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AXESOM CAPSULES (Esomeprazole)

COMPOSITION

Each capsule contains:
Esomeprazole 20mg (as Esomeprazole Magnesium Trihydrate in delayed release form).
Esomeprazole 40mg (as Esomeprazole Magnesium Trihydrate in delayed release form).

DESCRIPTION

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
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 is decreased 90% when measured 6–7 hours after dosing on day five. After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients.
Pharmacokinetic properties
Absorption and distribution
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. 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 decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.
Metabolism and excretion
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 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. 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
Elderly
The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years of age).
Liver Dysfunction
The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. 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 Dysfunction
The metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.
Paediatric
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 (tmax) in 12 to 18 year-olds was similar to that in adults for both esomeprazole doses.
Drug Interaction
Products with pH dependent absorption
In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease and the absorption of digoxin can increase during treatment with esomeprazole. Caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced. 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-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. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives. Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine. Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions. Caution should be exercised while prescribing clopidogrel with esomprazole.
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.

INDICATIONS

Adults
1. Gastro-Oesophageal Reflux Disease (GORD)
   a. Treatment of erosive reflux oesophagitis
   b. Long-term management of patients with healed oesophagitis to prevent relapse
   c. Symptomatic treatment of gastro-oesophageal reflux disease (GORD)
2. In combination with an appropriate antibacterial therapeutic regimen for the eradication of Helicobacter pylori and
   a. healing of Helicobacter pylori associated duodenal ulcer and
   b. Prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcers.
3. Patients requiring continued NSAID therapy
   a. Healing of gastric ulcers associated with NSAID therapy.
   b. Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.
4. Treatment of Zollinger Ellison Syndrome

Adolescents from the age of 12 years
1. Gastro-Oesophageal Reflux Disease (GORD)
   a. treatment of erosive reflux oesophagitis
   b. long-term management of patients with healed oesophagitis to prevent relapse
   c.symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori.

DOSAGE AND ADMINISTRATION

The capsules should be swallowed whole with some liquid.
Adults and adolescents from the age of 12 years.
1. Gastro-Oesophageal Reflux Disease (GORD)
   a. Treatment of erosive reflux oesophagitis: 40 mg once daily for 4 weeks. An additional 4 weeks treatment is

recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

b. Long-term management of patients with healed oesophagitis to prevent relapse: 20 mg once daily.

c. Symptomatic treatment of gastro-oesophageal reflux disease (GORD):20 mg once daily in patients without oesophagitis. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily. In adults, an on demand regimen taking 20 mg once daily, when needed, can be used.

Adults

1. In combination with an appropriate antibacterial therapeutic regimen for the eradication of Helicobacter pylori and
   a. healing of Helicobacter pylori associated duodenal ulcer and
   b. prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcers: 20 mg AXESOM with 1 g amoxicillin and 500 mg clarithromycin, all twice daily for 7 days.
2. Patients requiring continued NSAID therapy
   a. Healing of gastric ulcers associated with NSAID therapy: The usual dose is 20 mg once daily. The treatment duration is 4-8 weeks.
   b. Prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk: 20 mg once daily.
3. Treatment of Zollinger Ellison Syndrome: The recommended initial dosage is Axesom 40 mg twice daily. The dosage should then be individually adjusted and treatment continues as long as clinically indicated. 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.

Adolescents from the age of 12 years

1. Treatment of duodenal ulcer caused by Helicobacter pylori

The posology recommendation is:

Weight	Posology
30 - 40 kg	Combination with two antibiotics: Axesom 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered together twice daily for one week.
> 40 kg	Combination with two antibiotics: Axesom 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered together twice daily for one week.

Impaired renal function

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,

Impaired hepatic function

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 AXESOM should not be exceeded.

Elderly

Dose adjustment is not required in the elderly.

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation. Esomeprazole should not be used concomitantly with nelfinavir.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with AXESOM 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. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter. Increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be temporarily stopped for at least five days before CgA measurements.

SIDE EFFECTS

The reactions are classified according to frequency 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; not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Rare: Leukopenia, thrombocytopenia

Very rare: Agranulocytosis, pancytopenia Immune system disorders

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

Metabolism and nutrition disorders

Uncommon: Peripheral oedema

Rare: Hyponatraemia

Very rare: Hypomagnesaemia

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, confusion, depression

Very rare: Aggression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and labyrinth disorders

Uncommon: Vertigo

Respiratory, thoracic and mediastinal disorders

Rare: Bronchospasm

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Uncommon: Dry mouth

Rare: Stomatitis, gastrointestinal candidiasis

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice

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

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritus, rash, urticaria

Rare: Alopecia, photosensitivity

Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia

Very rare: Muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: Gynaecomastia

General disorders and administration site conditions

Rare: Malaise, increased sweating

PREGNANCY AND LACTATION

Caution should be exercised when prescribing to pregnant women.It is not known whether esomeprazole is excreted in human breast milk. Therefore AXESOM should not be used during breast-feeding.

OVERDOSE

There is very limited experience to date with deliberate overdose. 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 utilised.

STORAGE

Store below 25°C in a dry place. Protect from light.

PRESENTATION

1. Axesom 20mg Capsules: Blister pack of 2x7's.
2. Axesom 40mg Capsules: Blister pack of 2x7's.

TO BE SOLD ON THE PRESCRIPTION OF A REGISTERED MEDICAL PRACTITIONER ONLY

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN

ایکسَم

(ایسومیپرازول)

کیپسولز

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خوراک

ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت کی جائے۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 25°C سے کم درجہ حرارت پر، نمی اور روشنی سے محفوظ رکھیں۔

HIGHNOON LABORATORIES LTD.
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