

Venza

(Esomeprazole)

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COMPOSITION

Venza 20 mg each capsule contains: Esomeprazole magnesium trihydrate pellets eq. to Esomeprazole 20 mg.
Venza 40 mg each capsule contains: Esomeprazole magnesium trihydrate pellets eq. to Esomeprazole 40 mg.
 Esomeprazole is S-isomer of omeprazole & markedly differs from omeprazole in pharmacokinetic & pharmacodynamic properties.

PHARMACOKINETICS

Absorption: Esomeprazole after oral administration peak plasma levels (C_{max}) occur at approximately 1.5 hours (T_{max}). The C_{max} increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to Esomeprazole increases from 4.32 µmol/hr/l on day 1 to 11.2 µmol/hr/l on day 5 after 40 mg once daily dosing. The AUC after administration of a single 40 mg dose of Esomeprazole is decreased by 33 - 53% after food intake compared to fasting conditions. Esomeprazole should be taken at least one hour before meals.

Distribution: Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20 mmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

Metabolism: Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of Esomeprazole lack antisecretory activity. The major part of Esomeprazole metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of Esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are termed poor metabolizers. At steady state, the ratio of AUC in poor metabolizers to AUC in the rest of the population (Extensive metabolizers) is approximately 2. Following administration of equimolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher levels of the S- than of the R-isomer.

Excretion: The plasma elimination half-life of Esomeprazole is approximately 1-1.5 hours. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of Esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

Special Populations

Geriatric: The AUC and C_{max} values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment based on age is not necessary.

Pediatric: The pharmacokinetics of Esomeprazole had not been studied in patients < 18 years of age.

Gender: The AUC and C_{max} values were slightly higher (13%) in females than in males at steady state. Dosage adjustment based on gender is not necessary.

Hepatic Insufficiency: The steady state pharmacokinetics of Esomeprazole obtained after administration of 40 mg once daily to 4 patients each with mild (Child Pugh Class A), moderate (Child Pugh Class B), and severe (Child Pugh Class C) liver insufficiency were compared to those obtained in 36 male and female GERD patients with normal liver function. In patients with mild and moderate hepatic insufficiency, the AUCs were within the range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2 to 3 times higher than in the patients with normal liver function. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child Pugh Class C), a dose of 20 mg once daily should not be exceeded.

Renal Insufficiency: The pharmacokinetics of Esomeprazole in patients with renal impairment are not expected to be altered relative to healthy volunteers as less than 1% of Esomeprazole is excreted unchanged in urine.

Mechanism of Action: Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretions by specific inhibition of the H⁺/K⁺ -ATPase in the gastric parietal cell. The S- and R-isomers are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphonamide. By acting specifically on the proton pump, Esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

Serum Gastrin Effects

The effect of Esomeprazole on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1300 patients for up to 6-12 months. The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau within 2 to 3 months of therapy and returned to baseline levels within 4 weeks after discontinuation of therapy.

Endocrine Effects

Esomeprazole had no effect on thyroid function when given in doses of 20 mg or 40 mg for 4 weeks. Other effects of Esomeprazole on the endocrine system were assessed using Omeprazole studies. Omeprazole given in oral doses of 30 mg or 40 mg for 2 to 4 weeks had no effect on carbohydrate metabolism, circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

MICROBIOLOGY

Esomeprazole magnesium, amoxicillin and clarithromycin triple therapy has been shown to be active against most strains of *Helicobacter pylori* (H. pylori) in vitro and in clinical infections.

INDICATIONS

• Treatment of Gastroesophageal Reflux Disease (GERD)

• Healing of Erosive Esophagitis

Venza is indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4-8 weeks of treatment, an additional 4-8 week course of **Venza** may be considered.

• Maintenance of Healing of Erosive Esophagitis

Venza is indicated to maintain symptom resolution and healing of erosive esophagitis. Controlled studies do not extend beyond 6 months.

• Symptomatic Gastroesophageal Reflux Disease

Venza is indicated for treatment of heartburn and other symptoms associated with GERD.

• H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Venza in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate H. pylori. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence.

In patients who fail to respond to therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4-8 weeks of treatment, an additional 4-8 week course of **Venza** may be considered.

• Maintenance of Healing of Erosive Esophagitis

Venza is indicated to maintain symptom resolution and healing of erosive esophagitis. Controlled studies do not extend beyond 6 months.

DOSAGE AND ADMINISTRATION

Venza capsules should be swallowed whole and taken at least one hour before eating.

