Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Omeprazole Gastro-resistant Capsules IP
(Brand Name: OMEPREN® Capsules)

2. Qualitative and Quantitative Composition

Each Hard Gelatin Capsule Contains:
Omeprazole IP ……. 20 mg.
(as Gastro-Resistant pellets)
Excipients…….…….. q.s.
Colours used in capsule shell: Brilliant Blue FCF, Titanium Dioxide.
Methylparaben and Propylparaben used as antimicrobial preservatives.

3. Dosage Form and Strength

Dosage Form: Capsules.
Dosage Strength: Omeprazole 20 mg per capsule.

4. Clinical Particulars

4.1 Therapeutic Indication

OMEPREN Capsules are indicated in the following:

Adults

- Treatment of duodenal ulcers.
- Prevention of relapse of duodenal ulcers.
- Treatment of gastric ulcers.
- Prevention of relapse of gastric ulcers.
- Treatment of *Helicobacter pylori* (*H. pylori*)-associated peptic ulcers (in combination with appropriate antibiotics).
- Treatment of non-steroidal anti-inflammatory drug (NSAID)-associated gastric and duodenal ulcers.
- Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk.
- Treatment of erosive/reflux esophagitis.
- Maintenance therapy for healing of erosive esophagitis.
- Treatment of symptomatic (heartburn and acid regurgitation) gastro-esophageal reflux disease (GERD).
- Treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome.

Paediatric Patients (children over 1 year of age and ≥ 10 kg)

- Treatment of erosive/reflux esophagitis.
- Symptomatic treatment of GERD.

4.2Posology and Method of Administration

Adults

1. **Treatment of duodenal ulcers:** Usual recommended dose is 20 mg once daily for up to 4 weeks. In patients with poor response, 40 mg once daily is recommended.
2. **Prevention of relapse of duodenal ulcers:** Usual recommended dose is 20 mg once daily for up to 4 weeks. In case of therapy failure, the dose can be increased to 40 mg.
3. **Treatment of gastric ulcers:** Usual recommended dose is 20 mg once daily for 4 to 8 weeks. In patients with poor response, 40 mg once daily is recommended for up to 8 weeks.
4. **Prevention of relapse of gastric ulcers:** For the prevention of relapse in patients with poorly responsive gastric ulcer the recommended dose is 20 mg once daily. If needed, the dose can be increased to 40 mg once daily.
5. **Treatment of *H. pylori*-associated peptic ulcers:** Either of the following combination drug therapy is recommended for eradication of *H. pylori* in peptic ulcer disease:
    a. Omeprazole 20 mg + Clarithromycin 500 mg + Amoxicillin 1000 mg, each twice daily for one week. Or,
    b. Omeprazole 20 mg + Clarithromycin 250 mg/500 mg + Metronidazole 400 mg / 500 mg or Tinidazole 500 mg, each twice daily for one week. Or,
    c. Omeprazole 40 mg once daily with Amoxicillin 500 mg + Metronidazole 400 mg / 500 mg or Tinidazole 500 mg, both three times a day for one week.

    In each regimen, if the patient is still *H. pylori* positive, therapy may be repeated.
6. **Treatment of NSAID-associated gastric and duodenal ulcers:** Usual recommended dose is 20 mg once daily for 4 to 8 weeks. In patients with poor response, 40 mg once daily is recommended.
7. **Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk** (age > 60 years, previous history of gastric and duodenal ulcers, previous history of upper gastrointestinal - GI bleeding): Usual recommended dose is 20 mg once daily.
8. **Treatment of erosive esophagitis:** The usual recommended dose is 20 mg once daily for 4 to 8 weeks. In patients with severe esophagitis recommended dose is 40 mg once daily for up to 8 weeks.
9. **Maintenance therapy for healing of erosive esophagitis:** The recommended dose is 20 mg once daily. Data is available up to 12 months.
10. **Treatment of symptomatic GERD:** Usual recommended dose is 20 mg once daily for up to 4 weeks.
11. **Treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome:** The dose should be individually adjusted and treatment continued as long as

clinically indicated. The recommended initial dose is 60 mg daily. When dose exceed 80 mg daily, the dose should be divided and given twice daily. Some patients have been treated continuously for more than 5 years.

