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## E P Z
(Esomeprazole Tablets)

**COMPOSITION :**

**EPZ - 20 :** Each enteric coated tablet contains: Esomeprazole magnesium USP equivalent to Esomeprazole 20mg

**EPZ - 40 :** Each enteric coated tablet contains: Esomeprazole magnesium USP equivalent to Esomeprazole 40mg

**LIST OF EXCIPIENTS**

**For EPZ-20 and EPZ-40**

1. Esomeprazole Magnesium USP
2. Lactose BP
3. Crospovidone BP
4. Calcium hydroxide BP
5. Povidone K30 BP
6. Maize Starch BP
7. Titanium dioxide BP
8. Dichloromethane BP
9. Purified Talc BP
10. Colloidal Anhydrous Silica BP
11. Magnesium Stearate BP
12. Hypromellose E15 BP
13. Isopropyl Alcohol BP
14. Hypromellose Phthalate BP
15. Sunset yellow IHS
16. Iron Oxide of Yellow IHS
17. Acetone BP

**PHARMACOKINETICS :**

*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 40mg and increases to 89% after repeated once-daily administration. For 20mg 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 non-linear dose-AUC relationship 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 1-2% 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. The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years of age). Following a single dose of 40mg 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. 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 20mg 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.

**PHARMACODYNAMICS :**

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 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. 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.
One week treatment with esomeprazole 20 mg b.i.d. and appropriate antibiotics, results in successful eradication of *H. pylori* in approximately 90% of patients. After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.
*Other effects related to acid inhibition:* During treatment with antisecretory drugs serum gastrin increases in response to the decreased acid secretion. 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. During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

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**INDICATIONS :**

EPZ- (Esomeprazole tablets) are indicated for:
*Gastro-Oesophageal Reflux Disease (GORD)*
- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)
*In combination with an appropriate antibacterial therapeutic regimen for the eradication of Helicobacter pylori and* - healing of *Helicobacter pylori* associated duodenal ulcer and
- prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

**CONTRAINDICATIONS :**

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

**POSOLOGY & ADMINISTRATIONS :**

The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed. For patients who have difficulty in swallowing, the tablets can also be dispersed in half a glass of non-carbonated water. No other liquids should be used as the enteric coat may be dissolved. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.
For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered through a gastric tube. It is important that the appropriateness of the selected syringe and tube is carefully tested. *Gastro-Oesophageal Reflux Disease (GORD)* - 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. - long-term management of patients with healed oesophagitis to prevent relapse 20 mg once daily. - 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 an on-demand regimen taking 20 mg once daily, when needed. *In combination with an appropriate antibacterial therapeutic regimen for the eradication of Helicobacter pylori and* - healing of *Helicobacter pylori* associated duodenal ulcer and
- prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.
20 mg Esomeprazole with 1 g amoxicillin and 500 mg clarithromycin, all twice daily for 7 days.
*Children:* Esomeprazole should not be used in children since no data is available.
*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 Esomeprazole should not be exceeded. *Elderly:* Dose adjustment is not required in the elderly.

**WARNINGS & PRECAUTIONS :**

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

**POSSIBLE DRUG/FOOD INTERACTIONS:**
**For EPZ-20 and EPZ-40**

Contraindications of concomitant use
**Antiretroviral agents :** Omeprazole, the racemate of D+S omeprazole (esomeprazole), has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. 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, Cmax and Cmin). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC, Cmax and Cmin by 36–39% and mean AUC, Cmax and Cmin for the pharmacologically active metabolite M8 was reduced by 75-92%. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole. No interaction study has been performed with VIMOVO and atazanavir. However, due to the similar pharmacodynamic and pharmacokinetic properties of omeprazole and esomeprazole, the concomitant use of atazanavir and nelfinavir with esomeprazole is not recommended and concomitant administration with VIMOVO is contraindicated.

**Acetylsalicylic acid :** VIMOVO can be administered with low-dose acetylsalicylic acid (≤325 mg/day) therapy. In clinical trials, patients taking VIMOVO in combination with low-dose acetylsalicylic acid did not have an increased occurrence of gastric ulcers compared to patients taking VIMOVO alone (see section 5.1), However, the concurrent use of acetylsalicylic acid and VIMOVO may still increase the risk of serious adverse events.

