BADOMEPRAZOLE

20 mg delayed release capsule

Composition :

Each DR capsule contains:

Active ingredient :

Esomeprazole magnesium trihydrate 22.3 mg Equ. To 20 mg esomeprazole

Inactive ingredient (pellets composition) :

Sugar spheres, sodium carbonate, Povidone K-30,diosodium hydrogen orthophosphate,sucrose, sodium lauryl sulfate, Hypromellose (HPMC-E5),titanium dioxide, talc, hypromellose phthalate (HPMCO HP55)

Cetyl alcohol.

Pharmaceutical form

Delayed release hard gelatin capsule,

Pharmacological Properties:

1-pharmacodynamic Properties

Pharmacotherapeutic group : proton pump inhibitors

Esomeprazole is the S-isomer of omeprazolr 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 pharmacodynamics 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 Badomeprazole 20 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.

Therapeutic effects of acid inhibition

One week treatment with Esomeprazole 20 mg b.i.d. and appropriate antibiotics, results in successful ersdication of *H. pylori* in approximately 90 % of patients.

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory active substances for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

2- Pharmacokinetic properties

Absorption and distribution

Badomeprazole 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 . for 20 mg Esomeprazole is 50 % after a single dose and increased to 68 % after repeated once daily administration. The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 l/kg body weight Badomeprazole 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 (CYPP. The major part of the metabolism of esomeprazole is dependent on the polymorphic. CYP2C19 , Responsible for the formation of the hydroxyl-and desmethyl metabolites of Badomeprazole. The remaining part is dependent on another specific isomform, CYP3A4, responsible for the formation of Badomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individulas 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 1.3hours after repeated once-daily dosing. The pharmacokinetics of Badomeprazole 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 – dependend 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 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 rffect on gastric acid secretion. Almost 80% of an oral dose of Esomeprazole excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent compound is found in urine.

Impaired organ function

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, amaximum of 20 mg should not be exceeded in patients with severe dysfunction. esomeprazole or its major metabolites do not show any tendency to accoumlate 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 metabolism 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.

Paediatric

Adolescents 12-18 years

Following repeated dose administration of 20 mg, 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.

Indications

Badomeprazole capsules are indicated for:

Gastroesophageal Reflix Disease (GORD)

- treatment of erosive reflux oesophagitis
- long –term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastroesophageal reflux disease (GORD)

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*

Patient requiring continued NSAID therapy

Healing of gastric ulcers associated with NSAID therapy.
Preventiono of gastric and duodenal ulcers associated with NSAID therapy , in patients at risk.

Prolonged treatment after IV induced Prevention of rebleeding of peptic ulcers. Treatment of Zollinger Ellison syndrome.

Dosage & method of administration

The capsules should be swallowed whole with some water.the capsules should not be chewed or crushed .

For Patients who have difficulty in swallowing, the capsules can also be opened and the pellets mixed in half a glass of non-carbonated water. No other liquids should be used as the enteric coating may be dissolved. Drink the water 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 capsules can be opened and pellets mixed 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 before use (seesection 6.6).

Adults and adolescents from the age of 12 years

Gastroesophageal reflux disease (GORD)

-treatment of erosive reflux oesophagitis

20 mg twice 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 patient with healed oesophagitis to prevent relapse
20 mg once daily
-symptomatic treatment of gastroesophageal reflux disease(GORD)

20mg once daily in patients without oesophagitis. If symptom control has not been achieved after 4 weeks, the patient shoutd be futher investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20mg once daily. In adults,an on demand regimen taking 20 mg once daily when needed, can be used . in NSAID treated at risk of developing gastric and duodenal ulcers, subsequent symptom control using an on demand regimen is not recommended.

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 *Helicobater pylori* associated ulcers.

20 mg Badomeprazole 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 risl :20 mg once daily.

Prolonged treatment after IV induced prevention of rebleeding of peptic ulcers

20 mg twice daily for 4 weeks after IV induced prevention of rebleeding of peptic ulcers.

Treatment of Zollinger Ellision Syndrome

The recommended initial dosage is Badomeprazolr 20mg 4 times 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 patient can be controlled on doses between 80 to 160 mg Badomeprzole daily. With doses above 80 mg daily, the dose should be divided and gived twice daily.

Children below the age of 12 years

Badomeprazole sjould not be used in children younger than 12 years 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 sever 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 patient with severe liver impairment,a maximum dose of 20 mg Badomeprazole should not be exceesed.

Elderly

Dose adjustment is not required in the elderly .

Do not eat the desiccant capsule provided in the container.

Contraindications

Known hypersensitivity to Badomeprazole substituted benzimidazoles or any of the excipients.

Badomeprazole should not be used concomitantly with nelfinavir.

Precautions& Warnings

In the presence of any alarm symptom(e.g. significant unintentional weghit loss, recurrent vomiting dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malidnancy should be excluded, as treatment with Badomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a years) should be kept under regular surveillance.

Patient on demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing Badomebrazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of Badomeprazole should be considered.

When prescribing Badomeprazole for eradication of *Helicobacter pylori* possible active substance interactions for all components in triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interaction for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other medicinal Products metabolized via CYP3A4 such as cisapride.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infection such as *Salmonella* and *Campylobater*

Co-administration of Badomebrazole with atazanavir is not recommended. If the combination of atazanavir with a proton pump inhibitor is judged unavoidable , close clinical monitoring is recommended in conination

with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; Badomeprazole 20 mg should not be exceeded.

-several published observational studies suggest that proton pumb inhibitor (ppI) rherapy may be associated with an increased risk for osteoporosis- releated fractures of the hip, wrist, or spine. The risk of fracture was increased in pations who received high dose , defined as multiple daily doses, and long term PPI therapy (a year or longer). Patients should use the lowest dose and shortest durantion of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to the established treatment guideline.

