PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINAL PRODUCT
FLUXTRIN 20 gastro-resistant tablets
FLUXTRIN 40 gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FLUXTRIN 20
Each gastro-resistant tablet contains esomeprazole magnesium equivalent to 20 mg esomeprazole.
Contain sugar: sucrose 14,6 mg and lactose monohydrate 31,88 mg
FLUXTRIN 40
Each gastro-resistant tablet contains esomeprazole magnesium equivalent to 40 mg esomeprazole.
Contains sugar: sucrose 29,26 mg and lactose monohydrate 63,75 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Gastro-resistant tablets
FLUXTRIN 20
Brick red coloured, round shape, biconvex, film coated tablets, imprinted with "20" on one side with black ink and plain on other side.
FLUXTRIN 40
Brick red coloured, round shape, beveled edge, biconvex, film coated tablets, imprinted with "40" on one side with black ink and plain on other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
FLUXTRIN 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 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 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.

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

4.2 Posology and method of administration
Posology
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.
  If gastroesophageal 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

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 FLUXTRIN 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 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.

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 FLUXTRIN should be used.

Elderly:
Dose adjustment is not required in the elderly.

Paediatric population:
FLUXTRIN should not be used in children younger than 1 year since no data is available.

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

4.3 Contraindications
Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of FLUXTRIN.
Concomitant administration of FLUXTRIN with atazanavir or nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use
FLUXTRIN 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 FLUXTRIN may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Acute interstitial nephritis (AIN)
There is an increased risk of subclinical acute interstitial nephritis (AIN), associated with proton pump inhibitors (PPIs), such as FLUXTRIN 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.

On demand treatment
Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character.
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.
Helicobacter pylori eradication
When prescribing esomeprazole for eradication of *Helicobacter pylori*, possible interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other medicines
metabolised via CYP3A4 such as cisapride.

sAbsorption of vitamin B12
Esomeprazole, 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 esomeprazole 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 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 of the wrist, hips or spine
Proton pump inhibitors, 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 10-40 %. 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 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 FLUXTRIN SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

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 FLUXTRIN and clopidogrel should be avoided.

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, the esomeprazole treatment should be temporarily stopped 5 days before CgA measurements.

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.

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

Decreased gastric acidity due to any means including proton pump inhibitors such as FLUXTRIN tablets, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with FLUXTRIN may lead to increased risk of gastrointestinal infections such as Salmonella and Campylobacter and also *Clostridium difficile* in hospitalised patients.

FLUXTRIN contains lactose and sucrose
Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency, sucrase – isomaltase insufficiency, glucose-galactose malabsorption should not take FLUXTRIN.

4.5 Interactions with other medicines and other forms of interaction
Effects of FLUXTRIN on the pharmacokinetics of other medicines:
The gastric acid suppression during treatment with FLUXTRIN, 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 FLUXTRIN.
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 FLUXTRIN is given at high doses in elderly patients. Therapeutic monitoring of digoxin levels should be done.

FLUXTRIN inhibits CYP2C19, the major FLUXTRIN metabolising enzyme. Concomitant administration of 30 mg FLUXTRIN 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 FLUXTRIN resulted in a 13 % increase in trough plasma levels of phenytoin in epileptic patients.

Concomitant administration of 40 mg FLUXTRIN 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 FLUXTRIN at initiation of treatment, during the treatment and at ending treatment.

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 FLUXTRIN and clopidogrel should be avoided.

Omeprazole as well as esomeprazole act as inhibitors of CYP 2C19. Omeprazole given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and AUC for Page 11 of 24 cilostazol by 18 % and 26 % respectively, and one of its metabolites by 29 % and 69 % respectively. FLUXTRIN can be suspected to have a similar effect.

In concomitant administration of 40 mg FLUXTRIN 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.

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 FLUXTRIN may need to be considered.

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

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

Concomitant administration of FLUXTRIN may significantly reduce the plasma levels of atazanavir.

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.
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 %. FLUXTRIN 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 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.

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

Effects of other medicinal products on the pharmacokinetics of FLUXTRIN:
FLUXTRIN is metabolised by CYP2C19 and CYP3A4. Concomitant administration of FLUXTRIN and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to FLUXTRIN. Concomitant administration of FLUXTRIN and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than tripling of the FLUXTRIN exposure. Dose adjustment of FLUXTRIN is not required.

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.

4.6 Fertility, pregnancy and lactation
Pregnancy
Safety during pregnancy has not been established.

Breastfeeding
Safety during lactation has not been established.

4.7 Effects on ability to drive and use machines
FLUXTRIN may cause dizziness and blurred vision, thereby affecting the ability to drive or use machinery.

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). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations.

b) Tabulated summary of adverse reactions

Blood and lymphatic system disorders	
Less Frequent:	Leukopenia, thrombocytopenia
Immune System Disorders	
Less Frequent:	Hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders	
Less Frequent:	Peripheral oedema, hyponatraemia, hypomagnesaemia
Frequency Unknown:	Severe hypermagnesaemia 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:	Headache
Less Frequent:	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:	Abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation, fundic gland polyps (benign)
Less Frequent:	Dry mouth, Stomatitis, gastrointestinal candidiasis, gastrointestinal infections, microscopic colitis
Hepatobiliary disorders	
Less Frequent:	Increased liver enzymes, hepatitis with or without jaundice, hepatic encephalopathy
Skin and Subcutaneous Tissue Disorders	
Less Frequent:	Dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity
Frequency Unknown:	Subacute cutaneous lupus erythematosus
Musculoskeletal and connective tissue Disorders	
Less Frequent:	Arthralgia, myalgia, Muscular weakness.
Renal and urinary disorders	
Less Frequent:	Interstitial nephritis, in some patient's renal failure has been reported concomitantly
Reproductive system and breast disorders	
Less Frequent:	Gynaecomastia
General disorders and administration site conditions	
Less Frequent:	Malaise, hyperhidrosis

