

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

Prescribing Information

1. Generic Name

Omeprazole (GR) and Domperidone (SR) Capsules
(Brand Name: OMEPREN®-D Capsules)

2. Qualitative and Quantitative Composition

Each Hard Gelatin Capsule Contains:

Omeprazole IP 20 mg.
(as Gastro-Resistant Pellets)

Domperidone IP 30 mg
(as Sustained Release Pellets)

Excipients..... q.s.

Colour : Sunset Yellow FCF.

Colours used in capsule shell: Ponceau 4R, Carmoisine, Tartrazine, Titanium Dioxide IP.
Methylparaben and Propylparaben used as Antimicrobial Preservatives.

3. Dosage Form and Strength

Dosage Form: Capsule.

Dosage Strength: Omeprazole 20 mg and Domperidone 30 mg per capsule.

4. Clinical Particulars

4.1 Therapeutic Indication

OMEPREN-D Capsules are indicated for the treatment gastro-esophageal reflux disease (GERD) not responding adequately to omeprazole alone.

4.2 Posology and Method of Administration

For oral administration in adults.

Recommended dose is 1 capsule to be administered once daily for 4 to 8 weeks.

OMEPREN-D 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.

4.3 Contraindications

OMEPREN-D Capsules are contraindicated in the following:

- Patients with known hypersensitivity to omeprazole or to any substituted benzimidazole derivative or to domperidone or to any component of the formulation.
- In patients receiving rilpivirine-containing products.
- Prolactin-releasing pituitary tumor (prolactinoma).
- In patients with gastrointestinal (GI) hemorrhage, mechanical obstruction or perforation (i.e., when stimulation of the gastric motility could be harmful).
- In patients with moderate or severe hepatic impairment.
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc.
- Patients with significant electrolyte disturbances (hypokalemia, hyperkalemia, hypomagnesemia) or underlying cardiac disease such as congestive heart failure (CHF).
- Co-administration with QT-prolonging drugs.
- Co-administration with potent CYP3A4 inhibitors.

4.4 Special Warnings and Precautions for Use

Omeprazole

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 B₁₂ 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 B₁₂) 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.

Domperidone

Cardiovascular Effects: Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors.

Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolongation drugs or CYP3A4 inhibitors.

Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure (CHF) due to increased risk of ventricular arrhythmia. Electrolyte disturbances or bradycardia are known to be conditions increasing the proarrhythmic risk. Treatment with domperidone should be stopped if signs or symptoms occur that

may be associated with cardiac arrhythmia, and the patients should consult their physician. Patients should be advised to promptly report any cardiac symptoms.

Use with Apomorphine: Domperidone is contraindicated with QT prolonging drugs including apomorphine, unless the benefit of the co-administration with apomorphine outweighs the risks.

Use in Infants and Children: Although neurological side effects are rare, the risk of neurological side effects is higher in young children since metabolic functions and the blood-brain barrier (BBB) are not fully developed in the first months of life. Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.

4.5 Drug Interactions

Omeprazole

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.

Domperidone

The main metabolic pathway of domperidone is through CYP3A4. *In vitro* data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone.

There is increased risk of occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions.

1. Concomitant use of the following drugs is contraindicated.

A. QTc-prolonging medicinal products:

- Anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine).
- Anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol).
- Certain antipsychotics (e.g., haloperidol, pimozide, sertindole).
- Certain antidepressants (e.g., citalopram, escitalopram).
- Certain antibiotics (e.g., erythromycin, levofloxacin, moxifloxacin, spiramycin).
- Certain antifungal agents (e.g., pentamidine).
- Certain antimalarial agents (e.g., halofantrine, lumefantrine).
- Certain gastrointestinal medicines (e.g., cisapride, dolasetron, prucalopride).
- Certain antihistaminics (e.g., mequitazine, mizolastine).
- Certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine).
- Other medicines (e.g., bepridil, diphemanil, methadone).

B. Potent CYP3A4 inhibitors (regardless of their QT prolonging effects):

- Protease inhibitors.
- Systemic azole antifungals.
- Some macrolides (e.g., erythromycin, clarithromycin, and telithromycin).

2. Concomitant use of the following drugs is not recommended.

- Moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, and some macrolides).

3. Concomitant use of the following drugs requires caution.

- Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-interval prolongation: Azithromycin and roxithromycin.

Ketoconazole/Erythromycin and QTc Prolongation: Separate *in vivo* pharmacokinetic/pharmacodynamic interaction studies with oral ketoconazole or oral erythromycin in healthy subjects confirmed a marked inhibition of domperidone's CYP3A4 mediated first pass metabolism by these drugs (as both of these drugs significantly inhibit CYP3A4 enzyme). Both the C_{max} and AUC of domperidone at steady state were increased approximately

three-fold in each of these interaction studies. In these studies, concomitant use of domperidone and ketoconazole or erythromycin resulted in increase in QTc, over the observation period.

