1.3.1.1 Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TRUSFLUKS 20 Gastro resistant tablets

TRUSFLUKS 40 Gastro resistant tabets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRUSFLUKS 20: Each Gastro resistant tablet contains 20 mg esomeprazole.

TRUSFLUKS 40: Each Gastro resistant tablet contains 40 mg esomeprazole.

Contains sugar:

TRUSFLUKS 20:

Lactose monohydrate 18,76 mg & Sucrose 6,3 mg

TRUSFLUKS 40:

Lactose monohydrate 37,52 mg & Sucrose 12,6 mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Gastro resistant Tablets

TRUSFLUKS 20: Pink, oblong, biconvex (approx. 12.15 mm x 6.15 mm), film-coated tablet, engraved ‘20’ on one side and plain on other.

TRUSFLUKS 40: Pink, oblong, biconvex (approx. 16.15 mm x 8.15 mm), film-coated tablet, engraved ‘40’ on one side and plain on other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

TRUSFLUKS tablets are indicated for:

- *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 NSAID therapy:*
  - prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug (NSAID) therapy in patients at risk
- In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori*:
  - healing of Helicobacter pylori associated duodenal ulcer
  - prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcer disease
- **TRUSFLUKS** has been used in pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion.

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 weeks 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 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.

In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* and

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

20 mg **TRUSFLUKS** 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 **TRUSFLUKS** 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.

Special populations

Elderly population

Dose adjustment is not required in the elderly.

Renal impairment

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

Hepatic impairment

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 **TRUSFLUKS** should be used.

Paediatric population

Adolescents 12-18 years:

Gastro-oesophageal Reflux Disease (GORD):

- treatment of erosive reflux oesophagitis

40 mg once daily for 4 weeks.

An additional 4 weeks 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 using 20 mg once daily under medical supervision.

Children:

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

No data is available.

Method of administration

For oral administration.

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

The tablets can also be dispersed in half a glass of non-carbonated water. No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered through a gastric tube.

4.3. Contraindications

TRUSFLUKS is contraindicated in:

- Patients with hypersensitivity to esomeprazole , substituted benzimidazoles or to any excipients in **TRUSFLUKS** (see section 6.1).
- Concomitant administration of **TRUSFLUKS** with atazanavir or nelfinavir (see section 4.5).

4.4. Special warnings and precautions for use

- **TRUSFLUKS** 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 **TRUSFLUKS** may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Tubulointerstitial nephritis

- Increased risk of subclinical acute or chronic interstitial nephritis associated with protein pump inhibitors (PPI's) leading to chronic renal inflammation and reduced renal function. The preferred term to describe the histological findings of tubular injury being "tubulointerstitial nephritis". Acute tubulointerstitial nephritis is characterised by an inflammatory reaction within the tubulointerstitial space of the kidney. Acute interstitial inflammatory reactions are associated with damage to the tubulointerstitium, leading to acute kidney injury.

Tubulointerstitial nephritis may be medicine-related, infectious, systemic, autoimmune, genetic, and idiopathic with the most common cause being related to a medication or medicine exposure.

- The risk of tubulointerstitial nephritis leading to chronic inflammation and reduced renal function associated with the use of protein pump inhibitors such as **TRUSFLUKS**, is a class effect.

Clopidogrel

- Co-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 **TRUSFLUKS** and clopidogrel should be avoided.

Interference with laboratory tests

- During treatment with antisecretory medicines, serum gastrin increases in response to the decreased acid secretion. Also, chromogranin A (CgA) increase due to decreased gastric acidity. The increased CgA level may interfere with

investigations for neuroendocrine tumours. To avoid this interference, **TRUSFLUKS** should be temporarily stopped days before CgA measurements.

Special Precautions:

Long term treatment

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

Gastrointestinal infections and Clostridium difficile

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

Absorption of vitamin B12 (Cyanocobalamin)

- **TRUSFLUKS**, 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.

Hypomagnesaemia

- Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like **TRUSFLUKS** 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 arrhythmia 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 on **TRUSFLUKS** or who take PPIs with digoxin or medicines that may cause hypomagnesaemia (e.g., diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Risk of fracture

- Proton pump inhibitors such as **TRUSFLUKS**, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10 to 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 22 should have an adequate intake of vitamin D and calcium.

Subacute cutaneous lupus erythematosus (SCLE).

- Proton pump inhibitors like **TRUSFLUKS**, are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping **TRUSFLUKS**. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Paediatric population

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

Excipients

TRUSFLUKS contains lactose monohydrate and sucrose.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

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

Medicines with pH dependent absorption

- The decreased intragastric acidity during treatment with **TRUSFLUKS** might increase or decrease the absorption of medicines if the mechanism of absorption is influenced by gastric acidity.

In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole, itraconazole and erlotinib can decrease while the absorption of medicines such as digoxin can increase during treatment with **TRUSFLUKS**.