Paediatric Patients (children over 1 year of age and ≥ 10 kg)
For the treatment of symptomatic GERD and reflux esophagitis, the recommended daily dose of omeprazole for paediatric patients 1 to 16 years of age is as follows:

Age	Weight	Recommended Dosage
≥ 1 year	10 to 20 kg	10 mg once daily. If needed, the dose can be increased to 20 mg once daily.
≥ 2 years	> 20 kg	20 mg once daily. If needed, the dose can be increased to 40 mg once daily.

1. **Treatment of reflux esophagitis:** Treatment duration is 4 to 8 weeks.
2. **Symptomatic treatment of heartburn and acid regurgitation in GERD:** Treatment duration is 2 to 4 weeks.

OMEPREN Capsules should be administered on empty stomach, preferably in the morning or at least 1 hour prior to meal. The capsules should be swallowed whole with water and not to be opened, chewed or crushed.
Or, as prescribed by the physician.

4.3Contraindications

OMEPREN Capsules are contraindicated in the following:

- Hypersensitivity to omeprazole or to substituted benzimidazoles or to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria.
- As like other proton pump inhibitors (PPIs), concomitant use of omeprazole with nelfinavir is contraindicated.

4.4Special Warnings and Precautions for Use

Gastric Malignancy: Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy. In the presence of any alarm symptom (e.g., significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.
Atrophic Gastritis: Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

Acute Interstitial Nephritis: Acute interstitial nephritis has been observed in patients taking PPIs including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Vitamin B_{12} Deficiency: Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B_{12}) caused by hypo-or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

***Clostridium Difficile*-Associated Diarrhea (CDAD):** Published observational studies suggest that PPI therapy like omeprazole may be associated with an increased risk of CDAD, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Interaction with Clopidogrel: Avoid concomitant use of omeprazole with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as omeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with 80 mg omeprazole reduces the pharmacological activity of clopidogrel, even when administered 12 hours apart. When using omeprazole, an alternative anti-platelet therapy should be considered.

Risk of Bone Fracture: Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose/multiple daily doses and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines and they should have an adequate intake of vitamin D and calcium.

Hypomagnesemia: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), monitoring of magnesium levels prior to initiation of PPI treatment and periodically thereafter should be considered.

Subacute Cutaneous Lupus Erythematosus (SCLE): PPIs 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 omeprazole therapy should be stopped. SCLE after previous treatment with a PPI may increase the risk of SCLE with other PPIs.

4.5Drug Interactions

A. Effects of Omeprazole on Pharmacokinetics of Other Drugs

1. Active Substances With pH-Dependent Absorption

The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of active substances with a gastric pH dependent absorption.

Nelfinavir or Atazanavir: The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole. Concomitant administration of omeprazole with nelfinavir is contraindicated. Concomitant administration of omeprazole with atazanavir is also not recommended.

Digoxin: Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10%. Digoxin toxicity has been rarely reported. However, caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should be then reinforced.

Clopidogrel: Results from studies in healthy subjects have shown a pharmacokinetic/ pharmacodynamic interaction between clopidogrel (300 mg loading dose and 75 mg daily maintenance dose) and omeprazole (80 mg daily) resulting in a decreased exposure to the active metabolite of clopidogrel by an average of 46% and a decreased maximum inhibition of (adenosine diphosphate - ADP-induced) platelet aggregation by an average of 16%. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

Other Drugs: The absorption of posaconazole, erlotinib, ketoconazole and itraconazole is significantly reduced and thus clinical efficacy may be impaired. For posaconazole and erlotinib concomitant use should be avoided.

2. Active Substances Metabolized by CYP2C19

Omeprazole is a moderate inhibitor of CYP2C19, the major metabolizing enzyme. Thus, the metabolism of concomitant active substances also metabolized by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Cilostazol: Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Phenytoin: Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating omeprazole treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment is required upon ending omeprazole treatment.

3. Other Drug Interactions

Saquinavir: Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70% for saquinavir. Therefore, clinical and laboratory monitoring for saquinavir toxicity is recommended during concurrent use with omeprazole. Dose reduction of saquinavir should be considered from the safety perspective for individual patients.

Tacrolimus: Concomitant administration of omeprazole has been reported 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.
Methotrexate: Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. A temporary withdrawal of omeprazole therapy may be considered in some patients receiving high-dose of methotrexate.