Post marketing experience
Blood and 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
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.
Hepatobiliary disorders:
Increased liver enzymes, hepatitis with or without jaundice, hepatic encephalopathy, hepatic failure.
Skin and subcutaneous tissue disorders:
Dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
Musculoskeletal, connective tissue and bone disorders:
Arthralgia, myalgia, muscular weakness
Renal and urinary disorders:
Interstitial nephritis
Reproductive system and breast disorders:
Gynaecomastia
General disorders and administration site conditions:
Malaise, hyperhidrosis

4.9 Overdose
No specific antidote is known. FLUXTRIN 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 inhibitors.
ATC Code: A02B C05

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 one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased by 90 % when measured 6-7 hours after dosing on day five.

After five 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 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.

Metabolism
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 (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 CYP2C 19 enzyme by esomeprazole and/ or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

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

Special population
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 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 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 active substance concentration (t_{max}) in 12 to 18 year-olds was similar to that in adults for both esomeprazole doses.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sugar spheres (sucrose and maize starch), ethylcellulose, magnesium stearate, povidone (K-90), light magnesium oxide, sodium lauryl sulfate, polysorbate 80, methacrylic acid – ethyl acrylate copolymer, diethyl phthalate, talc (purified), cellulose microcrystalline, silica colloidal anhydrous, lactose monohydrate, maize starch, copovidone (K-28), macrogol 8000, crospovidone (type A), silica colloidal anhydrous, hypromellose, titanium dioxide (E171), ferric oxide red (E172), opacode S-1-17823 black ink (contains shellac glaze, isopropyl alcohol, iron oxide black, n-butyl alcohol, propylene glycol and ammonium hydroxide).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months
Shelf life after first opening of the bottle: 100 days

6.4 Special precautions for storage
Store at or below 30 °C.
Store in original package to protect from light and moisture.

6.5 Nature and contents of container
Aluminium – Aluminium blister pack using Aluminium foil with heat seal lacquer and cold formable blister aluminium foil. The blister strips are packed in cartons.
HDPE container (High Density Polyethylene container of neck finish with induction sealing wad and a silica gel canister as desiccant).

Pack sizes:
14, 28, 30, 56 and 100 gastro-resistant tablets
Not all packs and pack sizes may be marketed.

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

7. MARKETING AUTHORISATION HOLDER
TRINITY PHARMA (PTY) LTD
3 Gwen Lane, 4th Floor,
Sandton, 2031.
Contact No.: +27 (0)10 594 5610
PV Email Address: pv@trinitypharma.co.za

8. MARKETING AUTHORISATION NUMBER(S)
FLUXTRIN 20 : 50/11/4/3/0076
FLUXTRIN 40 : 50/11/4/3/0077

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 30 November 2021
Date of latest renewal: N.A

10. DATE OF REVISION OF THE TEXT
N.A

TRINITY PHARMA

Tel: 010 594 5610. Email: PV@kahmagroup.co.za

VOORGESTELDE PROFESSIONELE INLIGTING

SKEDULERINGSTATUS: S4

1. NAAM VAN DIE MEDISYNE
FLUXTRIN 20 gastries-bestande tablette
FLUXTRIN 40 gastries-bestande tablette

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

FLUXTRIN 20
Elke gastries-bestande tablet bevat esomeprasoolmagnesium gelykstaande aan 20 mg esomeprasool.
Bevat suiker: sukrose 14,6 mg en laktosemonohidraat 31,88 mg
FLUXTRIN 40
Elke gastries-bestande tablet bevat esomeprasoolmagnesium gelykstaande aan 40 mg esomeprasool.
Bevat suiker: sukrose 29,26 mg en laktosemonohidraat 63,75 mg

Vir 'n volledige lys van hulpstowwe, sien afdeling 6.1.

3. FARMASEUTIESE VORM
Gastries-bestande tablette.

FLUXTRIN 20
Baksteen-rooi gekleurde, ronde vorm, bikonvekse, film-bedekte tablette, ingeprent met '20' aan die een kant met swart ink en plein aan die ander kant.
FLUXTRIN 40
Baksteen-rooi gekleurde, ronde vorm, skuins-rand, bikonvekse, film-bedekte tablette, ingeprent met '40' aan die een kant met swart ink en plein aan die ander kant.

4. KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
FLUXTRIN is geïndikeerd vir die volgende (sien afdelings 4.4 en 5.1):
Gastroesofageale Reflukssiekte (GERS):
- behandeling van eroderende refluksesofagitis,
- langtermynbehandeling van pasiënte met geneesde esofagitis om 'n terugval te voorkom,
- simptomatiese behandeling van gastroesofageale Reflukssiekte (GERS).

Pasiënte wat volgehoue NSAIM-behandeling benodig:
- voorkoming van gastriese en duodenale ulkusse wat met nie-steroïed anti-inflammatoriese middel (NSAIM)-behandeling geassosieerd word by pasiënte wat in gevaar is daarvan.

In kombinasie met toepaslike antibakteriële terapeutiese regime vir die uitwissing van Helicobacter pylori:
- genesing van *Helicobacter pylori*-geassosieerde duodenale ulkus en,
- voorkoming van 'n terugkeer van 'n peptiese ulkus by pasiënte met *Helicobacter pylori*-geassosieerde ulkussiekte.

FLUXTRIN word gebruik by patologiese hipersekresie-aandoenings insluitend Zollinger-Ellison-sindroom en idiopatiese hipersekresie.

