**PROPOSED PROFESSIONAL INFORMATION (CLEAN)**

## SCHEDULING STATUS

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## 1. NAME OF THE MEDICINE

**TRULOC 20 mg** gastro-resistant film coated tablet

**TRULOC 40 mg** gastro-resistant film coated tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRULOC 20 mg: Each tablet contains 20 mg esomeprazole equivalent to 22,26 mg esomeprazole magnesium.

TRULOC 40 mg: Each tablet contains 40 mg esomeprazole equivalent to 44,53 mg esomeprazole magnesium.

TRULOC 20 mg: contains sugar (sucrose ± 12,31 mg and lactose monohydrate 31,875 mg per tablet).

TRULOC 40 mg: contains sugar (sucrose ± 24,62 mg and lactose monohydrate 63,750 mg per tablet).

For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Film coated tablet

TRULOC 20 mg: Brick red coloured, round shape, biconvex, film coated tablets, imprinted with “20” on one side with black ink and plain on the other side.

TRULOC 40 mg: Brick red coloured, round shape, bevelled edge, biconvex, film coated tablets,

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imprinted with “40” on one side with black ink and plain on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

*Gastro-oesophageal Reflux Disease (GORD):*

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of Gastro-oesophageal Reflux Disease (GORD).

*Patients requiring continued nonsteroidal anti-inflammatory drug (medicine) (NSAID) therapy:*

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

*In combination with appropriate antibacterial therapeutic regimen for the eradication of Helicobacter pylori:*

- healing of *Helicobacter pylori* associated duodenal ulcer, and
- prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcer disease.

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

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## 4.2 Posology and method of administration

### Posology

***Adults:***

*Gastro-oesophageal Reflux Disease (GORD):*

- treatment of erosive reflux oesophagitis:

  40 mg once daily for 4 weeks.

  An additional 4-week treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

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: 20 mg once daily
- symptomatic treatment of Gastro-oesophageal Reflux. Disease (GORD):

  20 mg once daily in patients without oesophagitis.

  If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen, taking 20 mg once daily, when needed.

*Patients requiring continued NSAID therapy:*

- prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk:

  20 mg or 40 mg once daily.

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*In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori and healing of Helicobacter pylori associated duodenal ulcer and prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcer disease:*

- 20 mg TRULOC with 1 g amoxicillin and 500 mg clarithromycin, all twice daily for 7 days.

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

- the recommended initial dosage is 40 mg twice daily. The dosage should then be individually adjusted, and treatment continued, as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

***Adolescents 12 - 18 years:***

*Gastro-oesophageal Reflux Disease (GORD):*

- treatment of erosive reflux oesophagitis:

  40 mg once daily for 4 weeks.

  An additional 4-week treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms
- long-term management of patients with healed oesophagitis to prevent relapse: 20 mg once daily
- symptomatic treatment of Gastro-oesophageal Reflux. Disease (GORD):

  20 mg once daily in patients without oesophagitis.

  If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved

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using an on-demand regimen, taking 20 mg once daily, when needed.

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

**Special populations**

*Impaired renal function*

Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution.

*Impaired hepatic function*

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum daily dose of 20 mg TRULOC should be used.

*Elderly*

Dose adjustment is not required in the elderly.

**Paediatric population**

The safety and efficacy of TRULOC in children younger than 12 years of age has not been established.

No data is available.

**Method of administration**

For oral use.

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

### 4.3 Contraindications

- hypersensitivity to esomeprazole, substituted benzimidazoles or to any of the ingredients of TRULOC
- concomitant administration of TRULOC with atazanavir or nelfinavir (see section 4.5).

### 4.4 Special warnings and precautions for use

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

Prior to treatment or in the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, the possibility of malignancy of gastric ulcer or a malignant disease of the oesophagus should be excluded, as the treatment with TRULOC may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

***Acute Interstitial Nephritis***

There is an increased risk of subclinical Acute Interstitial Nephritis (AIN), associated with Proton pump inhibitors (PPIs), such as TRULOC, 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.

