

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Protas 40 Tablet

2. Qualitative and quantitative composition

Each enteric coated tablet contains Esomeprazole 40 mg as Esomeprazole Magnesium Trihydrate USP.

3. Pharmaceutical form

A white to off-white round deep biconvex enteric-coated tablet. Both faces are plain.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of Gastroesophageal Reflux Disease (GERD)

-Healing of erosive esophagitis

-Maintenance of healing of erosive esophagitis

-Symptomatic Gastroesophageal Reflux Disease (GERD)

Risk Reduction of NSAID-associated gastric ulcer

H. pylori eradication (Triple therapy)

4.2 Posology and method of administration

Tablet and capsule: Recommended adult dosage schedule of Esomeprazole

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Healing of erosive esophagitis	20 mg or 40 mg	Once daily for 4 to 8 weeks*
Maintenance of healing of erosive esophagitis	20 mg	Once daily **
Symptomatic GERD	20 mg	Once daily for 4 weeks ***
Risk Reduction of NSAID- associated gastric ulcer	20 mg or 40 mg	Once daily for up to 6 months**
<i>H. pylori</i> eradication (Triple therapy)		
Esomeprazole	20 mg	Twice daily for 10 days
Amoxicillin	1000 mg	Twice daily for 10 days
Clarithromycin	500 mg	Twice daily for 10 days

Short term treatment of GERD: 20 mg or 40 mg once daily for up to 8 weeks.

* The majority of patients are healed within 4 to 8 weeks. For patients who do not heal after 4-8 weeks, an additional 4-8 weeks treatment may be considered.

** Controlled studies did not extend beyond six months.

*** If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.

SPECIAL POPULATION

Geriatric: No dosage adjustment is necessary.

Renal insufficiency: No dosage adjustment is necessary.

Hepatic insufficiency: No dosage adjustment is necessary in patients with mild to moderate liver impairment. For patients with severe liver impairment a dose of 20 mg should not be exceeded.

Gender: No dosage adjustment is necessary.

4.3 Contraindications

Esomeprazole is contraindicated in those patients who have known hypersensitivity to any other components of the formulation.

4.4 Special warnings and precautions for use

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with Esomeprazole Tablet may alleviate symptoms and delay diagnosis.

Long term use

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

On demand treatment

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

Helicobacter pylori eradication

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug 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 active substances metabolised via CYP3A4 such as cisapride.

Gastrointestinal infections

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

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 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 or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Risk of fracture

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 recognized 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.

Combination with other medicinal products

Co-administration of esomeprazole with atazanavir is not recommended. If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered.

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 Esomeprazole Gastro-resistant Tablets. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Sucrose

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for

neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be stopped for at least five days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of esomeprazole on the pharmacokinetics of other medicinal products

Protease inhibitors

Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP 2C19. For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max} and C_{min}). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg qd) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg qd without omeprazole 20 mg qd. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC, C_{max} and C_{min} by 36–39 % and mean AUC, C_{max} and C_{min} for the pharmacologically active metabolite M8 was reduced by 75–92%. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended (see section 4.4) and concomitant administration with esomeprazole and nelfinavir is contraindicated.

For saquinavir (with concomitant ritonavir), increased serum levels (80–100%) have been reported during concomitant omeprazole treatment (40 mg qd). Treatment with omeprazole 20 mg qd had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg qd had no effect on the

exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg qd had no effect on the exposure of lopinavir (with concomitant ritonavir).

Methotrexate

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

Tacrolimus

Concomitant administration of esomeprazole 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.

Medicinal products with pH dependent absorption

Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal products such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects). Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

Medicinal products metabolised by CYP2C19

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with other medicinal products metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these active substances may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Diazepam

Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase

in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Voriconazole

Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C and AUC by 15% and 41%, respectively.

Cilostazol

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

Cisapride

In healthy volunteers, 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 ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic (PK)/ pharmacodynamic (PD) 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 aggression by an average of 14%.

When clopidogrel was given together with a fixed dose combination of

esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups. Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution concomitant use of clopidogrel should be discouraged.

Investigated medicinal products with no clinically relevant interaction

Amoxicillin and quinidine

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

Naproxen or rofecoxib

Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.

Effects of other medicinal products on the pharmacokinetics of esomeprazole

Medicinal products which inhibit CYP2C19 and/or CYP3A4

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP 3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased esomeprazole AUC₀₋₂₄ by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Medicinal products which induce CYP2C19 and/or CYP3A4

Drugs 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.

Pediatric population

Interaction studies have only been performed in adults.

4.6 Pregnancy and Lactation

Pregnancy

Clinical data on exposed pregnancies with Esomeprazole 20 mg Gastro-resistant Tablets 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 foetal/ neonatal toxicity of esomeprazole.

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

It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore, Esomeprazole 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

Esomeprazole has minor influence on the ability to drive or use machines. Adverse reactions such as dizziness (uncommon) and blurred vision (rare) has been reported. If affected patients should not drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been 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. No

dose-related adverse reactions have been identified.

Tabulated list of adverse reactions

The following adverse drug reactions have been identified or suspected in the clinical trials programmed for esomeprazole and post-marketing. None was found to be dose-related. The reactions are classified according to frequency (very common > 1/10; common $\geq 1/100$ to <1/10; uncommon $\geq 1/1000$ to <1/100; rare $\geq 1/10000$ to <1/1000; very rare <1/10000); not known (cannot be estimated from the available data).