4.2 Posologie en metode van toediening
Posologie
Gastroesofageale Reflukssiekte (GERS):
- behandeling van eroderende refluks esofagitis:
  40 mg een maal per dag vir 4 weke.
  'n Addisionele 4-week-behandeling word aanbeveel vir pasiënte by wie esofagitis nog nie genees is nie, of wat volgehoue simptome toon.
  Indien gastroesofageale refluksiekte(GERS)-simptoombeheer nie bereik is na vier weke van behandeling met die voorgeskrewe daaglikse dosis nie, veral waar differensiasie van diagnose van GERS met angina en kongestiewe hartversaking teenwoordig is, word verdere ondersoek aanbeveel.
- langtermyn behandeling van pasiënte met geneesde esofagitis om 'n terugval te voorkom:
  20 mg een maal per dag.
- simptomatiese behandeling van gastroesofageale Reflukssiekte (GERS):
  20 mg een maal per dag by pasiënte sonder esofagitis.
  Indien simptoombeheer nie bereik word na 4 weke nie, moet die pasiënt verder ondersoek word. Sodra simptome opgeklaar het, kan daaropvolgende simptoombeheer verkry word deur behandeling op versoek met 20 mg een maal daagliks wanneer nodig.

Pasiënte wat volgehoue NSAIM-behandeling benodig:
- voorkoming van gastriese en duodenale ulkusse geassosieerd met NSAIM-behandeling by pasiënte op risiko:
  20 mg of 40 mg een maal daagliks.

In kombinasie met toepaslike antibakteriële terapeutiese regimes vir die uitwissing van Helicobacter pylori en genesing van Helicobacter pylori-geassosieerde duodenale ulkus en voorkoming van die terugkeer van peptiese ulkusse by pasiënte met Helicobacter pylori-geassosieerde ulkussiekte:
- 20 mg FLUXTRIN met 1 g amoksisillien en 500 mg klaritromisien, almal twee maal per dag vir 7 dae.

Patologiese hipersekresie-aandoenings insluitend Zollinger-Ellison-sindroom en idiopatiese hipersekresie:
- Die aanbevole aanvanklike dosis is 40 mg twee maal daagliks. Die dosis moet dan individueel aangepas word en die behandeling moet voortgesit word solank dit klinies aangedui is. Dosisse tot 120 mg twee maal per dag is al toegedien.

Adolessente 12-18 jaar:
Gastroesofageale reflukssiekte (GERS):
- behandeling van eroderende refluksesofagitis:
  40 mg een maal daagliks vir 4 weke
  'n Addisionele 4-week-behandeling word aanbeveel vir pasiënte by wie esofagitis nie genees het nie, of wat hardnekkige simptome ervaar.
- langtermynbehandeling van pasiënte met geneesde esofagitis om terugval te voorkom: 20 mg een maal daagliks.
- Simptomatiese behandeling van Gastroesofageale Reflukssiekte (GERS):
  20 mg een maal daagliks by pasiënte sonder esofagitis.
  Indien simptoombeheer nie bereik word na 4 weke nie, moet die pasiënt verder ondersoek word. Sodra simptome opgeklaar het, kan daaropvolgende simptoombeheer verkry word deur behandeling op versoek met 20 mg een maal daagliks wanneer nodig.

Dosisse bo 1 mg/kg/dag is nie bestudeer nie.

Spesiale populasies
Verswakte renale funksie:
Dosisaanpassing is nie nodig by pasiënte met verswakte renale funksie nie. As gevolg van beperkte ervaring by pasiënte met erge renale ontoereikendheid, moet sulke pasiënte met omsigtigheid behandel word.

Verswakte hepatiese funksie:
Dosisaanpassing is nie nodig by pasiënte met ligte tot matige lewer inkorting nie. Vir pasiënte met erge lewer inkorting, moet 'n maksimum daaglikse dosis van 20 mg FLUXTRIN gebruik word.

Bejaardes:
Dosisaanpassing is nie nodig by bejaardes nie.

Pediatriese populasie:
FLUXTRIN moet nie by kinders jonger as 1 jaar gebruik word nie, aangesien geen data beskikbaar is nie.

Metode van toediening
Die tablet moet heel ingesluk word met water. Die tablet moet nie gekou of fyngemaak word nie.

4.3 Kontraïndikasies
Bekende hipersensitiwiteit vir esomeprasool, gesubstitueerde bensimidasool of enige ander bestanddele van FLUXTRIN.
Gelyktydige toediening van FLUXTRIN met atasanavir of nelfinavir (sien afdeling 4.5).

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
FLUXTRIN is nie aangedui vir ligte gastrointestinale klagtes soos nerweuse dispepsie nie.

Voor die behandeling van of in die teenwoordigheid van enige waarskuwingsimptoom (bv. beduidende onbeplande gewigsverlies, herhalende braking, disfagie, hematemese of melena) en wanneer 'n gastriese ulkus vermoed word of teenwoordig is, behoort die moontlikheid van maligniteit van 'n gastriese ulkus of 'n maligne siekte van die esofagus uitgesluit te word, aangesien die behandeling met FLUXTRIN die simptome van maligne ulkusse kan verlig en sodoende diagnose kan vertraag.

Akute interstisiële nefritis (AIN)
Daar is 'n verhoogde risiko vir subkliniese akute interstisiële nefritis (AIN), geassosieerd met protonpompinhibeerders (PPIs), soos FLUXTRIN, wat kan lei tot akute renale skade en/of chroniese renale versaking. Simptome van interstisiële nefritis kan voortduur, selfs wanneer behandeling met die PPI gestaak word.

Behandeling op versoek
Pasiënte wat op versoek behandel word, moet opdrag gegee word om hul geneesheer te kontak indien hulle simptome verander in karakter.