-Prescribtion proton pump inhibitor (PPI)dugs may cause low serum magnesium levels hypomagnesemia)if taken for prolonged periods of time (in most cases, linger than one years),magnesium supplementation alone did not improve low serum magnesium levels and PPI had to be discontinued.

Low serum magnesium levels can result in serious adverse events including muscle spasm (tetany),irregular heartbeat (arrhythmias), and convulsions(seizures)however, patients do not always have these symptoms. Treatment of hypomagenesemia generally requires magnesium supplements. Treatment in patients taking a PPI and who have hypomamgnesemia may also require stopping the PPI.

Special information about some of the ingredients

Badomeprazole contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose – galactose malabsorption or sucrose-isomaltasr insufficiency should not take medicine.

Use caution when administering high-dose methotrexate to pations receiving proton pump inhibitor(PPI) therapy.case reports and published population.

Pharmacokinetic studies suggest that concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose),any elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. In two of these cases, delayed methotrexate elimination was observed when high-dose methotrexate was co-administered with PPIs, but was not observed when methotrexate was co-administraed with ranitidine. However, on formal drug interaction studies of methotrexate with ranitidine have been conducted.

- **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 {Drug name}. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Overdose

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280 mg were gastrointestinal sumptoms and weakness. Single doses of 80 mg Badomeprazole were uneventful. No specific antidote is Known . Badomeprazole is extensively plasma protein bound and is rherfore not readily

dialyzable. As in any case of overdose ,treatment should be symptomatic and general supportive measures should be utilized.

Side effects

- **Skin and subcutaneous tissue disorders**
  Frequency 'not known': Subacute cutaneous lupus erythematosus

The following adverse druge reactions have been identified or suspected in the clinical trials programme for badomeprazole and post-marketing. None was found to be dose-related.

The reaction 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, thromobocytopenia

Very rare : Agranulocytosis, Pancytopenia

Immune system disorders

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

Metabolism and nutrition disorders

Uncommon: Peripheral oedema

Rare: Hyponatraemia

Psychiatric disorders

Uncommon : insomnia

Rare : Agitation, confusion, depression

Very rare: Aggression, hallucinations

Nervous system disorders

Common L 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, diarrhea, flatulence, nausea/vomiting

Uncommon: dry mouth

Rare : stomatitis, gastrointestinal candidiasis

Hepatobiliary disorder

uncommonLincreased 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, urticarial

Rare : Alopecia, photosensitivity

Very rare : Erythema multiforme, stevens-johnson syndrome, toxic epidermal necrolysis(TEN)

Musculoskeletal,connective tissur and bone disorder

Rare : Arthralgia, myalgia

Very rare : Muscular weakness

Renal and urinary disorders

Very rare :interstitial nephritis

Reproductive system and breast disorder

Very rare : Gynaecomastria

General disorders and administration site conditions

Rare : Malaise, increased sweating

Post marketing reports

Muscloskeletal : bone fracture

Pregnancy and Lactation

Coution should be exercised when prescribing to pregnant women.

It is not known whether Badomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore Badomeprazole should be used during breast-feeding.

Drug interactions

Effect of Badomeprazole on the pharmacokinetics of other active substances

-Medicinal products with pH dependent absorption

The decreased intragastric acidity duration treatment with Badomperazole, might increase or decrease the absorption of active substance 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 Badomeprazole.

Esomeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interaction 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 recommmensed.

treatment with omeprazole 20 mg once daily had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir).treatment with esomeprazole 20 mg once daily had no effect on the exposure of amprenavir(with and without concomitant ritonavir).

Due to the similar pharmacodynamics effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with Badomeprazole and nelfinavir is contraindicated.

-Active substances metabolized by CYP2C19

Badomeprazole inhibits CYP2C19, the major Badomeprazole metabolising enzyme. Thus, when Badomeprazole is combined with active substances metabolisted by CYP2C19, such as diazepam,citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentration of these active substances may be increased and a dose reduction could be needed. This should be considered especially when prescribing Badomeprazole for on demand therapy. It is recommended to monitor the plasma concentration of phenytoin when treatment with Badomeprazole is introduced or withdrawn.

-monitoring is recommended when initiating and eding concomitant esomeprazole treatment during treatment with warfarin or other comarin 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 during short-time studies.

-Effects of other active substance on the pharmacokinetics of Badomeprazole.

Badomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of Badomebrazole and a CYP3A4 inhibitor, clarithromycin(500 mg b.i.d.),resulted in a doubling of the exposure(AUC) to Badomperazole.

Concomitant administration of Badomeprazole and acombined inhibitor of CYP2C19 and CYP3A4 may result in more than doubling of Badomeprazol exposure.

The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUCt by 280 %. A dose adjustment of Badomeprazole is not regulary 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.

Omeorazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over study, increased Cmax amd AUC of cilostazol by 18 % and 26% respectively. Cmax and AUC of one of its metabolites ,3,4 dihydrocilostazol, which has 4-7 time the activity of cilostazol, were increased by 29 % and 69% respectively.

Co-administration of cilostazol with esomeprazole is expected to increase concentration of cilostazol and its metabolite. Therefore a dose reduction of cilostazol form 100 mg b.i.d. to 50 mg b.i.d. should be considered .

Packing

Carton box containing high-density polyethylene (HDPE) bottle with an induction seal closure and (HDPE) cap containing 14 gastro-resistant capsules, and contains a sealed container with silica gel desiccant and an insert leaflet

Storage:

Stored at temp. not exceeding 30^{o}C and in dry place.

Manufactured by Badr pharma for pharmaceutical industries