

Summary of Product Characteristics

1. Name of the medicinal product

Esofast 40 (Esomeprazole Tablets 40mg)

2. Qualitative and quantitative composition

Each enteric-coated tablet contains

Esomeprazole Magnesium Trihydrate USP

Equivalent to Esomeprazole.....40mg

For a list of excipients, see Section 6.1.

3. Pharmaceutical form

Enteric Coated Tablet. A yellow color oval shape biconvex enteric coated tablet, plain on both the sides.

4. Clinical particulars

4.1 Therapeutic indications

Esomeprazole is indicated for the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults.

4.2 Posology and method of administration

Adults

20 or 40 milligrams (mg) once a day for 4 to 8 weeks. Your doctor may adjust your dose as needed. To prevent erosive esophagitis from coming back, your doctor may want you to take 20 mg once a day for up to 6 months.

Elderly patients (≥65 years old)

Dose adjustment is not required in elderly patients. Paediatric population Children 12 to 17 years of age—20 or 40 milligrams (mg) once a day for 4 to 8 weeks.

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. 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.

Method of administration:

The tablets should be swallowed whole with half a glass of water. The tablets must not be chewed or crushed.

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients. Esomeprazole must not be used concomitantly with nelfinavir.

4.4 Special warnings and precautions for use

General

Patients should be instructed to consult a doctor if:

- They have 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.
- They have had previous gastric ulcer or gastrointestinal surgery.
- They have been on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks.
- They have jaundice or severe liver disease.
- They are aged over 55 years with new or recently changed symptoms.

Patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Patients over 55 years taking any non-prescription indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor.

Patients should not take Esomeprazole as a long-term preventive medicinal product.

Treatment with proton pump inhibitors (PPIs) may lead to a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and in hospitalised patients, also possibly *Clostridium difficile*.

Patients should consult their doctor before taking this medicinal product if they are due to have an endoscopy or urea breath test.

Combination with other medicinal products

Co-administration of esomeprazole with atazanavir is not recommended. If the combination of atazanavir with a PPI 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 medicinal products metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole. The clinical relevance of this interaction is uncertain. The use of esomeprazole with clopidogrel should be discouraged. Patients should not take another PPI or H₂ antagonist concomitantly.

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 5 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Effects of esomeprazole on the pharmacokinetics of other medicinal products

As esomeprazole is one enantiomer of omeprazole, it is reasonable to advise about interactions reported with omeprazole.

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 CYP2C19.

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 (20 mg once a day) 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 once a day without

omeprazole 20 mg once a day. Co-administration of omeprazole (40 mg once a day) 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 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 once a day). Treatment with omeprazole 20 mg once a day had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg once a day had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg once a day 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 the dose of tacrolimus adjusted if needed.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical study 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 orally 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%

Diazepam

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

4.6 Pregnancy and Lactation

Fertility: Animal studies with the racemic mixture omeprazole, given by oral administration, do not indicate effects with respect to fertility.

Pregnancy: A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformative or fetotoxicity of esomeprazole. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Esomeprazole during pregnancy.

Lactation: It is unknown whether esomeprazole/metabolites are excreted in human milk. There is insufficient information on the effects of esomeprazole in newborns/infants. Esomeprazole should not be used during breast-feeding

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 and visual disturbances are uncommon. If affected, patients should not drive or use machines.

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 studies (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.

b) Tabulated summary of adverse reactions

The following adverse reactions have been identified or suspected in the clinical studies programme for esomeprazole and post-marketing. The reactions are classified according to MedDRA frequency convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1,000$ to $<1/100$); rare ($\geq 1/10,000$ to $<1/1,000$); very rare ($<1/10,000$); not known (cannot be estimated from the available data).

	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			leukopenia , thrombocytopenia	agranulocytosis, pancytopenia	
Immune system disorders			hypersensitivity reactions e.g.		
			fever, angioedema and anaphylactic reaction/s hock		
Metabolism and nutrition disorders		peripheral oedema	hyponatraemia		hypomagnesaemia; severe hypomagnesaemia can correlate with hypocalcaemia; hypomagnesaemia may also result in hypokalaemia
Psychiatric disorders		insomnia	agitation, confusion, depression	aggression, hallucinations	
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, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)	dry mouth	stomatitis, gastrointestinal candidiasis		microscopic colitis
Hepatobiliary disorders		increased liver enzymes	hepatitis with or without jaundice	hepatic failure, hepatic encephalopathy in patients with pre-existing liver disease	
Skin and subcutaneous tissue disorders		dermatitis, pruritus, rash urticaria	alopecia, photosensitivity	erythema multiforme, StevensJohnson	Subacute cutaneous lupus erythematosus
				syndrome, toxic epidermal necrolysis (TEN)	
Musculoskeletal and connective tissue disorders			arthralgia, myalgia	muscular weakness	

Renal and urinary disorders				Interstitial nephritis	
Reproductive system and breast disorders				gynaecomastia	
General disorders and administration site disorders			malaise, increased sweating		

c) **Description of selected adverse reactions**

Dyspepsia, or indigestion: Symptoms include nausea, heartburn, and upper abdominal fullness and pain.

Peptic ulcer disease: There is a gap in the lining of the stomach, esophagus, or intestine.

Gastroesophageal reflux disease (GERD): A chronic condition where stomach acid comes up from the stomach into the esophagus and damages the mucosa, leading to heartburn.

Zollinger-Ellison syndrome: A pancreatic tumor overstimulates the production of stomach acid.

Esomeprazole may be used by patients who are taking nonsteroidal anti-inflammatory drugs (NSAIDs). This is due to NSAIDs' propensity to produce stomach ulcers; Esomeprazole helps prevent their formation.

d) **Paediatric population**

There is no relevant use of Esomeprazole 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)".

e) **Other special population(s)**

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.