Tydens langtermyn orale behandeling met esomeprasool vorm daar gastriese klieragtige siste. Hierdie veranderinge is 'n fisiologiese gevolg van 'n uitgesproke inhibering van suurafskeiding, is benigne en skynbaar omkeerbaar.

Helicobacter pylori uitwissing
Wanneer esomeprasool voorgeskryf word vir die uitroei van *Helicobacter pylori*, moet moontlike interaksies vir alle komponente in die drievoudige terapie oorweeg word. Klaritromisien is 'n kragtige inhibeerder van CYP3A4 en dus moet kontraïndikasies en interaksies vir klaritromisien oorweeg word wanneer die drievoudige terapie gebruik word by pasiënte wat gelyktydig ander medisyne neem wat deur CYP3A4 gemetaboliseer word, soos sisaprid.

Absorpsie van vitamien B_{12}
Esomeprasool, soos alle suur-blokkerende medisyne, kan die opname van vitamien B_{12} (sianokobalamien) verminder as gevolg van hipo- of achloorhidrie. Hierdie moet oorweeg word by pasiënte met verminderde liggaamsstore of risikofaktore vir verminderde opname van vitamien B_{12} op langtermynterapie.

Hipomagnesemie
Erge hipomagnesemie is aangemeld by pasiënte wat met protonpompinhibeerders (PPIs), soos esomeprasool, behandel was vir minstens drie maande en in die meeste gevalle vir 'n jaar. Erge manifestasies van hipomagnesemie soos moegheid, tetanie, delirium, konvulsies, duiseligheid en ventrikulêre disritmie kan voorkom, maar dit kan bedrieglik begin en oor die hoof gesien word. In die pasiënte wat die meeste geaffekteer was, het hipomagnesemie verbeter na die vervanging van magnesium en staking van die PPI.
Vir pasiënte wat verwag word om op langtermynbehandeling te wees of dié wat PPIs met digoksien of medisyne neem wat hipomagnesemie kan veroorsaak (bv. diuretika), moet gesondheidsorg deskundiges dit oorweeg om magnesiumvlakke te meet voordat PPI-behandeling begin word en periodiek tydens behandeling.

Risiko vir frakture van die pols, heupe of ruggraat
Protonpompinhibeerders, veral as dit in hoë dosisse en oor 'n lang duur (> 1 jaar) gebruik word, kan die risiko van heup-, pols- en ruggraatfrakture matig verhoog, hoofsaaklik by bejaardes of in teenwoordigheid van ander erkende risikofaktore. Waarnemingsstudies dui daarop dat protonpompinhibeerders die totale risiko van frakture met 10-40 % kan verhoog. Sommige van hierdie verhogings kan wees as gevolg van ander risikofaktore. Pasiënte op risiko vir osteoporose, moet sorg ontvang volgens die huidige kliniese riglyne en hulle moet voldoende vitamien D en kalsium inname hê.

Sub-akute Kutaneuse Lupus Eritematose (SKLE)
Protonpompinhibeerders word geassosieer met seldsame gevalle van SKLE. As letsels voorkom, veral in son-blootgestelde areas van die vel, en as dit gepaard gaan met artralgie, moet die pasiënt onmiddellik mediese hulp soek en die gesondheidsorg deskundige moet dit oorweeg om FLUXTRIN te staak. SKLE na vorige behandeling met 'n protonpompinhibeerder kan risiko van SKLE met ander protonpompinhibeerders verhoog.

Gelyktydige toediening van klopidogrel en esomeprasool het gelei tot 'n afname in blootstelling aan die aktiewe metaboliet van klopidogrel met 'n gemiddeld van 40 %. Die maksimum inhibisie van (ADP-geïnduseerde) plaatjie-aggregasie het afgeneem met 'n gemiddeld van 14 %. Op grond van hierdie data, moet die gesamentlike gebruik van FLUXTRIN en klopidogrel vermy word.

Tydens behandeling met anti-sekretoriese medisyne neem die serum-gastrien toe in reaksie op die verminderde suurafskeiding. Chromogranien A (CgA) neem ook toe as gevolg van die verminderde gastriese asiditeit. Die verhoogde CgA-vlak kan inmeng met die ondersoeke vir neuro-endokriene gewasse. Om hierdie inmenging te voorkom, moet die esomeprasool-behandeling 5 dae voor CgA-metings tydelik gestaak word.

Clostridium difficile is 'n bakterie wat erge uitmergelende diarree kan veroorsaak wat nie verbeter nie. Simptome kan waterige stoelgange, abdominale pyn, en koors insluit, en pasiënte kan erger intestinale toestande ontwikkel.

Pasiënte op langtermynbehandeling (veral diegene wat langer as 'n jaar behandel word) moet onder gereelde toesig gehou word.

Verlaagde gastriese asiditeit as gevolg van enige middel, insluitend protonpompinhibeerders soos FLUXTRIN tablette, verhoog die gastriese telling van bakterieë wat normaalweg in die spysverteringskanaal voorkom. Behandeling met FLUXTRIN kan lei tot 'n verhoogde risiko vir gastrointestinale infeksies soos *Salmonella* en *Campylobacter*, asook *Clostridium difficile* by gehospitaliseerde pasiënte.