B. Effects of Other Drugs on Pharmacokinetics of Omeprazole

1. Drugs That Inhibits CYP2C19 and/or CYP3A4

Clarithromycin or Voriconazole: Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated, adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

2. Drugs That Induces CYP2C19 and/or CYP3A4

St. John's Wort or Rifampin: Drugs which induce CYP2C19 or CYP3A4 or both (such as St. John's Wort or rifampin) can substantially decrease omeprazole plasma concentrations by increasing omeprazole's rate of metabolism. Avoid concomitant use of omeprazole with St. John's Wort or rifampin.

Drug/Laboratory Tests Interactions

Increased Chromogranin A (CgA) Levels: Serum chromogranin A (CgA) level increases secondary to drug-induced decrease in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop omeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

4.6Use in Special Populations

Pregnant Women

Pregnancy Category C. Animal studies does not indicate any harm to the fetus. There are however, no adequate and well-controlled studies with omeprazole in pregnant women. Available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use. OMEPREN Capsules should be used during pregnancy only if the potential benefit justifies the possible risk to the fetus.

Lactating Women

Omeprazole secrets in breast milk following oral administration of omeprazole 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200 ml of milk. Caution should be exercised when OMEPREN Capsules are administered to a nursing woman.

Paediatric Patients

Safety of omeprazole has not been established in children below 1 year of age. Omeprazole can be used in children above 1 year of age for the treatment of symptomatic GERD and esophagitis. The safety and effectiveness of omeprazole for other paediatric uses have not been established. In general, OMEPREN Capsules are not suitable for use in children as there is no dosage feasibility with this formulation.

Geriatric Patients

There are no differences in safety and effectiveness between the elderly and younger subjects. However, greater sensitivity of some older individuals cannot be ruled out. Dose adjustment is not needed in the elderly population.

Renal Impairment Patients

Dose adjustment is not needed in patients with impaired renal function.

Hepatic Impairment Patients

In patients with chronic hepatic disease, the bioavailability of omeprazole increased to approximately 100% compared with intravenous (I.V.) dose, reflecting decreased first-pass effect; also, the plasma half-life of the drug increased to nearly 3 hours compared to 0.5 to 1 hour in healthy individuals. Plasma clearance averaged 70 ml/min, compared to 500 to 600 ml/min in normal subjects. Dose reduction should be considered, particularly for maintenance therapy for healing of erosive esophagitis. In patients with impaired hepatic function a daily dose of 10 to 20 mg of omeprazole may be sufficient.

4.7Effect on Ability to Drive and Use Machines

Omeprazole is not likely to affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machinery.

4.8Undesirable Effects

Clinical Trials Experience

The most common adverse reactions reported (i.e., with an incidence rate ≥ 2%) from omeprazole-treated patients enrolled in clinical studies include: Headache (6.9%), abdominal pain (5.2%), nausea (4.0%), diarrhea (3.7%), vomiting (3.2%), and flatulence (2.7%).

Additional adverse reactions that were reported with an incidence ≥ 1% include: Acid regurgitation (1.9%), upper respiratory infection (1.9%), constipation (1.5%), dizziness (1.5%), rash (1.5%), asthenia (1.3%), back pain (1.1%), and cough (1.1%).
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

Post-Marketing Experience

Acute kidney injury as an adverse drug reaction reported with the use of proton pump inhibitors. The following adverse reactions have been identified during post-approval use of omeprazole. Because these reactions are voluntarily reported from a population of uncertain size, it is not always possible to reliably estimate their actual frequency or establish a causal relationship to drug exposure.

Body as a Whole: Hypersensitivity reactions including anaphylaxis, anaphylactic shock, angioedema, bronchospasm, interstitial nephritis, urticaria, fever, pain, fatigue, malaise.

Cardiovascular: Angina, tachycardia, bradycardia, palpitations, elevated blood pressure, peripheral edema.

Endocrine: Gynecomastia.