***Hypomagnesaemia***

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs)

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like TRULOC 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, with digoxin or medicine that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting TRULOC treatment and periodically during treatment.

***Concomitant use with other medicines***

Concomitant administration with TRULOC 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).

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with medicines metabolised through CYP2C19 should be considered. 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 and clopidogrel should be avoided.

When prescribing esomeprazole for on demand therapy, the implications for interactions with other

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medicines, due to fluctuating plasma concentrations of esomeprazole, should be considered (see section 4.5).

***Absorption of vitamin $B_{12}$***

TRULOC, 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.

***Gastric glandular cysts***

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.

***Risk of fracture***

Proton pump inhibitors, including TRULOC, especially if used in high doses and over long durations, 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.

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***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. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

***Interference with laboratory tests***

During treatment with antisecretory medicines, serum gastrin increases in response to the decreased acid secretion. Also, Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference, the esomeprazole treatment should be temporarily stopped 5 days before CgA measurements.
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.

***Long term treatment***

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

***Gastrointestinal infections***

Decreased gastric acidity due to any means, including proton pump inhibitors such as TRULOC tablets, increases gastric counts of bacteria normally present in the gastrointestinal tract.
Treatment with TRULOC may lead to increased risk of gastrointestinal infections such as Salmonella

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and Campylobacter and also *Clostridium difficile* in hospitalised patients. *Clostridium difficile* is a bacterium that can cause severe debilitating diarrhoea that does not improve. Symptoms may include watery stools, abdominal pain, fever, and patients may develop more serious intestinal conditions.

***Serious cutaneous adverse reactions (SCARs)***

Serious cutaneous adverse reactions (SCARs) such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening, have been reported very rarely in association with esomeprazole treatment.

Patients should be advised of the signs and symptoms of the severe skin reaction EM/SJS/TEN/DRESS and should seek medical advice from their doctor immediately when observing any indicative signs or symptoms.

TRULOC should be discontinued immediately upon signs and symptoms of severe skin reactions and additional medical care/close monitoring should be provided as needed.

Re-challenge should not be undertaken in patients with EM/SJS/TEN/DRESS.

***On demand treatment***

Patients on on-demand treatment should be instructed to contact their doctor if their symptoms change in character.

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***Sucrose and lactose:***

TRULOC tablets contain sucrose and lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with rare hereditary problems of galactose/fructose intolerance, total lactase/sucrase/isomaltase deficiency or glucose-galactose malabsorption should not take TRULOC.

**4.5 Interaction with other medicines and other forms of interaction**

**Effects of TRULOC on the pharmacokinetics of other medicines:**

***Medicines with pH dependent absorption***

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

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

**Medicines metabolised by CYP2C19**

***Diazepam***

TRULOC inhibits CYP2C19, the major TRULOC metabolising enzyme. Concomitant administration of 30 mg TRULOC 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 TRULOC

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resulted in a 13 % increase in trough plasma levels of phenytoin in epileptic patients.

***Warfarin***

Concomitant administration of 40 mg TRULOC to warfarin-treated patients showed that, despite elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range.

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

***Clopidogrel***

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40 % and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14 %. Based on these data, concomitant use of TRULOC and clopidogrel should be avoided.

***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. TRULOC can be expected to have a similar effect.

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***Cisapride***

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

***Methotrexate***

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

***Tacrolimus***

Concomitant administration of TRULOC 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.

***Phenytoin***

Concomitant administration of 40 mg esomeprazole resulted in a 13 % increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with TRULOC is introduced or withdrawn.

***Antiretroviral medicines***

Omeprazole has been reported to interact with some antiretroviral medicines. Increased gastric pH

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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.

Concomitant administration of TRULOC may significantly reduce the plasma levels of atazanavir. 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 %. TRULOC substantially decreases the concentration of nelfinavir. Concomitant administration with esomeprazole and antiretroviral medicines, such as atazanavir and nelfinavir, is not recommended.

For other antiretroviral medicines, such as saquinavir, increased serum levels of 80 - 100 % have been reported. There are also some antiretroviral medicines for which unchanged serum levels have been reported when given with omeprazole. Close monitoring or dose alteration is recommended.