FLUXTRIN bevat laktose
Pasiënte met die seldsame oorerflike toestande van galaktose-onverdraagsaamheid, totale laktase-tekort, glukose-galaktose wanabsorpsie moet nie FLUXTRIN neem nie

4.5 Interaksie met ander medisyne en ander vorms van interaksie
Effekte van FLUXTRIN op die farmakokinetika van ander medisyne:
Die gastriese suur-onderdrukking tydens behandeling met FLUXTRIN, kan die opname van medisyne met 'n pH-afhanklike absorpsie van die maag verminder of verhoog. Die absorpsie van medisyne soos ketokonasool, itrakonasool en erlotinib kan afneem, terwyl die absorpsie van medisyne soos digoksien kan toeneem tydens behandeling met FLUXTRIN.
Gelyktydige behandeling met omeprasool (20 mg daagliks) en digoksien by gesonde proefpersone het die biobeskikbaarheid van digoksien met 10 % verhoog (tot 30 % by 2 uit 10 proefpersone). Digoksientoksisiteit was aangemeld. Sorg word aanbeveel wanneer FLUXTRIN gegee word teen hoë dosisse by ouer pasiënte. Terapeutiese monitering van digoksienvlakke moet gedoen word.

FLUXTRIN inhibeer CYP2C19, die belangrikste FLUXTRIN metaboliserende ensiem. Gelyktydige toediening van 30 mg FLUXTRIN het gelei tot 'n 45 % afname in die opruiming van hierdie CYP2C19-substraat van diasepaam. Dit is onwaarskynlik dat hierdie interaksie van kliniese belang is. Gelyktydige toediening van 40 mg FLUXTRIN het gelei tot 'n toename van 13 % in die trogplasmavlakke van fenitoïen by epileptiese pasiënte.

Gelyktydige toediening van 40 mg FLUXTRIN aan pasiënte wat met warfarien behandel word, het getoon dat, ondanks 'n verhoging in die trogplasmakonsentrasie van die minder kragtige R-isomeer van warfarien, was die stoltye binne die aanvaarde perke .

Vanuit na-bemarking gebruike, is gevalle van verhoogde IGV van kliniese belang aangemeld tydens gelyktydige behandeling met warfarien. Noukeurige monitering word aanbeveel wanneer warfarien gesamentlik toegedien word met FLUXTRIN by die aanvang van die behandeling, tydens behandeling en met die beëindiging van behandeling.

Resultate uit studies by gesonde proefpersone het getoon dat daar 'n farmakokinetiese/ farmakodinamiese interaksie is tussen klopidogrel (300 mg ladingsdosis/75 mg daaglikse onderhoudsdosis) en esomeprasool (40 mg p.o. daagliks) wat lei tot 'n verminderde blootstelling aan die aktiewe metaboliet van klopidogrel met 'n gemiddeld van 40 % en lei tot 'n verminderde maksimum inhibisie van (ADP-geïnduseerde) plaatjie-aggregasie met 'n gemiddeld van 14 %. Op grond van hierdie data, moet die gesamentlike gebruik van FLUXTRIN en klopidogrel vermy word.

Omeprasool sowel as esomeprasool dien as inhibeerders van CYP 2C19. Omeprasool gegee in dosisse van 40 mg aan gesonde proefpersone in 'n oorkruis studie, het C_{maks} en AOK vir silostasool met onderskeidelik 18 % en 26 % verhoog, en een van sy metaboliete met onderskeidelik 29 % en 69 %. FLUXTRIN kan verwag word om 'n soortgelyke effek te toon.

Gelyktydige toediening van 40 mg FLUXTRIN het gelei tot 'n 32 % toename in die area onder die plasmakonsentrasie-tydkurwe (AOK) en 'n 31 % verlenging van die eliminasie-halfleeftyd (t½), maar geen noemenswaardige toename in die piekplasmavlakke van sisaprid nie. Hierdie interaksie het nie die invloed van sisaprid op die kardiale elektrofisiologie verander nie.

As dit saam met protonpompinhibeerders gegee word, is dit by sommige pasiënte aangemeld dat metotreksaatvlakke toeneem. By hoë dosis metotreksaat toediening moet 'n tydelike onttrekking van FLUXTRIN oorweeg word.

FLUXTRIN het geen klinies relevante uitwerking getoon op die farmakokinetika van amoksisillien of kinidien nie.

Studies wat die gelyktydige toediening van FLUXTRIN en óf naproksen (nie-selektiewe NSAIM) óf rofekoksib (SOK-2-selektiewe NSAIM) evalueer, het geen klinies relevante interaksie geïdentifiseer nie.

Gelyktydige toediening van FLUXTRIN kan die plasmavlakke van atasanavir aansienlik verlaag.

Daar is gerapporteer dat omeprasool interaksies het met sommige antiretrovirale medisyne. Verhoogde gastriese pH tydens omeprasoolbehandeling kan die absorpsie van die antiretrovirale medisyne verander. Ander moontlike interaksiemeganismes is deur middel van CYP2C19. Vir sommige antiretrovirale medisyne, soos atasanavir en nelfinavir, is verlaagde serumvlakke gerapporteer wanneer dit saam met omeprasool gegee word, en gelyktydige toediening word nie aanbeveel nie.
Gelyktydige toediening van esomeprasool (40 mg een maal per dag) het gelei tot die gemiddelde blootstelling aan nelfinavir van ongeveer 40 % verminder en die gemiddelde blootstelling aan die farmakologies aktiewe metaboliet is met ongeveer 75-90 % verminder. FLUXTRIN verlaag die konsentrasie van nelfinavir aansienlik. Gelyktydige toediening met esomeprasool en antiretrovirale medisyne soos atasanavir en nelfinavir word nie aanbeveel nie.
Vir ander antiretrovirale medisyne, soos sakinavir is verhoogde serumvlakke van 80-100 % gerapporteer. Daar is ook 'n paar antiretrovirale medisyne waarvoor onveranderde serumvlakke gerapporteer is wanneer dit saam met omeprasool gegee is. Noukeurige monitering of dosisverandering word aanbeveel.

Tipranavir kan die konsentrasie van FLUXTRIN verlaag. Gelyktydige toediening word nie aanbeveel nie. Alhoewel, indien dit gelyktydig gebruik word, moet die dosis FLUXTRIN verhoog word.