**Tacrolimus :** As with all NSAIDs, there is a possible risk of nephrotoxicity when naproxen is co-administered with tacrolimus. Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus. During treatment with VIMOVO, a reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

**Ciclosporin :** As with all NSAIDs, caution is advised when ciclosporin is co-administered because of the increased risk of nephrotoxicity.

**Diuretics :** Clinical studies, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.

**Selective Serotonin Reuptake Inhibitors (SSRIs)** Concomitant use of NSAIDs, including COX-2 selective inhibitors, and SSRIs increases the risk of gastrointestinal bleeding.

**Corticosteroids :** There is an increased risk of gastrointestinal bleeding when corticosteroids are combined with NSAIDs including COX–2 selective inhibitors. Caution should be used when NSAIDs are administered concomitantly with corticosteroids.

**ACE-inhibitors/Angiotensin II receptor antagonists :** Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors and angiotensin II receptor antagonists. NSAIDs may also increase the risk of renal impairment associated with the use of ACE-inhibitors or angiotensin II receptor antagonists. The combination of NSAIDs and ACE-inhibitors or angiotensin II receptor antagonists should be given with caution in patients who are older, volume-depleted, or with impaired renal function.

**Digoxin :** NSAIDs may increase plasma cardiac glycoside levels when co-administered with cardiac glycosides such as digoxin.

**Lithium** NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

**Methotrexate :** When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model. This may indicate that both esomeprazole and naproxen could enhance the toxicity of methotrexate. The clinical relevance is likely to be greater in patients receiving high doses of methotrexate and in patients with renal dysfunction. Caution should be used when VIMOVO is administered concomitantly with methotrexate. In high-dose methotrexate administration a temporary withdrawal of VIMOVO is recommended.

**Sulphonylureas, Hydantoins:** Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as sulphonylureas, and hydantoins. Patients simultaneously receiving naproxen and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

**Beta receptor-blockers :** Naproxen and other NSAIDs can reduce the antihypertensive effect of propranolol and other beta-blockers.

**Probenecid :** Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

**DRUG INTERACTIONS :**

*Effects of esomeprazole on the pharmacokinetics of other drugs:* The decreased intragastric acidity during treatment with esomeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole. 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. 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. Concomitant administration of 40mg 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 treatment. 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(t1/2) 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 or quinidine. Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.
*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. Dose adjustment of esomeprazole is not required.

**ADVERSE REACTIONS :**

The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. None was found to be dose-related.
Common (>1/100, <1/10) : Headache, abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation.
Uncommon (>1/1000, <1/100): Dermatitis, pruritus, urticaria, dizziness, dry mouth
Rare (>1/10000, 1<1000): Hypersensitivity reactions e.g. angioedema, anaphylactic reaction and Increased liver enzymes.
The following adverse drug reactions have been observed for the racemate (omeprazole) and may occur with esomeprazole:
*Central and peripheral nervous system:* Paraesthesia, somnolence, insomnia, vertigo. Reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients.
*Endocrine: Gynaecomastia.*
*Gastrointestinal:* Stomatitis and gastrointestinal candidiasis.
*Haematological:* Leukopenia, thrombocytopenia, agranulocytosis and pancytopenia.
*Hepatic:* Encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure.
*Musculoskeletal:* Arthralgia, muscular weakness and myalgia.
*Skin:* Rash, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia.
*Other:* Malaise. Hypersensitivity reactions e.g. fever, bronchospasm, interstitial nephritis. Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia.

**PREGNANCY & LACTATION :**

For esomeprazole no data on exposed pregnancies are available. 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. It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore EPZ should not be used during breast-feeding.

**OVERDOSE :**

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280mg 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 utilised.

**STORAGE :** Store below 30°C. Protect from light and moisture.

**SHELF LIFE :** 24 Months.

**PRESENTATION :**

**EPZ - 20** : Alu Blister pack of 10 tablets.
**EPZ - 40** : Alu Blister pack of 10 tablets.

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