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

Medicines metabolised by CYP2C19

Diazepam

- **TRUSFLUKS** inhibits CYP2C19, the major **TRUSFLUKS** metabolising enzyme. Concomitant administration of 30 mg **TRUSFLUKS** resulted in a 45 % decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

Phenytoin

- Concomitant administration of 40 mg **TRUSFLUKS** 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 is introduced or withdrawn.

Voriconazole

- **TRUSFLUKS** (40 mg once daily) increases voriconazole (a CYP2C19 substrate) Cmax and AUC by 15% and 41%, respectively.

Warfarin

- Concomitant administration of 40 mg **TRUSFLUKS** 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 International Normalised Ratio (INR) of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when warfarin is co-administered with **TRUSFLUKS** at initiation of treatment, during the treatment and at ending treatment.

Clopidogrel

- Concomitant use of **TRUSFLUKS** and clopidogrel should be avoided in healthy subjects due to 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 %.

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 Cmax

and AUC for cilostazol by 18 % and 26 % respectively, and one of its metabolites by 29 % and 69 % respectively.

- **TRUSFLUKS** can be suspected to have a similar effect.

Cisapride

- concomitant administration of 40 mg **TRUSFLUKS** resulted in a 32 % increase in area under the plasma concentration-time curve (AUC) and a 31 % prolongation of elimination half-life (t1/2) 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 by up to three-fold. In high-dose methotrexate administration a temporary withdrawal of **TRUSFLUKS** may need to be considered.

Tacrolimus

- Concomitant administration of **TRUSFLUKS** 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.

Antiretroviral medicines

- Omeprazole has been reported to interact with some antiretroviral medicines. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral medicines. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral medicines, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral medicines, such as saquinavir, increased serum levels have been

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

- Concomitant administration of **TRUSFLUKS** and antiretroviral medicines such as atazanavir and nelfinavir is not recommended. **TRUSFLUKS** substantially decreases the concentration of atazanavir and nelfinavir (see section 4.3).
- Co-administration of **TRUSFLUKS** (40 mg once daily) reduced mean nelfinavir exposure by approximately 40 % and the mean exposure of the pharmacological active metabolite was reduced by approximately 75 – 90 %.
- Tipranavir may decrease the concentration of **TRUSFLUKS**. Co-administration is not recommended. However, if used concurrently, the dose of **TRUSFLUKS** should be increased.

Investigated medicines with no clinically relevant interaction

- **ULICIUM** has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.
- Studies evaluating concomitant administration of **TRUSFLUKS** and either naproxen (non-selective NSAID) or rofecoxib (COX-2-selective NSAID) did not identify any clinically relevant interaction.

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

Medicines which inhibit CYP2C19 and/or CYP3A4

- **TRUSFLUKS** is metabolised by CYP2C19 and CYP3A4. Concomitant administration of **TRUSFLUKS** and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to **TRUSFLUKS**. Concomitant administration of **TRUSFLUKS** and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than tripling of the **TRUSFLUKS** exposure. Dose adjustment of **TRUSFLUKS** is not required.

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 rifampicin and St. John's Wort) may lead to decreased **TRUSFLUKS** esomeprazole serum levels by increasing the metabolism of **TRUSFLUKS**.

4.6 Fertility, pregnancy and lactation

The safety of **TRUSFLUKS** in pregnancy and lactation has not been established.

Pregnancy

Clinical data on exposed pregnancies with **TRUSFLUKS** 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

It is not known whether **TRUSFLUKS** is excreted in human breast milk. There is insufficient information on the effects of esomeprazole in newborns/infants. **TRUSFLUKS** should not be used during breast-feeding.

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

TRUSFLUKS has moderate influence on the ability to drive and use machines. Since adverse reactions such as dizziness and blurred vision have been reported in patients receiving **TRUSFLUKS**, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that **TRUSFLUKS** does not adversely affect their ability to do so (see section 4.4 and/or 4.8).

4.8 Undesirable effects

a) Summary of the safety profile

Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported in clinical trials (and also from post-marketing use) for **TRUSFLUKS**. In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.

b) Tabulated list of adverse reactions

The following adverse reactions have been identified or suspected in the clinical trials programme for **TRUSFLUKS**. None, however, were found to be dose related.

