Primazol®

Esomeprazole Magnesium Dihydrate

FORMS AND PRESENTATION
Primazol® 20: Gastro resistant capsules: Box of 28.
Primazol® 40: Gastro resistant capsules: Box of 28.
COMPOSITION
Primazol® 20: Each capsule contains Esomeprazole Magnesium Dihydrate eq. to Esomeprazole 20mg.
Primazol® 40: Each capsule contains Esomeprazole Magnesium Dihydrate eq. to Esomeprazole 40mg.
Excipients: Hypromellose, sugar spheres, polysorbate, mannitol, Diacetylated monoglyceride, talc, eudragit, triethyl citrate, gelucire, gelatin, methyl paraben, propyl paraben, silica, bronopol, sodium lauryl sulphate, glycerine, polydimethylsiloxane, octylphenoxy polyethoxy ethanol, polyethylene glycol sorbitan monolaurate, propylene glycol, sodium benzoate, methyl parahydroxybenzoate, propyl parahydroxybenzoate.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Drugs for acid-related disorders proton pump inhibitors,
ATC Code: A02BC05.
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.
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.
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 its effect 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.
INDICATIONS
Primazol® is indicated in adults and adolescents (≥ 12 years old) for:
Gastro-Esophageal Reflux Disease (GERD)
- treatment of erosive reflux esophagitis
- long-term management of patients with healed esophagitis to prevent relapse
- symptomatic treatment of gastro-esophageal reflux disease (GERD)

Additional indications in adults:
In combination with appropriate antibacterial therapeutic regimens 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.

Patients requiring continued NSAID therapy
- healing of gastric ulcers associated with NSAID therapy
- prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk

Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers
Treatment of Zollinger Ellison Syndrome
Additional indication in adolescents:
In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori
CONTRAINDICATIONS
Hypersensitivity to the active substance, to substituted benzimidazoles or to any of the excipients listed.
Esomeprazole should not be used concomitantly with nelfinavir.
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.
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 should be considered when the triple therapy is used in patients concurrently taking other active substances 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 achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.
Hypomagnesemia: Severe hypomagnesemia was diagnosed 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 hypomagnesemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care 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. Patients at risk of osteoporosis should receive care and 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.
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. 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.
Serious cutaneous adverse reactions (SCARs): Serious cutaneous adverse reactions (SCARs) such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening, have been diagnosed very rarely in association with Esomeprazole treatment. Patients should be advised of the signs and symptoms of the severe skin reaction EM/SJS/TEN/DRESS and should seek medical advice from their physician promptly and Esomeprazole should be discontinued immediately and additional medical care/close monitoring should be provided as needed. Re-challenge should not be undertaken in patients with EM/SJS/TEN/DRESS.
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.
Effects on ability to drive and use machines
Esomeprazole has minor influence on the ability to drive or use machines due to possible adverse reactions such as dizziness (uncommon) and blurred vision (rare). If affected patients should not drive or use machines.
FERTILITY, PREGNANCY AND LACTATION
Pregnancy
A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of Esomeprazole. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
Breast-feeding
It is not known whether Esomeprazole is excreted in human breast milk. There is insufficient information on the effects of Esomeprazole in newborns/infants, it should not be used during breast-feeding.
Fertility
Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.
DRUG INTERACTIONS
Effects of Esomeprazole on the pharmacokinetics of other drugs
Protease inhibitors
For atazanavir and nelfinavir, decreased serum levels is possible when given together with Esomeprazole and concomitant administration is not recommended. Omeprazole and/or Esomeprazole 20mg dq can increase serum levels (80-100%) during treatment with saquinavir (with concomitant ritonavir). However, treatment with Esomeprazole 20mg dq has no effect on the exposure of darunavir (with concomitant ritonavir) and 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 the potential 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 can increase the bioavailability of digoxin by 10%. Digoxin toxicity has a rare occurrence. 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 other medicinal products metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine,

phenytoin etc., the plasma concentrations of these active substances 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 can result in a 45% decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin

Concomitant administration of 40 mg Esomeprazole can result 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) Cmax and AUC by 15% and 41%, respectively.

Cilostazol

Esomeprazole act as inhibitors of CYP2C19 and can increase Cmax and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Cisapride

Concomitant administration of 40 mg Esomeprazole result 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.

Warfarin

Monitoring is recommended when initiating and ending concomitant Esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

Clopidogrel

The pharmacokinetic (PK)/ pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and Esomeprazole (40 mg p.o.daily) results in decreased exposure to the active metabolite of clopidogrel by an average of 40% and in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. As a precaution concomitant use of clopidogrel should be discouraged.

Effects of other medicinal products on the pharmacokinetics of Esomeprazole

Medicinal products which inhibit CYP2C19 and/or CYP3A4

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 its 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, it 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.

ADVERSE EFFECTS

Adverse effects are listed below by system organ class and frequency. Frequencies are defined as: 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: Leukopenia, thrombocytopenia (Rare); Agranulocytosis, pancytopenia (Very rare).

Immune system disorders: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock (Rare).

Metabolism and nutrition disorders: Peripheral oedema (Uncommon); Hyponatraemia (Rare); Hypomagnesaemia, hypocalcaemia, hypokalaemia (Not known).

Psychiatric disorders: Insomnia (Uncommon); Agitation, confusion, depression (Rare); Aggression, hallucinations (Very rare).