Effekte van ander medisyne op die farmakokinetika van FLUXTRIN:
FLUXTRIN word gemetaboliseer deur CYP2C19 en CYP3A4. Gelyktydige toediening van FLUXTRIN en 'n CYP3A4-inhibeerder, klaritromisien (500 mg b.i.d.) het gelei tot 'n verdubbeling van die blootstelling (AOK) van FLUXTRIN gelei. Gelyktydige toediening van FLUXTRIN en 'n gekombineerde inhibeerder van CYP2C19 en CYP3A4, soos vorikonasool, kan lei tot meer as verdriedubbeling van die blootstelling aan FLUXTRIN. Dosisaanpassing van FLUXTRIN word nie vereis nie.

Medisyne wat bekend is dat dit CYP2C19 of CYP3A4 of albei induseer (soos rifampisien en Sint-Janskruid) kan lei tot verlaagde esomeprasoolserumvlakke deur die esomeprasool-metabolisme te verhoog.

4.6 Vrugbaarheid, swangerskap en laktasie
Swangerskap
Veiligheid tydens swangerskap is nie vasgestel nie.

Borsvoeding
Veiligheid tydens laktasie is nie vasgestel nie.

4.7 Uitwerking op die vermoë om te bestuur en masjiene te gebruik
FLUXTRIN kan duiseligheid en dowwe visie veroorsaak, en sodoende die vermoë om te bestuur of masjinerie te hanteer beïnvloed.

4.8 Newe-effekte
a) Opsomming van die veiligheidsprofiel
Hoofpyn, abdominale pyn, diarree en naarheid is van die newe-effekte wat die meeste in kliniese proewe (en ook na-bemarking) gerapporteer is. Daarbenewens is die veiligheidsprofiel soortgelyk vir verskillende formulerings, behandeling indikasies, ouderdomsgroepe en pasiënt populasies.

b) Getabuleerde opsomming van newe-effekte

Bloed- en Limfatiese Sisteemversteurings:	
Minder gereeld:	Leukopenie, trombositopenie
Immuunstelselversteurings:	
Minder gereeld:	Hipersensitiwiteitsreaksies, bv. angioedeem en anafilaktiese reaksie/skok
Metabolisme- en voedingsversteurings:	
Minder gereeld:	Perifere edeem, Hiponatremie, Hipomagnesemie
Frekwensie onbekend:	Erge hipermagnesemie kan korreleer met hipokalsemie. Hipomagnesemie kan ook geassosieerd word met hipokalemie.
Psigiatriese versteurings:	
Minder gereeld:	Insomnie, agitasie, verwarring, depressie, aggressie, hallusinasie.
Senusisteemversteurings:	
Gereeld:	Hoofpyn
Minder gereeld:	Duiseligheid, parestesie, slaperigheid, smaakversteuring
Oogversteurings:	
Minder gereeld:	Dowwe visie
Oor- en doolhofversteurings:	
Minder gereeld:	Vertigo
Respiratories-, torakale- en mediastinale versteurings:	
Minder gereeld:	Brongospasma
Gastroïntestinale versteurings:	
Gereeld:	Abdominale pyn, diarree, winderigheid, naarheid/braking, konstipasie, fundiese klier poliepe (benigne)
Minder gereeld:	Droë mond, stomatitis, gastroïntestinale kandidiase, gastroïntestinale infeksie, mikroskopiese kolitis
Hepato-biliêre versteurings:	
Minder gereeld:	Verhoogde lewerensieme, Hepatitis met óf sonder geelsug, hepatiese enkefalopatie
Vel- en Onderhuidse weefselversteurings:	
Minder gereeld:	Dermatitis, pruritus, urtikarie, uitslag, alopesie, fotosensitiwiteit
Frekwensie onbekend:	Sub-akute kutaneuse lupus eritematose
Muskuloskeletale bindweefselversteurings:	
Minder gereeld:	Artralgie, mialgie, spierswakheid
Nier- en urienweg afwykings:	
Minder gereeld:	Interstisiële nefritis, in sommige pasiënte was renale versaking gesamentlik aangemeld
Voortplantingstelsel- en borsafwykings:	
Minder gereeld:	Ginekomastie
Algemene siektes en toedieningsarea toestande	
Minder gereeld:	Malaise, hiperhidrose

Na-bemarkingservaring
Bloed- en Limfatiese Sisteemversteurings:
Leukopenie, trombositopenie, agranulositose, pankitopenie
Immuunstelselversteurings:
Hipersensitiwiteitsreaksies, bv. angioedeem en anafilaktiese reaksie/skok.
Metabolisme- en voedingsversteurings:
Perifere edeem, hiponatremie
Psigiatriese versteurings:
Insomnie, agitasie, verwarring, depressie, aggressie, hallusinasie
Senusisteemversteurings
Hoofpyn, duiseligheid, parestesie, slaperigheid, smaakversteuring
Oogversteurings:
Dowwe visie
Oor- en doolhofversteurings:
Vertigo
Respiratories-, torakale- en mediastinale versteurings:
Brongospasma
Gastroïntestinale versteurings:
Abdominale pyn, diarree, winderigheid, naarheid/braking, konstipasie, droë mond, stomatitis, gastroïntestinale kandidiase.
Hepato-biliêre versteurings:
Verhoogde lewer ensieme, hepatitis met óf sonder geelsug, hepatiese enkefalopatie, hepatiese versaking.
Vel- en Onderhuidse weefselversteurings:
Dermatitis, pruritus, urtikarie, uitslag, alopesie, fotosensitiwiteit, eriteem multiforme, Stevens-Johnson sindroom, toksiese epidermale nekrolise (TEN)
Muskuloskeletale bindweefselversteurings:
Artralgie, mialgie, spierswakheid
Nier- en urienweg afwykings:
Interstisiële nefritis
Voortplantingstelsel- en borsafwykings:
Ginekomastie
Algemene siektes en toedieningsarea toestande:
Malaise, hiperhidrose

4.9 Oordosering
Geen spesifieke teenmiddel is bekend nie. FLUXTRIN is ekstensief plasmaproteïen gebonde en is dus nie maklik dialiseerbaar nie. In geval van oordosering, moet behandeling simptomaties wees en algemene ondersteunende maatreëls moet toegepas word.