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

***Investigated medicines with no clinically relevant interaction***

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

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

***Effects of other medicines on the pharmacokinetics of TRULOC:***

***Medicines which inhibit CYP2C19 and/or CYP3A4***

TRULOC is metabolised by CYP2C19 and CYP3A4. Concomitant administration of TRULOC and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to TRULOC.

Concomitant administration of TRULOC and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than tripling of the TRULOC exposure.

Dose adjustment of TRULOC is not required.

A dose adjustment of TRULOC is not regularly required in either of these situations. However, 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 CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

**Paediatric population**

Interaction studies have only been performed in adults.

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## 4.6 Fertility, pregnancy and lactation

### Pregnancy

Safety during pregnancy has not been established.

Clinical data on exposed pregnancies with TRULOC are insufficient. With the racemic mixture omeprazole data on a larger number of exposed pregnancies from epidemiological studies indicate no malformative nor foetotoxic effect. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/foetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of esomeprazole.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

### Breastfeeding

Safety during lactation has not been established.

It is not known whether esomeprazole is excreted in human breast milk. There is insufficient information on the effects of esomeprazole in newborns/infants. TRULOC 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.

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## 4.7 Effects on ability to drive and use machines

Esomeprazole has minor influence on the ability to drive and use machines.

TRULOC 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 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.

### Tabulated list of adverse effects

The following adverse reactions have been identified or suspected in the clinical trials programme for omeprazole, as in TRULOC.

| **System Organ Class** | **Frequency** | **Side effects** |
|---|---|---|
| Blood and lymphatic system disorders | Less frequent Frequency unknown | Leukopenia*, thrombocytopenia*, Agranulocytosis*, pancytopenia* |
| Immune system disorders | Less frequent | Hypersensitivity reactions* e.g. angioedema* and anaphylactic reaction/shock* |

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|---|---|---|
| Metabolism and nutrition disorders | Less frequent<br><br><br><br><br>Frequency unknown | Peripheral oedema*, hyponatraemia*, hypomagnesaemia, vitamin $B_{12}$ malabsorption<br>Severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia |
| Psychiatric disorders | Less frequent | Insomnia*, agitation*, confusion*, depression*, aggression*, hallucination* |
| Nervous system disorders | Frequent<br>Less frequent | Headache*<br>Dizziness*, paraesthesia*, somnolence*, taste disturbance* |
| Eye disorders | Less frequent | Blurred vision* |
| Ear and labyrinth disorders | Less frequent | Vertigo* |
| Respiratory, thoracic and mediastinal disorders | Less frequent | Bronchospasm* |
| Gastrointestinal disorders | Frequent<br><br><br><br>Less frequent | Abdominal pain*, diarrhoea*, flatulence*, nausea/vomiting*, constipation*, fundic gland polyps (benign)<br>Dry mouth*, stomatitis*, gastrointestinal candidiasis*, gastrointestinal infections, microscopic colitis |
| Hepatobiliary disorders | Less frequent<br><br><br>Frequency unknown | Increased liver enzymes*, hepatitis with or without jaundice*, hepatic encephalopathy*<br>Hepatic failure* |

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| | | |
|---|---|---|
| Skin and subcutaneous tissue disorders | Less frequent<br><br>Frequency unknown | Dermatitis*, pruritus*, urticaria*, rash*, alopecia*, photosensitivity*<br>Subacute cutaneous lupus erythematosus, erythema multiforme*, Stevens Johnson syndrome*, Toxic Epidermal Necrolysis (TEN)*, drug reaction with eosinophilia and systemic symptoms (DRESS)* |
| Musculoskeletal, connective tissue and bone disorders | Less frequent | Arthralgia*, myalgia*, muscular weakness*, fracture of the hips, wrists or spine |
| Renal and urinary disorders | Less frequent | Interstitial nephritis which may progress to acute kidney injury and/or chronic renal failure*, in some patient's renal failure has been reported concomitantly |
| Reproductive system and breast disorders | Less frequent | Gynaecomastia* |
| General disorders and administrative site conditions | Less frequent | Malaise*, hyperhidrosis* |

***Post marketing experience:**

The indicated (*) adverse events have also been reported during the post marketing use of TRULOC. Because these are spontaneous reports from a population of uncertain size, it is not possible to reliably estimate their frequency.