Blood and lymphatic system

disorders Rare: Leukopenia, thrombocytopenia Very rare: Agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: Peripheral

oedema Rare:

Hyponatraemia

Not known: Hypomagnesaemia; severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, confusion, depression

Very rare: Aggression,

hallucinations **Nervous system**

disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and labyrinth disorders

Uncommon: Vertigo

Respiratory, thoracic and mediastinal disorders

Rare: Bronchospasm

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)

Uncommon: Dry mouth

Rare: Stomatitis, gastrointestinal candidiasis Not known: microscopic colitis

Hepatobiliary disorders

Uncommon: Increased liver enzymes Rare: Hepatitis with or without jaundice

Very rare: Hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritus, rash, urticaria

Rare: Alopecia, photosensitivity

Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) Not known: Subacute cutaneous lupus erythematosus.

Musculoskeletal and connective tissue disorders Uncommon: Fracture of the hip, wrist or spine Rare: Arthralgia, myalgia

Very rare: Muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis; in some patients renal failure has been reported concomitantly.

Reproductive system and breast disorders

Very rare: Gynaecomastia

General disorders and administration site conditions

Rare: Malaise, increased sweating

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions to report any suspected adverse reactions to the National Regulatory Agents

4.9 Overdose

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid related disorders/ Drugs for peptic ulcer and gastro-esophageal reflux disease (GORD)/Proton pump inhibitor ATC Code: A02B C05

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R-and S-isomer of omeprazole have similar pharmacodynamic activity.

Mechanism of action

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme $H^+K^+-ATPase$ – the acid pump and inhibits both basal and stimulated acid secretion.

Pharmacodynamic effects

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 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 GORD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for esomeprazole 20 mg 76%, 54% and 24%. Corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

Healing of reflux esophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks.

One week treatment with esomeprazole 20 mg b.i.d. and appropriate antibiotics, results in successful eradication of *H. pylori* in approximately 90% of patients.

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory medicinal products for effective ulcer

healing and symptom resolution in uncomplicated duodenal ulcers.

In a randomized, double blind, placebo-controlled clinical study, patients with endoscopically confirmed peptic ulcer bleeding characterized as Forrest Ia, Ib, IIa or IIb (9%, 43%, 38% and 10% respectively) were randomized to receive esomeprazole solution for infusion (n=375) or placebo (n=389). Following endoscopic hemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72-hour period, all patients received open-label 40 mg oral esomeprazole for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the esomeprazole treated group compared to 10.3% for the placebo group. At 30 days post-treatment, the occurrence of rebleeding in the esomeprazole treated versus the placebo treated group 7.7% vs. 13.6%.

During treatment with antisecretory medicinal products serum gastrin increases in response to the decreased acid secretion. Also, CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumors.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in both children and adults during long term treatment with esomeprazole. The findings are considered to be of no clinical significance.

During long-term treatment with antisecretory medicinal products gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

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

Clinical efficacy

In two studies with ranitidine as an active comparator, Esomeprazole Tablet showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs.

In two studies with placebo as comparator, Esomeprazole Tablet showed better effect in the prevention of gastric and duodenal ulcers in patients

using NSAIDs (aged >60 and/or with previous ulcer), including COX-2 selective NSAIDs.

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 64% after a single dose of 40 mg and increases to 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 L/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.

Elimination

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

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

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

Linearity/non-linearity

The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg b.i.d. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC 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.

Special patient populations

Poor metabolizers

Approximately $2.9 \pm 1.5\%$ of the population lack a functional CYP2C19 enzyme and are called poor metabolizers. In these individuals the metabolism of esomeprazole is probably mainly catalyzed 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 metabolizers than in subjects having a functional CYP2C19 enzyme (extensive metabolizers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of esomeprazole.

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 posology of esomeprazole.

Hepatic impairment

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 impairment

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

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

Pediatric population

Adolescents 12-18 years:

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

6. Pharmaceutical Particulars

6.1 List of Excipients

Core

Materials

Microcrystalline Cellulose (PH 101) Sodium Starch Glycolate (Primojel) Polyvinyl Pyrolidone (Povidone) Colloidal Anhydrous Silica (Aerosil 200) Magnesium Stearate Isopropyl Alcohol

Coating Materials

Opadry – OY-S38921 (White) Methanol Dichloromethane Methacrylic Acid Copolymer Dispersion (Eudragit L-30 D-55) Purified Talc Triethyl Citrate

6.2 Incompatibilities

None

6.3 Shelf-Life

2 years

6.4 Special Precautions for storage

Keep the blister in the outer carton in order to protect from light.

6.5 Nature and Content of container

Alu –Alu blister pack
30's/100's tablets in
blister/strip pack.
Not all pack sizes may be
marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. Marketing Authorization Holder

Square Pharmaceuticals Kenya EPZ

**Ltd. Corporate Address of
manufacturer**

Square Centre

48, Mohakhali C.A, Dhaka –
1212, Bangladesh

Tel : +880 2 8833047-56, +880 2 8859007 (10 lines)

Fax : +880 2 8828768, +880 2 8834941

E-mail : info@squaregroup.com

Manufacturing Site Address

Square Pharmaceuticals Kenya EPZ Ltd.

Simba Road, Athi River EPZ, P.O. Box: 30500, Machakos. Cell:
+254113835299; +254707708945; +254715676588

8. Marketing Authorization Number

H2017/CTD374A/171

9. Date of first authorization/renewal of the authorization

05 May 2017

10. Date of revision of the text

Not Applicable

Ref:

<https://www.medicines.org.uk/emc/product/2328/smpc>

<https://www.squarepharma.com.bd/downloads/Nexum%20DS.PDF>