System organ **class**	**Frequent**	**Less frequent**
Blood and the lymphatic **System disorders**		Leukopenia, thrombocytopenia

Immune system **disorders**		*Hypersensitivity reactions e.g. angioedema and* anaphylactic reaction/shock.
Metabolism and **Nutrition disorders**		*Peripheral oedema, hyponatraemia, hypomagnesaemia, severe hypomagnesaemia may result in hypocalcaemia,* hypomagnesaemia may also result in hypokalaemia.
Psychiatric **disorders**		*Insomnia, agitation, confusion, depression, aggression,* hallucination.
Nervous system **disorders**	Headache	Dizziness, paraesthesia, somnolence, taste disturbance.
Eye disorders		Blurred vision
Ear and labyrinth **disorders**		Vertigo
Respiratory, thoracic and mediastinal **disorders**		Bronchospasm
Gastrointestinal **disorders**	*Abdominal pain, diarrhoea, flatulence,* nausea/vomiting, constipation.	*Dry mouth, stomatitis, gastrointestinal candidiasis,* gastrointestinal infections, microscopic colitis.
Hepato-biliary **disorders**		*Increased liver enzymes, hepatitis with or without* jaundice, hepatic encephalopathy.
Skin and subcutaneous **tissue disorders**		Dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity.
Musculoskeletal and connective **tissue disorders**		Arthralgia, myalgia, fracture of the hip, wrist or spine.
Reproductive system and **breast disorders**		Gynaecomastia.
General disorders and administrative		Malaise, hyperhydrosis

site conditions		

Post marketing experience:

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

***System organ* class**	**Frequency unknown**
***Blood and the lymphatic system* disorders**	Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia.
***Immune system* disorders**	Hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock.
***Metabolism and* nutrition disorders**	*Peripheral oedema, hyponatraemia, hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia, hypomagnesaemia may also* result in hypokalaemia.
***Psychiatric* disorders**	Insomnia, agitation, confusion, depression, aggression, hallucination.
***Nervous system* Disorders**	Headache, dizziness, paraesthesia, somnolence, taste disturbance.
Eye disorders	Blurred vision
***Ear and labyrinth* Disorders**	Vertigo
***Respiratory, thoracic and mediastinal* disorders**	Bronchospasm
***Gastrointestinal* disorders**	*Abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation, dry* mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis.
***Hepato-biliary* Disorders**	Increased liver enzymes, hepatitis with or without jaundice, hepatic encephalopathy, hepatic failure.
Skin and subcutaneous	Dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity, erythema multiforme, Stevens-

tissue disorders	Johnson syndrome, toxic epidermal necrolysis (TEN).
***Musculoskeletal and connective* tissue disorders**	Arthralgia, myalgia, muscular weakness.
***Renal and urinary* disorders**	Interstitial nephritis.
***Reproductive system and breast* disorders**	Gynaecomastia.
***General disorders and administrative* site conditions**	Malaise, hyperhidrosis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are 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.

HOTLINE for reporting of side effects directly to Innovata Pharmaceuticals (Pty) Ltd:

086 999 0912

4.9 Overdose

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).

Treatment

No specific antidote is known. **TRUSFLUKS** is extensively plasma protein bound and is therefore not readily dialysable. Treatment should be symptomatic and general supportive measures should be utilised.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and class: A 11.4.3 Medicines acting on gastro-intestinal tract.

Pharmacotherapeutic group: Proton pump inhibitors.

ATC code: A02BC05.

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 to 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.

Other effects related to acid inhibition:

During treatment with antisecretory medicines serum gastrin increases in response to the decreased acid secretion.

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 to 2 hours after dose.

Distribution

The absolute bioavailability is 89 % after repeated once-daily administration. The apparent volume of distribution at steady state in healthy subjects is approximately 0, 22 litres per 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.

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.

Special patient populations:

Approximately 1-2 % 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 %.

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

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.

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.

Elimination

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 populations

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Acetone, croscarmellose sodium, crospovidone, ethanol, ethyl alcohol, glyceryl monostearate, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, methacrylic

acid-ethyl acrylate copolymer (1:1), microcrystalline cellulose, opadry pink: (hypromellose, iron oxide red, &yellow, macrogol/PEG and titanium dioxide), polysorbate, povidone, purified water, silica colloidal anhydrous, sodium hydroxide, sodium stearyl fumarate, sugar sphere: (povidone, starch & sucrose), talc and triethyl citrate.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store in a cool, dry place, at or below 30 ˚C. protect from light and moisture.

6.5. Nature and contents of container

TRUSFLUKS 20 mg

Forming film: Alu/Alu Base Foil (OPA(25µ) + Alu (45µ) + PVC (60µ)film)

Lidding foil: Plain Aluminum Foil (heat seal lacquer coating)

Pack sizes: 28’s (4x7) packed in a pre-printed cartons with a packaging leaflet.

TRUSFLUKS 40 mg

Forming film: Alu/Alu Base Foil (OPA(25µ) + Alu (45µ) + PVC (60µ)film)

Lidding foil: Plain Aluminum Foil (heat seal lacquer coating)

Pack sizes: 28’s (4x7) packed in a pre-printed cartons with a packaging leaflet.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product.

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

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals (Pty) Ltd

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. REGISTRATION NUMBER

TRUSFLUKS 20: 59/11.4.3/0325
TRUSFLUKS 40: 59/11.4.3/0326

9. DATE OF FIRST AUTHORISATION

[To be allocated by SAHPRA upon registration]

10. DATE OF REVISION OF TEXT