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.

Reporting of suspected adverse reactions: Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>.

4.9 Overdose

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280 mg esomeprazole 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 dialysable. Treatment should be symptomatic and general supportive measures should be utilised.

5. Pharmacological properties

Pharmacotherapeutic group and ATC Code: Drugs for acid related disorders, proton pump inhibitors, ATC code: A02BC05.

5.1 Pharmacodynamic properties

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 gastroesophageal reflux disease (GERD) 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.

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 tumours.

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 some patients during long-term treatment with esomeprazole.

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

Clinical efficacy and safety

Clinical efficacy

Esomeprazole 20 mg has been demonstrated to effectively treat frequent heartburn in subjects receiving one dose per 24 hours over 2 weeks. In two multicentre, randomised, double-blind, placebo-controlled pivotal studies 234 subjects with a recent history of frequent heartburn were treated with 20 mg esomeprazole for 4 weeks. Symptoms associated with acid reflux (such as heartburn and acid regurgitation) were evaluated retrospectively over a 24 hour period. In both studies esomeprazole 20 mg was significantly better compared to placebo for the primary endpoint, complete resolution of heartburn, defined as no heartburn episodes during the last 7 days prior to the final visit (33.9% - 41.6% vs. placebo 11.9 - 13.7%, ($p < 0.001$)). The secondary endpoint of complete resolution of heartburn, defined as no heartburn on the patient's diary card for 7 consecutive days, was statistically significant at both week 1 (10.0% -

15.2% vs. placebo 0.9% - 2.4%, $p = 0.014$, $p < 0.001$) and week 2 (25.2% - 35.7% vs. placebo 3.4% - 9.0%, $p < 0.001$).

Other secondary endpoints were supportive of the primary endpoint, including relief of heartburn at week 1 and week 2, percentage of 24 hour days without heartburn at week 1 and week 2, mean heartburn severity at week 1 and week 2, and time to initial and sustained resolution of heartburn over a 24 hour period and during the night compared to placebo. Approximately 78% of the subjects on 20 mg esomeprazole reported first resolution of heartburn within the first week of treatment compared to 52 - 58% for placebo. Time to sustained resolution of heartburn, defined as when 7 consecutive days of no heartburn was first recorded, was significantly shorter in the esomeprazole 20 mg group (39.7% - 48.7% by day 14 vs. placebo 11.0% - 20.2%). The median time to first resolution of night-time heartburn was 1 day, statistically significant compared to placebo in one study ($p = 0.048$) and approaching significance in the other ($p = 0.069$). About 80% of nights were heartburn free during all time periods and 90% of nights were heartburn free by week 2 of each clinical study, compared to 72.4 - 78.3% for placebo. The investigators' assessments of heartburn resolution were consistent with the subjects' assessments, showing statistically significant differences between esomeprazole (34.7% - 41.8%) compared to placebo (8.0% - 11.4%). The investigators also found esomeprazole to be significantly more effective than placebo in resolving acid regurgitation (58.5% - 63.6% vs. placebo 28.3% - 37.4%) during the week 2 evaluation.

Following Overall Treatment Evaluation (OTE) of patients at week 2, 78.0 - 80.7% of patients on esomeprazole 20 mg, compared to 72.4 - 78.3% for placebo, reported their condition as improved. The majority of these rated the importance of this change to be Important to Extremely Important in performing their activities of daily living (79 - 86% at week 2).

5.2 Pharmacokinetic properties

a. General introduction

Esomeprazole is the S-enantiomer of Chemical omeprazole. Esomeprazole is a prodrug that is activated by the acid environment in the stomach to an acid or sulfonamide form. Esomeprazole is metabolized primarily by CYP2C19 and CYP3A4. White to slightly colored powder. Soluble in methanol; slightly soluble in water; practically insoluble in heptane.

Esomeprazole is used to treat conditions where there is too much acid in the stomach. It is used to treat duodenal and gastric ulcers, erosive esophagitis, gastroesophageal reflux disease (GERD), and Zollinger-Ellison syndrome, a condition wherein the stomach produces too much acid.

b. General Characteristics 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 compound 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.

c. Characteristics in specific groups of subjects or patients

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.

Paediatric population

There is no relevant use of Esomeprazole 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)”.

Elderly

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

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

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 oncedaily administration. These findings have no implications for the posology of esomeprazole

d. Pharmacokinetic / pharmacodynamics relationship

The pharmacokinetics of esomeprazole are time- and dose-dependent. There was a good correlation between AUC and effect for esomeprazole.

5.3 Preclinical safety data

Non-clinical data reveal no particular hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and 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 hypergastrinaemia 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

Crospovidone
Mannitol
Heavy Magnesium Oxide
Microcrystalline Cellulose
Hydroxypropylcellulose
Titanium Dioxide
Purified Talc
Colloidal Anhydrous Silica
Magnesium Stearate
Hypromellose E15
Titanium Dioxide
Hypromellose Phthalate
Iron Oxide of Yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

24 Months

6.4 Special Precautions for Storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and Content of container

Commercial Presentation: 4's, 10's, 20's, 30's & 100's
1 x 10's (10 tablets are packed in one Alu-Alu blister and 1 Alu-Alu blister is kept in one carton along with package insert).

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder

Marketing authorization holder:

INNOCIA LIFESCIENCES PVT. LTD.,
Block A, No.12, Balaji Nagar, Ambattur, Chennai-600 053
India.

Manufacturing Site address:

ATOZ Pharmaceuticals Pvt. Ltd.,
No.12, Balaji Nagar, Ambattur, Chennai-600053,
India

8. Marketing Authorization Number

CTD 3899

9. Date of first authorization/renewal of the authorization

12/12/2016

10. Date of revision of the text

12/12/2023