Nervous system disorders: Headache (Common); Dizziness, paraesthesia, somnolence (Uncommon); Taste disturbance (Rare).

Eye disorders: Blurred vision (Rare).

Ear and labyrinth disorders: Vertigo (Uncommon).

Respiratory, thoracic and mediastinal disorders: Bronchospasm (Rare).

Gastrointestinal disorders: Abdominal pain, constipation, diarrhoea, flatulence, nausea /vomiting, fundic gland polyps (benign) (Common); Dry mouth(Uncommon);Stomatitis, gastrointestinal candidiasis (Rare); Microscopic colitis (Not known).

Hepatobiliary disorders: Increased liver enzymes (Uncommon); Hepatitis with or without jaundice(Rare);Hepatic failure, encephalopathy in patients with pre-existing liver disease (Very rare).

Skin and subcutaneous tissue disorders: Dermatitis, pruritus, rash, urticaria(Uncommon) ; Alopecia, photosensitivity(Rare); Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) (Very rare); Subacute cutaneous lupus erythematosus(Not known).

Musculoskeletal and connective tissue disorders: Fracture of the hip, wrist or spine(Uncommon); Arthralgia, myalgia (Rare); Muscular weakness (Very rare).

Renal and urinary disorders: Interstitial nephritis; in some patients renal failure has been reported concomitantly (Very rare).

Reproductive system and breast disorders: Gynaecomastia(Very rare).

General disorders and administration site conditions: Malaise, increased sweating(Rare).

DOSAGE AND 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 oesophagitis has not healed or who have persistent symptoms.

- long-term management of patients with healed esophagitis to prevent relapse: 20 mg once daily.

- symptomatic treatment of gastroesophageal reflux disease (GERD): 20 mg once daily in patients without oesophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily. An on-demand regimen taking 20 mg once daily, when needed, can be used. In NSAID treated patients at risk of developing gastric and duodenal ulcers, subsequent symptom control using an on-demand regimen is not recommended.

In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori

-healing of Helicobacter pylori associated duodenal ulcer and prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcers: 20 mg of Primazol® with 1 g amoxicillin and 500 mg clarithromycin, all twice daily for 7 days.

Patients requiring continued NSAID therapy

- healing of gastric ulcers associated with NSAID therapy: The usual dose is 20 mg once daily. The treatment duration is 4-8 weeks.

- prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk: a dose of 20mg of Primazol® once daily

Prolonged treatment after IV induced prevention of rebleeding of peptic ulcers: 40 mg once daily for 4 weeks after IV induced prevention of rebleeding of peptic ulcers.

Treatment of Zollinger Ellison Syndrome: The recommended initial dosage is 40 mg of Primazol® twice daily. The dosage should 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 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 Primazol® should not be exceeded.

Elderly

Dose adjustment is not required in the elderly.

Paediatric population

Adolescents from the age of 12 years

Gastro-Esophageal Reflux Disease (GERD)

- treatment of erosive reflux esophagitis: 40mg of Primazol® 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.

- long-term management of patients with healed esophagitis to prevent relapse: a dose of 20mg of Primazol® once daily.

- symptomatic treatment of gastro-esophageal reflux disease (GERD): 20mg once daily in patients without esophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20mg once daily.

Treatment of duodenal ulcer caused by Helicobacter pylori

When selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents. The treatment should be supervised by a specialist.

The posology recommendation is:

Weight	Posology
30 - 40 kg	Combination with two antibiotics: Esomeprazole 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: Esomeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered together twice daily for one week.

Children below the age of 12 years

Esomeprazole capsules should not be used in children younger than 12 years since no data is available. Other pharmaceutical forms of Esomeprazole may be more suitable for this age group.

Method of administration

The capsules should be swallowed whole with liquid, not chewed or crushed.

For patients who have difficulty in swallowing, open the capsules and disperse the content in half a glass of non-carbonated water. No other liquids should be used as the enteric coating may be dissolved. Drink the liquid with the pellets immediately. 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 capsules 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.

Administration through gastric tube

1. Put the capsule content into an appropriate syringe and fill the syringe with approximately 25 ml water and approximately 5mL air. For some tubes, dispersion in 50 ml water is needed to prevent the pellets from clogging the tube.
2. Immediately shake the syringe to disperse the content.
3. Hold the syringe with the tip up and check that the tip has not clogged.
4. Attach the syringe to the tube whilst maintaining the above position.
5. Shake the syringe in a circular motion and position it with the tip pointing down. Immediately inject 5 – 10 ml into the tube. Invert the syringe after injection and shake (the syringe must be held with the tip pointing up to avoid clogging of the tip)
6. Turn the syringe with the tip down and immediately inject another 5-10 ml into the tube. Repeat this procedure until the syringe is empty.
7. Fill the syringe with 25 ml of water and 5 ml of air and repeat step 5 if necessary to wash down any sediment left in the syringe. For some tubes, 50 ml water is needed.

OVERDOSAGE

There is very limited experience to date with deliberate 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 utilised.

STORAGE CONDITIONS

Store below 25°C.

Keep in original pack in intact conditions.

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Marketing Authorization Holder

Benta S.A.L. - Lebanon

Manufacturer

Manufactured by **Benta Lyon** SAS Saint Genis Laval, France

For Benta S.A.L. – Lebanon

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