Gastrointestinal: Pancreatitis, anorexia, irritable colon, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, stomatitis, abdominal swelling, dry mouth, microscopic colitis. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued. Gastro-duodenal carcinoids have been reported in patients with Zollinger-Ellison syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Hepatic: Hepatocellular disease, hepatic necrosis, hepatic encephalopathy, cholestatic disease, mixed hepatitis, jaundice, and elevations of liver function tests (ALT, AST, GGT, alkaline phosphatase, and bilirubin).

Infections and Infestations: *Clostridium difficile*-associated diarrhea (CDAD).

Metabolism and Nutritional Disorders: Hypoglycemia, hypocalcemia, hypokalemia, hyponatremia, hypomagnesemia, weight gain.

Musculoskeletal: Muscle weakness, myalgia, muscle cramps, joint pain, leg pain, bone fracture.

Nervous System/Psychiatric: Depression, agitation, aggression, hallucinations, confusion, insomnia, nervousness, apathy, somnolence, anxiety, dream abnormalities, tremors, paresthesia, vertigo.

Respiratory: Epistaxis, pharyngeal pain.

Skin: Severe generalized skin reactions including toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, photosensitivity, urticaria, rash, skin inflammation, pruritus, petechiae, purpura, alopecia, dry skin, hyperhidrosis.

Special Senses: Tinnitus, taste perversion.

Ocular: Optic atrophy, anterior ischemic optic neuropathy, optic neuritis, dry eye syndrome, ocular irritation, blurred vision, double vision.
Urogenital: Interstitial nephritis, hematuria, proteinuria, elevated serum creatinine, microscopic pyuria, urinary tract infection, glycosuria, urinary frequency, testicular pain.
Hematologic: Agranulocytosis, hemolytic anemia, pancytopenia, neutropenia, anemia, thrombocytopenia, leukopenia, leukocytosis.

4.9Overdose

Symptoms: Overdose with omeprazole has been reported in humans with doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Symptoms were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. Symptoms were transient, and no serious clinical outcome has been reported when omeprazole was taken alone.
Treatment: No specific antidote for omeprazole overdose is known. Omeprazole is extensively protein bound and therefore, not readily dialyzable. In the event of overdose, treatment should be symptomatic and supportive.

5. Pharmacological Properties

5.1 Mechanism of Action

Omeprazole is a racemic mixture of two enantiomers (S-omeprazole and R-omeprazole). Omeprazole belongs to class of antisecretory compounds (substituted benzimidazole proton pump inhibitors - PPIs). Omeprazole suppress gastric acid (hydrochloric acid – HCl) secretion by specific inhibition of the acid/proton pump i.e., H+/K+-ATPase enzyme system at the secretory surface of the gastric parietal cell.
Omeprazole is a weak base and is concentrated and converted to the active form (sulphenamide) in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H+ K+-ATPase - the acid pump. Thus, omeprazole blocks the final step of acid production. This effect is dose-dependent and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

5.2Pharmacodynamic Properties

Antisecretory Activity

After oral administration, the onset of the antisecretory effect of omeprazole occurs within one hour, with the maximum effect occurring within two hours. Inhibition of acid secretion is about 50% at 24 hours and the duration of inhibition lasts up to 72 hours. When the drug is discontinued, secretory activity returns gradually, over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days. Oral dosing with omeprazole once daily provides rapid and effective inhibition of daytime and night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment. Oral dosing

with omeprazole 20 mg maintains an intragastric pH of ≥ 3 for a mean time of 17 hours over a 24 hours period.

Serum Gastrin Effects

In studies involving more than 200 patients, serum gastrin levels increased during the first 1 to 2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine H_2-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3 to 3.6 fold versus 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

5.3Pharmacokinetic Properties

Absorption: OMEPREN Capsule contains omeprazole in the form of gastro-resistant pellets. This is necessary because, like other PPIs, omeprazole is acid-labile. Absorption of omeprazole, therefore, begins only after the pellets leave the stomach. Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1 to 2 hours after oral dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3 to 6 hours. The bioavailability from a single oral dose of omeprazole 20 to 40 mg is approximately 30 to 40%. After repeated once-daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on the bioavailability of omeprazole. Peak plasma concentration of omeprazole and AUC (area under the curve of plasma concentration of a drug versus time) is proportional in doses up to 40 mg. Because of a saturable first-pass effect (decrease of first-pass metabolism and systemic clearance), a non-linear response/increase in peak plasma concentration and AUC occurs with doses greater than 40 mg.