- For GERD: 20 or 40 mg once daily for 4 to 8 weeks.
- For Maintenance of healing of erosive esophagitis: 20 mg once daily.
- For symptomatic reflux disease: 20 mg once daily for 4 weeks.
- For H. pylori eradication to reduce risk of duodenal ulcer: **Venza** 40 mg once daily or **Venza** 20 mg twice daily for 10 days along with Amoxicillin 1000 mg twice daily for 10 days & Clarithromycin 500 mg twice daily for 10 days.

WARNINGS

Special Populations

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 (Child Pugh Classes A and B). For patients with severe liver impairment (Child Pugh Class C), a dose of 20 mg of Esomeprazole should not be exceeded.

SIDE EFFECTS

Esomeprazole is generally well tolerated & side effects are comparable with that of placebo. In rare cases following effects have been seen.

Body as a Whole: Abdomen enlarged, allergic reaction, asthenia, back pain, substernal chest pain, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors.

Cardiovascular: Flushing, hypertension, tachycardia.

Endocrine: Goner.

Gastrointestinal: Bowel irregularity, constipation aggravated, dyspepsia, dysphagia, GI dysplasia, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, stomatitis, vomiting.

Hearing: Earache, tinnitus.

Hematologic: Anemia, hypochromic anemia, cervical lymphadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia.

Hepatic: Bilirubinemia, abnormal hepatic function, SGOT increased, SGPT increased.

Metabolic / Nutritional: Glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, B12 deficiency, weight increase, weight decrease.

Musculoskeletal: Arthralgia, arthritis aggravated arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica.

Nervous System/Psychiatric: Anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect.

Reproductive: Dysmenorrhea, menstrual disorder, vaginitis.

Respiratory: Asthma aggravated coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis.

Skin and Appendages: Acne, angioedema, dermatitis, pruritus, pruritus ani, rash erythematous, rash maculo-papular, skin inflammation, increased sweating, urticaria.

Special Senses: Otitis media, parosmia, taste loss, taste perversion.

Urogenital: Abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria.

Visual: Conjunctivitis, abnormal vision.

The incidence of treatment-related adverse events during 6-month maintenance treatment was similar to placebo. There were no differences in types of related adverse events seen during maintenance treatment upto 12 months compared to short-term treatment.

DRUG INTERACTIONS

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4. In vitro and in vivo studies have shown that Esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 3M. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that Esomeprazole does not have any clinically interactions with phenytoin, warfarin, quinidine, clarithromycin or amoxicillin. Esomeprazole may potentially interfere with CYP2C19, the major Esomeprazole metabolizing enzyme. Coadministration of Esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam. Increased plasma levels were observed 12 hours after dosing and onwards. However, at that time, the levels of diazepam were below the therapeutic index, and thus this interaction is unlikely to be of clinical relevance. Esomeprazole inhibits gastric acid secretion. Therefore, Esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, salts and digoxin). Coadministration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of Esomeprazole.

PRECAUTIONS:

General

Symptomatic response to therapy with Esomeprazole does not preclude the presence of gastric malignancy. Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of Esomeprazole was assessed using omeprazole studies. In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times the human dose of 20 mg/day expressed on a body surface area basis) produced gastric ECI cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECI cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 5.6 times the human dose on a body surface area basis) for 1 year, and then followed for an additional year without the drug. No carcinoids were seen in these rats.

Esomeprazole was negative in the Ames mutation test, in the in vivo rat bone marrow cell chromosome aberration test, and the in vivo mouse micronucleus test. Esomeprazole, however, was positive in the in vitro human lymphocyte chromosome aberration test. Omeprazole was positive in the in vitro human lymphocyte chromosome aberration test, the in vivo mouse bone marrow cell chromosome aberration test, and the in vivo mouse micronucleus test.

Pregnancy

Teratogenic Effects: Pregnancy Category B: Teratology studies have been performed in rats at oral doses upto 280 mg/kg/day (about 57 times the human dose on a body surface area basis) and in rabbits at oral doses upto 86 mg/kg/day (about 35 times the human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to Esomeprazole. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: The excretion of Esomeprazole in milk has not been studied. Esomeprazole is likely to be excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: No overall differences in safety and efficacy were observed between the elderly and younger individuals but greater sensitivity of some older individuals cannot be ruled out.

CONTRAINDICATIONS

Esomeprazole is contraindicated in patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles.

PRESENTATION

Venza 20 mg Capsule: 2x7's/pack

Venza 40 mg Capsule: 2x7's/pack

Dosage:

As directed by the physician.

Instructions:

Store below 30°C.
Protect from sunlight & moisture.
Keep out of reach of children.

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Detailed prescribing information is available on request.

Manufactured by:
AsianContinental (Pvt.) Ltd.
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Karachi-Pakistan.



An ISO Certified Company

LFT/035/00

خوراک :
ڈاکٹر کی ہدایت کے مطابق۔
ہدایات :
دوا کو 30 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