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metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite.

Special patient populations

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.

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.

Elderly

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

Paediatric 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 concentration (t_{max}) 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 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

Mannitol
Sucrose
Sodium Lauryl Sulphate
Disodium Hydrogen Phosphate
Sodium Carbonate
Povidone 30
Hypromellose
Methacrylic Acid and Ethyl Acrylate Copolymer Dispersion
Diethyl phthalate
Titanium Dioxide
Purified Talc
N.P. Seeds
Empty Hard Gelatin Capsule size '1'

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

30 Months from the date of manufacture.

6.4. Special precautions for storage

Store at a temperature not exceeding 30°C, protect from moisture.
Keep out of the reach and sight of children.

6.5 Nature and contents of container

10 x 10 Capsules in Alu-Alu Blister pack.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Manufactured by :

ZIM LABORATORIES LIMITED
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 441 501,
Maharashtra State, India

zim
Zeal & Innovation in Medicine

8. Marketing Authorization Number(S)

NA

9. Date of First Authorization/Renewal of the Authorization

NA

10. Date of Revision of the Text

29 Jun 2019

*PB389/X/XX/XX

ESOZIM-40

Esomeprazole Magnesium
Delayed-Release Capsuels USP 40 mg

1. Name of the Finished Pharmaceutical Product

1.1 Trade Name : ESOZIM-40 (Esomeprazole Magnesium Delayed-Release Capsules USP 40 mg)
1.2 Strength : 40 mg
1.3 Pharmaceutical Form : *"Hard Gelatin Capsule"*

2. Qualitative And Quantitative Composition

Each hard gelatin capsule contain:
Esomeprazole 40 mg
(As Esomeprazole Magnesium Trihydrate USP)
(As enteric coated pellets)
For the full list of excipients, see section 6.1

3. Pharmaceutical Form

"Hard Gelatin Capsule
Orange/ clear transparent, Size '1' hard gelatin capsule filled with white to off white enteric coated pellets.

4. Clinical Particulars

4.1 Therapeutic indications

Esomeprazole capsules are indicated in adults for:
Gastroesophageal Reflux Disease (GERD)
– Treatment of erosive reflux esophagitis.
Prolonged treatment after i. v. induced prevention of rebleeding of peptic ulcers.
Treatment of Zollinger Ellison Syndrome
Esomeprazole Capsule are indicated in adolescents from the age of 12 years for:
Gastroesophageal Reflux Disease (GERD)
- Treatment of erosive reflux esophagitis

4.2 Posology and method of administration

Posology
Adults
Gastroesophageal Reflux Disease (GERD)
- Treatment of erosive reflux esophagitis
40 mg once daily for 4 weeks.
An additional 4 weeks treatment is recommended for patients in whom esophagitis has not healed or who have persistent symptoms.
Prolonged treatment after i. v. induced prevention of rebleeding of peptic ulcers.
40 mg once daily for 4 weeks after i. v. nduced prevention of rebleeding of peptic ulcers.
Treatment of Zollinger Ellison Syndrome
The recommended initial dosage is Esomeprazole 40 mg twice daily. The dosage shoulc then be individually adjusted and treatment continued as long as clinically indicated. Based on the clinical data available, the majority of patients can be controlled on doses between 80 to 160 mg esomeprazole daily. With doses above 80 mg daily, the dose should be divided and given twice daily.
Special Populations
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.
Hepatic impairment
Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum dose of 20 mg Esomeprazole should not be exceeded.
Elderly
Dose adjustment is not required in the elderly.
Paediatric population
Adolescents from the age of 12 years
Gastroesophageal Reflux Disease (GERD)
- Treatment of erosive reflux esophagitis
40 mg once daily for 4 weeks.
An additional 4 weeks treatment is recommended for patients in whom esophagitis has not healed or who have persistent symptoms.

Mode of Administration:
Oral Administration
The Capsule should be swallowed whole with liquid. The Capsule should not be chewed or crushed.

4.3 Contraindication

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

4.4 Special warnings and special 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.
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 drugs 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

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BACK SIDE

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 improvec after magnesium replacement and discontinuatio n 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), healthcare 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 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.

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.

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 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.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of esomeprazole on the pharmacokinetics of other drugs

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 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 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 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.

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_{max} and 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.

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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Pregnancy and lactation

Pregnancy

With the racemic mixture omeprazole data on a larger number of exposed pregnancies stemmed from epidemiological studies indicate no malformative nor foetotoxic effects. 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.

Breast-feeding

Esomeprazole should not be used during breast-feeding.

Fertility

Animal studies with the racemic mixture omeprazole, given by oral administration do notindicate effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Esomeprazole has minor influence on the ability to drive and 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

The frequencies of adverse reactions are ranked according to the following convention The frequency grouping is defined using the following convention: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000) and Not known.

Common: Headache, Abdominal pain, Constipation, Diarrhoea, Flatulence, Nausea/vomiting, Fundic gland polyps (benign).

Uncommon: Peripheral oedema, Insomnia, Dizziness, Paraesthesia, Somnolence, Vertigo, Dry mouth, Increased liver enzymes, Dermatitis, Pruritus, Rash, Urticaria, Fracture of the hip, Wrist or spine.

Rare: Leukopenia, Thrombocytopenia, Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock, Hyponatraemia, Agitation, confusion, Depression, Taste disturbance, Blurred vision, Bronchospasm, Stomatitis, Gastrointestinal candidiasis, Hepatitis with or without jaundice, Alopecia, Photosensitivity, Arthralgia, Myalgia, Malaise, Increased sweating,

Very rare: Agranulocytosis, Pancytopenia, Aggression, Hallucinations, Hepatic failure, Encephalopathy in patients with pre-existing liver disease, Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis (TEN), Muscular weakness, Interstitial nephritis, in some patients renal failure has been reported concomitantly., Gynaecomasta.

Not known: Hypomagnesaemia; severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia. Microscopic colitis, subacute cutaneous lupus erythematosus.

4.9 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 proton pump inhibitors

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.

Paediatric population

In a study in paediatric GERD patients (<1 to 17 years of age) 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 tumours.

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

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