Distribution: The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight. Plasma protein binding of omeprazole is approximately 95%.

Metabolism: Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulfone. These metabolites have very little or no antisecretory activity.

Excretion: In healthy subjects the plasma half-life is 0.5 to 1 hour, and the total body clearance is 500 to 600 ml/min. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. Almost 80% of an oral dose of omeprazole is excreted as metabolites (at least 6 metabolites) in the urine, the remainder in the faeces, primarily originating from bile secretion.

6. Nonclinical Properties

6.1 Animal Toxicology

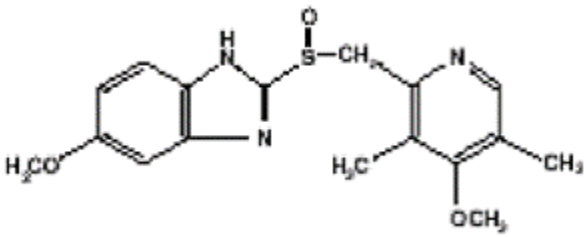
Carcinogenicity: In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.4 to 34 times a human dose of 40 mg/day, as expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male 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, ECL cell hyperplasia was present in all treated groups of both sexes.
In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.1 to 3.9 times the human dose of 40 mg/day, based on a body surface area basis). No astrocytomas were observed in female rats in this study.
In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males or females at the high dose of 140.8 mg/kg/day (about 34 times the human dose of 40 mg/day on a body surface area basis).
Mutagenesis: Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames test, an in vitro mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay.
Impairment of Fertility: Omeprazole at oral doses up to 138 mg/kg/day in rats (about 34 times an oral human dose of 40 mg on a body surface area basis) was found to have no effect on fertility and reproductive performance.
Teratogenicity: Reproductive studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole.
In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 3.4 to 34 times the human dose of 40 mg/day on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 3.4 to 34 times the human dose of 40 mg/day on a body surface area basis).

7. Description

OMEPREN Capsules are blue coloured hard gelatin capsules filled with white omeprazole pellets. Each capsule of OMEPREN contains 20 mg of omeprazole for oral administration.

Omeprazole is a substituted benzimidazole compound that inhibits gastric acid secretion by selective and irreversible inhibition of proton pump activity.
Omeprazole is a white to off-white crystalline powder. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water.

Omeprazole is not stable in acidic pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.
Molecular Weight: 345.42 g/mol.
Molecular Formula: C17H19N3O3S.
Chemical Name: 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole.
Structural Formula:



Inactive ingredients (excipients) of omeprazole pellets include Hypromellose, Mannitol, Sucrose, Crospovidone, HPMC Phthalate, Diethyl Phthalate, Isopropyl Alcohol, Dicloromethane and E.H.G. Capsules.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2 Shelf-life

24 months.

8.3 Packaging Information

15 capsules in aluminium strip.

8.4 Storage and Handling Instructions

Store protected from light and moisture, at a temperature not exceeding 30°C.
Capsules should be swallowed whole and not opened, chewed or crushed.
Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions

- Instruct patients not to use OMEPREN Capsules if they are allergic to omeprazole or to any other Proton Pump Inhibitor (PPI) medicine.
- Instruct patients to take OMEPREN Capsules exactly as prescribed by doctor. Do not change the dose or stop therapy without consulting to doctor.

- Instruct patients to take OMEPREN Capsules at least 1 hour before meal, preferably in the morning.
- Instruct patients to swallow OMEPREN capsules as a whole and not to open, chew or crush the capsules.
- Instruct patients not to take this medicine during pregnancy and lactation unless advised by healthcare professionals.
- Instruct patients not to share this medication with other people even though symptoms are similar. It may harm them.

10.Details of Manufacturer

Pure & Cure Healthcare Pvt. Ltd.
(A subsidiary of Akums Drugs & Pharmaceutical Ltd.)
Plot No. 26A, 27-30, Sector -8A, I.I.E., SIDCUL,
Haridwar – 249 403, Uttarakhand, India.

11. Details of Permission or License Number with Date

DCG(I) approval: April 1991.
Manufacturing License No: 31/UA/2013.
Date of Product Permission: 10/06/2019.

12. Date of Revision

February 2021.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
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