PROFESSIONAL INFORMATION

SCHEDULING STATUS: S2

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
FLUXTRIN OTC
Each gastro-resistant tablet contains esomeprazole magnesium equivalent to 20 mg esomeprazole.
Contain sugar: sucrose 14,6 mg and lactose monohydrate 31,88 mg.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Gastro-resistant tablets

FLUXTRIN OTC
Brick red coloured, round shape, biconvex, film coated tablets, imprinted with "20" on one side with black ink and plain on other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Short-term treatment of reflux symptoms such as heartburn and regurgitation in adults.

4.2 Posology and method of administration
Posology
The recommended dose is 20 mg esomeprazole (one tablet) per day. It might be necessary to take the tablet for 2 – 3 consecutive days to achieve improvement of symptoms. The duration of treatment is up to 2 weeks. Once complete relief of symptoms has occurred, treatment should be discontinued. If no symptom relief is obtained within 2 weeks of continuous treatment, the patient should consult a doctor.

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 OTC should be used.

Elderly:
Dose adjustment is not required in the elderly.

Paediatric population:
There is no relevant use of FLUXTRIN OTC in the paediatric population below 18 years of age for the indication of short-term treatment of reflux symptoms (e.g., heartburn and acid regurgitation).

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 OTC.
Concomitant administration of FLUXTRIN OTC with atazanavir or nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use
FLUXTRIN OTC 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 OTC 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 esomeprazole 40 mg, 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.

Absorption 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 CHELOTEN 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 OTC 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 OTC tablets, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with FLUXTRIN OTC may lead to increased risk of gastrointestinal infections such as Salmonella and Campylobacter and also *Clostridium difficile* in hospitalised patients.

FLUXTRIN OTC contains lactose. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency, glucose-galactose malabsorption should not take FLUXTRIN OTC.

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

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

Concomitant administration of 40 mg esomeprazole 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 OTC 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 OTC 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 C_{max} and AUC for Page 11 of 24 cilostazol by 18 % and 26 % respectively, and one of its metabolites by 29 % and 69 % respectively. FLUXTRIN OTC can be suspected to have a similar effect.

In concomitant administration of 40 mg esomeprazole resulted in a 32 % increase in area under the plasma concentration-time curve (AUC) and a 31 % prolongation of elimination half-life (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 OTC may need to be considered.

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

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

Concomitant administration of FLUXTRIN OTC 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 OTC 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 OTC. Co-administration is not recommended. However, if used concurrently, the dose of FLUXTRIN OTC should be increased.

Effects of other medicinal products on the pharmacokinetics of FLUXTRIN OTC:
FLUXTRIN OTC is metabolised by CYP2C19 and CYP3A4. Concomitant administration of FLUXTRIN OTC and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to FLUXTRIN OTC. Concomitant administration of FLUXTRIN OTC and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than tripling of the FLUXTRIN OTC exposure. Dose adjustment of FLUXTRIN OTC 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 OTC 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 beassociated 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 OTC 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
24 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:
7 and 14 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, Fourth Floor, Sandton, Gauteng, South Africa, 1686.

8. MARKETING AUTHORISATION NUMBER(S)
FLUXTRIN OTC: 47/11.4.3/0318

9. DATE OF FIRST AUTHORISATION
28 October 2021

10. DATE OF REVISION OF THE TEXT
N.A

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