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows

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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:

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Management of overdose:

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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

ATC code: A02B C05

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

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## Mechanism of action

Esomeprazole, the S-isomer of omeprazole, reduces gastric acid secretion through specific inhibition of the acid pump in the parietal cell, where it is concentrated and converted to the active form in the acidic environment of the secretory canaliculi and inhibits the enzyme H+K+-ATPase – the acid pump. This effect on the final step of the gastric acid secretion is dose-dependent and provides for effective inhibition of both basal and stimulated acid secretion.

*Effect on gastric acid secretion*

After oral dosing with esomeprazole 20 mg and 40 mg, the onset of effect occurs within 1 hour. After repeated administration with 20 mg esomeprazole once daily for 5 days, mean peak acid output after pentagastrin stimulation is decreased by 90 % when measured 6 - 7 hours after dosing on day 5.
After 5 days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic Gastro-oesophageal Reflux Disease (GORD) patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours were 76 %, 54 % and 24 % respectively for esomeprazole 20 mg. Corresponding proportions for esomeprazole 40 mg were 97 %, 92 % and 56 % respectively.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.
Food intake had no significant influence on the effect of esomeprazole on intragastric acidity.

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*Other effects related to acid inhibition*

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

## 5.2 Pharmacokinetic properties

**Absorption:**

Esomeprazole is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1 - 2 hours after dose. The absolute bioavailability is 89 % after repeated once-daily administration.

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

**Distribution:**

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

**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.

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**Elimination:**

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme (extensive metabolisers).

Total plasma clearance is about 17 litres per hour after a single dose and about 9 litres per hour after repeated administration. The plasma elimination half-life is about 1,3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose-dependency is due to a decrease of first pass metabolism and systemic clearance, probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses, with no tendency for accumulation during once-daily administration.

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80 % of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1 % of the parent compound is found in urine.

**Pharmacokinetics in special patient groups**

*Poor Metabolisers*

Approximately 2,9 ± 1,5 % of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100 % higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60 %. These findings have no implications for the posology of

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esomeprazole.

*Hepatic Insufficiency*

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

*Renal Insufficiency*

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

*Gender*

Following a single dose of 40 mg esomeprazole, the mean area under the plasma concentration-time curve is approximately 30 % higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of esomeprazole.

*Elderly*

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

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age).

**Paediatric population**

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

## 5.3 Preclinical safety data

Not applicable.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

*Tablet cores:*

Copovidone (K28)

Crospovidone (Type A)

Diethyl phthalate

Ethyl cellulose

Hypromellose

Macrogol 8000

Magnesium oxide

Magnesium stearate

Maize starch

*Methacrylic acid - ethyl acrylate copolymer dispersion - (consist of methacrylic acid - ethyl acrylate*

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*copolymer, sodium lauryl sulphate, polysorbate 80)*

Povidone

Silica colloidal anhydrous

*Silicified microcrystalline cellulose (Prosolv HD 90) (consist of cellulose microcrystalline and silica colloidal anhydrous)*

Starlac (consists of lactose monohydrate and maize starch)

Sugar spheres (consist of maize, starch and sucrose)

Talc

*Film coating*

Hypromellose

Macrogol 8000

Talc

Titanium dioxide (E171)

Silica colloidal anhydrous

Ferric oxide red (E172)

*Printing ink*

*Opacode S-1-17823 black ink.*

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

24 months

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### 6.4 Special precautions for storage

Store at or below 25 °C

Store in the original package in order to protect from light and moisture.

### 6.5 Nature and contents of container

Alu/Alu blister packs containing 14, 28, 30, 60 or 90 tablets each, packed in a printed outer carton.

*Not all pack sizes will be marketed.*

### 6.6 Special precautions for disposal

No special requirements

## 7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

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Silverwood Close

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## 8. REGISTRATION NUMBER(S)

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