5. FARMAKOLOGIESE EIENSKAPPE

5.1 Farmakodinamiese eienskappe
Farmakoterapeutiese groep: Middels vir suurverwante afwykings, protonpompinhibeerders.
ATC Kode: A02B C05

Meganisme van werking
Esomeprasool, die S-isomeer van omeprasool, verminder gastriese suurafskeiding deur 'n spesifieke inhibisie van die protonpomp in die pariëtale sel, waar dit konsentreer en omgeskakel word na die aktiewe vorm in die suuromgewing van die afskeidende kanalikuli en inhibeer die ensiem H^+K^+-ATPase – van die protonpomp. Hierdie effek op die laaste stap van die gastriese suurafskeiding is dosisafhanklik en bied effektiewe inhibisie van beide basale en gestimuleerde suurafskeiding.

Uitwerking op gastriese suurafskeiding:
Na orale dosering met esomeprasool 20 mg en 40 mg vind die aanvang van die effek binne een uur plaas.
Na herhaalde toediening met 20 mg esomeprasool een maal per dag vir vyf dae, word die gemiddelde piek suuruitset na pentagastrien stimulasie met 90 % verminder as dit 6-7 uur na toediening op dag vyf gemeet word.
Na vyf dae van orale dosering met 20 mg en 40 mg esomeprasool, is die intra-gastriese pH bo 4 gehandhaaf vir 'n gemiddelde tyd van 13 uur en 17 uur, onderskeidelik gedurende 24 uur in simptomatiese Gastroesofageale Reflukssiekte(GERS)-pasiënte. Die proporsie pasiënte wat 'n intragastriese pH bo 4 vir ten minste 8, 12 en 16 uur gehandhaaf het, was onderskeidelik 76 %, 54 % en 24 % vir esomeprasool 20 mg. Ooreenstemmende proporsies vir esomeprasool 40 mg was onderskeidelik 97 %, 92 % en 56 %.

Met behulp van AOK as surrogaatparameter vir plasmakonsentrasie, is 'n verband tussen die inhibering van suurafskeiding en blootstelling getoon.

Voedselinname het geen beduidende invloed op die uitwerking van esomeprasool op intragastriese asiditeit nie.

Ander uitwerkings verwant aan suurinhibering:
Tydens langtermynbehandeling met antisekretoriese medisyne kom gastriese klieragtige siste voor. Hierdie veranderinge is 'n fisiologiese gevolg van 'n uitgesproke inhibering van suurafskeiding, is benigne en skynbaar omkeerbaar.

5.2 Farmakokinetiese eienskappe

Absorpsie
Esomeprasool is suurlabiel en word oraal toegedien as enteries-bedekte korrels. *In vivo*-omskakeling na die R-isomeer is weglaatbaar klein. Absorpsie van esomeprasool is vinnig, met 'n piekplasmavlakke wat binne ongeveer 1-2 uur na dosering bereik word. Die absolute biobeskikbaarheid is 89 % na herhaalde toediening een maal per dag. Vir 20 mg esomeprasool is die ooreenstemmende waardes onderskeidelik 50 % en 68 %. Voedselinname beide vertraag en verminder die absorpsie van esomeprasool, hoewel dit geen noemenswaardige invloed op die effek van esomeprasool op intragastriese asiditeit het nie.

Verspreiding
Die oënskynlike distribusievolume teen gelykvlaktoestande by gesonde proefpersone is ongeveer 0,22 liter/kg liggaamsgewig. Esomeprasool is 97 % aan plasmaproteïen gebonde.

Metabolisme
Esomeprasool word volledig gemetaboliseer deur die sitochroom P450-stelsel (CYP). Die grootste deel van die metabolisme van esomeprasool is afhanklik van die polimorfiese CYP2C19, wat verantwoordelik is vir die vorming van die hidroksi- en desmetielmetaboliete van esomeprasool. Die oorblywende deel is afhanklik van 'n ander spesifieke isovorm, CYP3A4, wat verantwoordelik is vir die vorming van esomeprasool-sulfoon, die belangrikste metaboliet in plasma.

Eliminasie
Die onderstaande parameters weerspieël hoofsaaklik die farmakokinetika by individue met 'n funksionele CYP2C19-ensiem (ekstensiewe metaboliseerders).

Die totale plasmaopruiming is ongeveer 17 liter per uur na 'n enkele dosis en ongeveer 9 liter per uur na herhaalde toediening. Die plasma-eliminasie-halfleeftyd is ongeveer 1,3 uur na herhaalde dosering een maal per dag. Die area onder die plasmakonsentrasie-tydkurwe neem toe met herhaalde toediening van esomeprasool. Hierdie toename is dosisafhanklik en lei tot 'n nie-lineêre dosis-AOK-verhouding na herhaalde toediening. Hierdie tyd en dosisafhanklikheid is te wyte aan 'n afname in die eerstedeurgangsmetabolisme en sistemiese opruiming, waarskynlik veroorsaak deur 'n inhibering van die CYP2C 19-ensiem deur esomeprasool en/of die sulfoonmetaboliet. Esomeprasool word heeltemal uit plasma geëlimineer tussen dosisse sonder neiging tot akkumulering tydens enkele daaglikse toediening.