4.6 Use in Special Populations

Pregnant Women

Omeprazole: Pregnancy Category C; Domperidone: Pregnancy Category C. Data from animal studies did not disclose any evidence for a teratogenic potential of omeprazole. Available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use. There are limited post-marketing data on the use of domperidone in pregnant women. Studies in animals have shown reproductive toxicity at maternally toxic doses.

There are no adequate and well controlled studies available for use of omeprazole with domperidone combination therapy during pregnancy. OMEPREN-D Capsules should be used during pregnancy only if the potential benefit justifies the possible risk to the fetus.

Lactating Women

Omeprazole is present in human milk. Omeprazole concentrations were measured in breast milk of a woman following oral administration of 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.

Domperidone is excreted in human milk and breast-fed infants receive less than 0.1 % of the maternal weight-adjusted dose. Occurrence of adverse effects, in particular cardiac effects cannot be excluded after exposure via breast milk. Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants.

OMEPREN-D Capsules should not be used during breast feeding. Accordingly, a decision should be made whether to discontinue nursing or to discontinue/abstain from therapy, taking into account the benefit of the drug to the mother.

Paediatric Patients

Safety and efficacy of omeprazole with domperidone combination therapy has not been established in paediatric patients. Thus, OMEPREN-D Capsules are not recommended for use in children.

Geriatric Patients

No overall differences in safety or effectiveness were observed between elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. Dose adjustment is not needed in the elderly population.

Renal Impairment Patients

With omeprazole, no dosage adjustment is necessary in patients with impaired renal function. On repeated administration, the elimination half-life of domperidone is prolonged in patients with

severe renal impairment. OMEPREN-D Capsules can be administered in patients with mild to moderate renal dysfunction. In patients with severe renal impairment, OMEPREN-D Capsules should be used with caution and dose/dosage frequency may need to be reduced depending on the severity of the renal dysfunction.

Hepatic Impairment Patients

In patients with chronic hepatic disease, the bioavailability of omeprazole increased to approximately 100% compared with intravenous 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. In patients with impaired hepatic function, dose reduction should be considered and a daily dose of 10 to 20 mg of omeprazole may be sufficient. With domperidone, no dosage adjustment is necessary in patients with mild hepatic impairment. OMEPREN-D Capsules can be administered in patients with mild hepatic dysfunction. However, OMEPREN-D Capsules are contraindicated in patients with moderate to severe hepatic impairment.

4.7 Effect on Ability to Drive and Use Machines

Omeprazole is not likely to affect the ability to drive or use machines. Domperidone has also no or negligible influence on the ability to drive or use machines. However, adverse drug reactions such as dizziness and visual disturbances may occur with omeprazole. If affected, patients should not drive or operate machinery.

4.8 Undesirable Effects

Omeprazole

Clinical Trials Experience

The most common adverse reactions reported (i.e., with an incidence rate $\geq 2\%$) 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 $\geq 1\%$ 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.

Domperidone

Central Nervous System: As the pituitary gland is outside the blood-brain barrier, domperidone may cause an increase in prolactin levels. In rare cases this hyperprolactinaemia may lead to neuro-endocrinological side effects such as galactorrhoea, gynaecomastia and amenorrhoea. Extrapyramidal side effects are very rare in neonates and infants, and exceptional in adults. These side effects reverse spontaneously and completely as soon as the treatment is stopped. Other central

nervous system-related effects of convulsion, agitation and somnolence also are very rare and primarily reported in infants and children.

The adverse drug reactions are ranked below by frequency, using the following convention: Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); very rare ($< 1/10,000$), not known (cannot be estimated from available data).

General Disorders: *Uncommon:* Asthenia.

Immune System Disorder: *Not known:* Anaphylactic reactions including anaphylactic shock and angioedema.

Psychiatric Disorders: *Uncommon:* Anxiety, loss of libido; *Not known:* Agitation, nervousness.

Nervous System Disorders: *Uncommon:* Somnolence, headache; *Not known:* Extrapyrarnidal disorder, convulsions.

Eye Disorders: *Not known:* Oculogyric crisis.

Cardiac Disorders: *Not known:* Ventricular arrhythmias, QTc prolongation, Torsade de Pointes, sudden cardiac death.

Gastrointestinal Disorders: *Common:* Dry mouth; *Uncommon:* Diarrhea.

Skin and Subcutaneous Tissue Disorders: *Uncommon:* Rash, pruritus; *Not known:* Urticaria, angioedema.

