

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product:

ESOXIUM 40 (Esomeprazole Magnesium Tablets 40 mg)

2. Qualitative and Quantitative Composition

Esomeprazole Magnesium Tablets 40 mg

EXOIME 20

Each enteric coated tablet contains:

Esomeprazole magnesium Trihydrate BP

equivalent to Esomeprazole: 40 mg

Excipients: q.s

Colour: Brilliant Blue, Carmoisine, Ponceau 4R and Titanium Dioxide

For a full list of excipients see section 6.1

3. Pharmaceutical Form: Tablet

Purple coloured, caplet shaped, enteric coated tablets plain on both sides.

4. Clinical Particulars

4.1 Therapeutic indications:

Esomeprazole 40 mg tablets are indicated for:

Gastro oesophageal Reflux Disease (GORD)- treatment of erosive reflux oesophagitis Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers. Treatment of Zollinger Ellison Syndrome

4.2 Posology and method of administration:

The recommended dose is 40 mg esomeprazole (one capsule) per day. It might be necessary to take the tablets for 2-3 consecutive days to achieve improvement in 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 be instructed to consult a doctor.

Special populations

Patients with renal impairment:

Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution (see section 5.2). Patients with hepatic impairment Dose adjustment is not required in patients with mild to moderate liver impairment. However, patients with severe liver impairment should be advised by a doctor before taking Esomeprazole.

Elderly patients (≥ 65 years old)

Dose adjustment is not required in elderly patients.

This medicine is not recommended in children and adolescents under 18 years of age

Method of administration the Tablet should be swallowed whole with half a glass of water. The tablet must not be chewed or crushed.

4.3 Contraindications

Hypersensitivity to esomeprazole, substituted benzimidazoles or to any of the excipients listed in section 6.1. Esomeprazole should not be used concomitantly with nelfinavir.

4.4 Special warning 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 may alleviate symptoms and delay diagnosis. Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance. Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on-demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see section 4.5). 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 drugs metabolised via CYP3A4 such as cisapride. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Co-administration of esomeprazole with atazanavir is not recommended (see section 4.5). 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 40 mg should not be exceeded.

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.

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 omeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

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.

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

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

Interference with laboratory tests

Increased CgA level may interfere with investigations for neuroendocrine tumors. To avoid this interference, esomeprazole treatment should be temporarily stopped for at least five days before CgA measurements.

This medicinal product contains sucrose and lactose monohydrate

Sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase isomaltose insufficiency should not take this medicine.

Lactose monohydrate: Patients with rare hereditary problem of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of Interactions

Interaction studies have only been performed in adults.

Effects of esomeprazole on the pharmacokinetics of other drugs

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.

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. Co-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 (40 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 40 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%. For saquinavir (with concomitant ritonavir), increased

serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg qd). Treatment with omeprazole 40 mg qd had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 40 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). Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated.

Drugs metabolised by CYP2C19

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolizing enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these drugs may be increased, and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy. Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam. 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. Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC by 15% and 41%, respectively.

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.

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

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.

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

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.

In a crossover clinical study, clopidogrel (300 mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days. The

exposure to the active metabolite of clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) was diminished by 47% (24 hours) and 30% (Day 5) when clopidogrel and omeprazole were administered together. In another study it was shown that administering clopidogrel and omeprazole at different times did not prevent their interaction that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19. Inconsistent data on the clinical implications of this PK/PD interaction in terms of major cardiovascular events have been reported from observational and clinical studies.

Unknown mechanism

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

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Effects of other drugs on the pharmacokinetics of esomeprazole

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 CYP3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC 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. 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.

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4.6 Fertility, Pregnancy and lactation:

Pregnancy:

For esomeprazole clinical data on exposed pregnancies are insufficient. With the racemic mixture, omeprazole, data on a larger number of exposed pregnancies from epidemiological studies indicate no malformative nor fetotoxic effect. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/fetal 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.

Breastfeeding:

It is not known whether esomeprazole is excreted in breast milk. No studies in lactating women have been performed. Therefore, Esomeprazole gastro resistant tablets should not be used during breast-feeding.

Fertility:

There are no data on the effects of esomeprazole on human fertility

4.7 Effects on ability to drive and use Machines:

No effects have been observed.

4.8 Undesirable effects:

The following adverse drug reactions have been identified or suspected in the clinical trials program for esomeprazole and post-marketing.

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

Psychiatric disorders:

Uncommon : Insomnia

Rare: Agitation, confusion, depression

Very rare: Aggression, hallucinations

Nervous system disorder

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and labyrinth disorders

Uncommon: Vertigo

General disorder and administration site

Rare: Malaise, increased sweating

Reporting of suspected adverse reactions:

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

4.9 OVERDOSAGE

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: 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.

Site and 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.

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 decreases 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.

Therapeutic effects of acid inhibition

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

Pediatric population

In a study in pediatric GORD patients receiving long-term PPI treatment, 61% of the children developed minor degrees of ECL cell hyperplasia with no known clinical significance and with no development of atrophic gastritis or carcinoid tumors.

5.2 Pharmacokinetic Properties

Absorption and distribution

Esomeprazole is acid labile and is administered orally as gastro-resistant 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. 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.

Food intake both delays and decrease the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Biotransformation and elimination

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolizers. 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. 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. 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 patient populations 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 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 metabolizers than in subjects having a functional CYP2C19 enzyme (extensive metabolizers). Mean peak plasma concentrations increased by about 60%. These findings have no implications for the posology of esomeprazole.

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years of age). Following a single dose of 40 mg esomeprazole the mean area under the plasma concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications

for the posology of esomeprazole. Impaired organ function 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. 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. 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 (t_{max}) in 12 to 18 year-olds was similar to that in adults for both esomeprazole doses.

5.3 Preclinical safety data

Preclinical bridging studies reveal no particular hazard for humans based on conventional studies of repeated-dose toxicity, genotoxicity, and toxicity to reproduction. 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 hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

No new unexpected toxicity findings were observed in juvenile rats and dogs, after administration of esomeprazole for up to 3 months, as compared to adult animals.

6. Pharmaceutical particulars

6.1. List of excipients:

Lactose BP
Mannitol BP
*Microcrystalline Cellulose BP
**Maize Starch BP
Light magnesium oxide BP
Povidone K 30 USP
Dichloromethane BP
Isopropyl alcohol BP
Purified Talc BP
Magnesium Stearate BP
Collodial Anhydrous Silica BP

Sodium Starch Glycolate BP
Idealcoat IJ-MS-1011 white IH
Wincoat WT-N-02400 (Purple) IH

6.2 Incompatibilities: None

6.3 Shelf life: 36 Months

6.4 Special precautions for storage:

Store at a temperature not exceeding 30°C. Protect from light.

Keep medicine out of reach of children.

6.5 Nature and contents of container:

Alu Alu blisters of 10 Tablets. Such 3 blisters to be packed in a carton with pack insert.

6.6. Special precautions for disposal: None

7.0 Marketing Authorization Holder and Manufacturing Site Addresses

Name : MR. MOHAMMAD

Company name: SIGNATURE HEALTHCARE LTD.

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8. Marketing Authorization Numbers:

CTD13441

9. Date of first authorization/renewal of the authorization

01/06/2026

10. Date of revision of the text

01/06/2026