Die belangrikste metaboliete van esomeprasool het geen effek op gastriese suurafskeiding nie. Byna 80 % van 'n orale dosis esomeprasool word as metaboliete in die urine uitgeskei, die res in die feses. Minder as 1 % van die moederverbinding word in urine aangetref.

Spesiale pasiëntgroepe
Swak metaboliseerders
Ongeveer 2,9 ± 1,5 % van die bevolking ervaar 'n funksionele tekort aan die CYP2C19-ensiem en word swak metaboliseerders genoem. By hierdie individue word die metabolisme van esomeprasool waarskynlik hoofsaaklik deur CYP3A4 gekataliseer. Na herhaalde toediening van 40 mg esomeprasool een maal per dag, was die gemiddelde area onder die plasmakonsentrasie-tydkurwe ongeveer 100 % hoër by swak metaboliseerders as by persone met 'n funksionele CYP2C19-ensiem (ekstensiewe metaboliseerders). Die gemiddelde piekplasmakonsentrasies is met ongeveer 60 % verhoog. Hierdie bevindings het geen gevolge op die dosering van esomeprasool nie.

Hepatiese ontoereikendheid
Die metabolisme van esomeprasool by pasiënte met ligte tot matige lewerdisfunksie kan ingekort wees. Die metaboliese tempo is stadiger by pasiënte met erge lewerdisfunksie, wat lei tot 'n verdubbeling van die area onder die plasmakonsentrasie-tydkurwe van esomeprasool. Daarom moet 'n maksimum van 20 mg nie oorskry word by pasiënte met erge disfunksie nie. Esomeprasool of die belangrikste metaboliete daarvan toon geen neiging om tydens dosering van een maal per dag te akkumuleer nie.

Renale ontoereikendheid
Geen studies is uitgevoer by pasiënte met 'n verswakte nierfunksie nie. Aangesien die nier verantwoordelik is vir die uitskeiding van die metaboliete van esomeprasool, maar nie vir die eliminasie van die moederverbinding nie, word daar nie verwag dat die metabolisme van esomeprasool by pasiënte met verswakte nierfunksie ander sal wees nie.

Geslag
Na 'n enkele dosis van 40 mg esomeprasool is die gemiddelde area onder die plasmakonsentrasie-tydkurwe ongeveer 30 % hoër by vroue as by mans. Geen geslagsverskil word gesien na herhaalde een maal per dag toediening nie. Hierdie bevindings het geen gevolge op die dosering esomeprasool nie.

Bejaardes
Die metabolisme van esomeprasool is nie beduidend anders by ouer persone (71-80 jarige ouderdom) nie.

Pediatriese populasie
Na herhaalde dosis toediening van 20 mg en 40 mg esomeprasool, was die totale blootstelling (AOK) en die tyd om die maksimum plasma-middelkonsentrasie (t_{maks}) by 12 tot 18-jariges te bereik, soortgelyk aan dié by volwassenes vir beide esomeprasool dosisse.

6 FARMSEUTIESE BESONDERHEDE
6.1 Lys van hulpstowwe
Suikersfere (sukrose en mieliestysel), etielsellulose, magnesiumstearaat, povidoon (K-90), ligte magnesiumoksied, natriumlaurielsulfaat, polisorbaat 80, metakrielsuur-etielakrilaat-kopolimeer, dietielftalaat, talk (gesuiwer), sellulose mikrokristallyn, silika kolloïdaal anhidriese, laktosemonohidraat, mieliestysel, kopovidoon (K-28), makrogol 8000, krospovidoon (tipe A), hipromellose, titaandioksied (E171), ferrioksied rooi (E172), opacode S-1-17823 swart ink (bevat sjellak glasuur, isopropielalkohol, ysteroksied swart, n-butielalkohol, propileenglikol en ammoniumhidroksied).

6.2 Onverenigbaarheid
Nie van toepassing nie.

6.3 Rakleeftyd
36 maande.
Rakleeftyd na opening van die bottel: 100 dae.

6.4 Spesiale voorsorgmaatreëls tydens berging
Bêre teen of benede 30 ºC
Bêre in oorspronklike verpakking om te beskerm teen lig en vog.

6.5 Aard en inhoud van die houer
Aluminium - Aluminium stolpverpakking met aluminiumfoelie, hitteverseëling lakvernis en koud-vormbare stolpverpakking aluminiumfoelie. Die stolpverpakking stroke word in kartonne verpak.
HDPE-houer (Hoëdigtheid Poliëtileenhouer van nek-afwerking met induksieseël-voering en 'n silikagelhouer as droogmiddel).

Pakgroottes:
14, 28, 30, 56 en 100 gastries-bestande tablette.
Nie alle verpakkings en pakgroottes word noodwendig bemark nie.

6.6 Spesiale voorsorgmaatreëls vir die wegdoen van 'n gebruikte medisyne of afvalstowwe afkomstig van sodanige medisyne en ander hantering van die produk
Enige ongebruikte medisyne of afvalmateriaal moet weggedoen word volgens die plaaslike vereistes.

7. HOUER VAN REGISTRASIESERTIFIKAAT
Trinity Pharma (Edms.)
Bpk. 3 Gwen Laan, 4th Vloer, Sandton, Gauteng, 2031.
Kontaknommer: +27 (0)10 594 5610
PV E-posadres: pv@trinitypharma.co.za

8. REGISTRASIENOMMER(S)
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FLUXTRIN 40 : 50/11/4/3/0077

9. DATUM VAN EERSTE MAGTIGING / HERNUWING VAN DIE MAGTIGING
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Datum van laaste hernuwing: N.A

10. DATE OF REVISION OF THE TEXT
N.A