines which induce CYP2C19 and/or CYP3A4

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.

Investigated medicines with no clinically relevant interaction

Amoxicillin or quinidine

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

Naproxen or rofecoxib

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Limited clinical data on exposed pregnancies are available for esomeprazole.

A moderate amount of data on pregnant women (between 300 - 1000 pregnancy outcomes) indicated no malformative or foeto/neonatal toxicity of esomeprazole. However, caution should be exercised when prescribing TRULOC IV 40 mg to pregnant women.

Breastfeeding

It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore TRULOC IV 40 mg 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

TRULOC IV 40 mg 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.

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 effects

The following adverse reactions have been reported:

System Organ Class	Frequency	Side effects
Infections and Infestations	Less frequent Frequency unknown	Gastrointestinal candidiasis 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 Frequency unknown	Hyponatraemia Hypomagnesaemia, hypocalcaemia, hypokalaemia, malabsorption (cyanocobalamine, vitamin C and calcium)

Psychiatric disorders	Less frequent	Insomnia, agitation, confusion, depression, aggression, hallucination
Nervous system disorders	Frequent Less frequent Frequency unknown	Headache Dizziness, paraesthesia, somnolence, taste disturbance Ataxia, anxiety with panic attacks, episodic night terrors, attention deficit
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 Less frequent Frequency unknown	Abdominal pain, diarrhoea, flatulence, nausea or vomiting, constipation, fundic gland polyps (benign) Dry mouth, stomatitis, gastrointestinal candidiasis Microscopic colitis
Hepatobiliary disorders	Less frequent	Increased liver enzymes, hepatitis with or without jaundice, hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous eruption, drug reaction with eosinophilia and systemic symptoms (DRESS) Sub-acute cutaneous lupus erythematosus
Musculoskeletal, connective tissue and bone disorders	Less frequent Frequency unknown	Arthralgia, myalgia, muscular weakness, fracture of the hip, wrist or spine Myopathy
Renal and urinary disorders	Less frequent	Interstitial nephritis, may progress to acute kidney injury and/or chronic renal failure, renal failure
Reproductive system and breast disorders	Less frequent	Gynaecomastia, impotence
General disorders and administrative site conditions	Frequent Less frequent Frequency unknown	Administration site reactions* Malaise, hyperhidrosis, peripheral oedema 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.

a. Description of selected adverse reactions

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.

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. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms

The symptoms described in connection with deliberate esomeprazole, as in TRULOC IV 40 mg, 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 TRULOC IV 40 mg over 24 hours were uneventful.

Management of overdose

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

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

ATC code: A02B C05

Pharmacological classification: A 11.4.3 – Medicines acting on gastrointestinal tract. Other.

Mechanism of action

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. 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.

Linearity/non-linearity:

The area under the plasma concentration-time curve increases in a non-linear fashion 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.

Pharmacokinetics in special patient groups

These findings have no implications for the dosing of esomeprazole.

Elderly

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

Gender

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.

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 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.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

TRULOC IV must not be used with other medicines other than the diluents mentioned in section 6.6.

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 6.6. 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

2 years.

Reconstituted solution for injection and infusion

Ideally, reconstituted solution should be used immediately and any unused portion discarded. Stability of the reconstituted solution has been demonstrated for 12 hours in 0,9 % sodium chloride solution for intravenous use. The reconstituted solution can be kept in normal in- door light at up to 30 °C.

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the outer container to protect the vials from light.

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

TRULOC IV 40 mg should be used immediately after reconstitution and any unused portion discarded. If not used immediately, the reconstituted solution should be refrigerated at 2 - 8 °C and used within 24 hours.

6.5 Nature and contents of container

TRULOC IV 40 mg powder for solution for injection/infusion is presented in type I clear glass vials of 5 mL and sealed with a dark grey bromobutyl rubber stopper and grey aluminium cap with a grey plastic flip-off seal.

The pack sizes are 1 or 10 vials in an outer carton.

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.

Reconstitution instructions

Injection (40 mg vial)

A solution for injection (8 mg/mL) is prepared by adding 5 mL of 0,9 % sodium chloride for intravenous use to the esomeprazole 40 mg vial.

Infusion (40 mg vial)

A solution for infusion is prepared by dissolving the content of one vial of TRULOC IV 40 mg in up to 100 mL of 0,9 % sodium chloride for intravenous use.

Continuous infusion (40 mg vial)

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

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8. REGISTRATION NUMBER(S)

A48/11.4.3/0120

9. DATE OF FIRST AUTHORISATION

30 November 2021

10. DATE OF REVISION OF THE TEXT

23 September 2025

MOZAMBIQUE

TRULOC IV 40 mg: A6802