Reproductive System and Breast Disorders: *Uncommon:* Breast pain, breast tenderness, galactorrhoea; *Not known:* Gynaecomastia, amenorrhoea.

Renal and Urinary Disorders: *Not known:* Urinary retention.

Investigations: *Not known:* Abnormal liver function test, increased blood prolactin.

4.9 Overdose

Omeprazole

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.

Domperidone

Symptoms: Symptoms of domperidone overdose may include agitation, altered consciousness, convulsions, disorientation, somnolence, and extrapyramidal reactions.

Treatment: There is no specific antidote to domperidone, but in the event of overdose, gastric lavage as well as the administration of activated charcoal, may be useful. Close medical

supervision and supportive therapy is recommended. Anticholinergic, antiparkinson drugs may be helpful in controlling the extrapyramidal reactions.

5. Pharmacological Properties

5.1 Mechanism of Action

Omeprazole

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.

Domperidone

Domperidone is a dopamine receptor (D₂) antagonist. Domperidone act predominantly on peripheral dopamine receptors and produces anti-emetic and gastrokinetic effects. Domperidone does not readily cross the blood-brain barrier (BBB). Thus, in domperidone users, especially in adults, extrapyramidal side effects are very rare (unlike metoclopramide). Anti-emetic effect of domperidone is due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone (CTZ), which lies outside the BBB in the area postrema.

Oral domperidone also increases lower esophageal sphincter (LES) pressure, thus, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

5.2 Pharmacodynamic Properties

Omeprazole

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 H₂-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.

Domperidone

Prokinetic Effect: The prokinetic (gastrokinetic) properties of domperidone are related to its peripheral dopamine receptor blocking action.

Antiemetic Effect: Domperidone produces antiemetic effect by blocking dopamine receptors (D₂) peripherally. Inhibition of peripheral D₂ receptor signaling prevents or relieves various GI symptoms, such as nausea and vomiting, and also relieves reflux and other symptoms associated with upper GI disorders.

5.3 Pharmacokinetic Properties

Omeprazole

Absorption: OMEPREN-D 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.

Domperidone

Pharmacokinetics of domperidone in sustained release formulation is not available. Conventional formulation of domperidone (i.e., immediate release) has following pharmacokinetic properties:

Absorption: Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1 hour after dosing. The C_{max} and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut and liver.

Distribution: Oral domperidone does not appear to accumulate or induce its own metabolism. The peak plasma concentration (C_{max}) of 18 ng/ml to 21 ng/ml occurs 1.5 hours (T_{max}) after the oral dose. Domperidone is 91 to 93% bound to plasma proteins. Distribution studies with domperidone have shown wide tissue distribution, but low brain concentration.

Metabolism: Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion: After oral dose, domperidone is excreted mainly by renal (31%) and biliary (66%) routes. The proportion of the drug excreted unchanged is small (10% of fecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7 to 9 hours in healthy subjects, but is prolonged in patients with severe renal insufficiency.

6. Nonclinical Properties

6.1 Animal Toxicology

Omeprazole

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).

Domperidone

Safety margins in *in vitro* proarrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 9- up to 45-fold. In *in vivo* models the no effect levels for QTc prolongation in dogs and induction of arrhythmias in a rabbit model sensitized for torsade de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by more than 22-fold and 435-fold, respectively. In the anesthetized guinea pig model following slow intravenous infusions, there were no effects on QTc at total plasma concentrations of 45.4ng/ml, which are 3-fold higher than the total plasma levels in humans at maximum daily dose (10 mg administered 3 times a day).

At a high, maternally toxic dose (more than 40 times the recommended human dose), teratogenic effects were seen in the rat. No teratogenicity was observed in mice and rabbits. Development abnormalities observed in rats at a high exposure. Risk of carcinogenicity, mutagenicity or sensitisation cannot be excluded.

7. Description

OMEPREN-D Capsules are red and white coloured hard gelatin capsules containing white and orange colour pellets.

Each capsule of OMEPREN-D contains 20 mg of omeprazole and 30 mg of domperidone for oral administration.

Omeprazole

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.

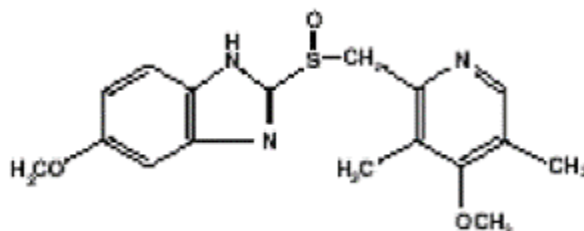
Omeprazole is not stable in acidic pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

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:



Domperidone

Domperidone is a dopamine receptor antagonist drug with antiemetic and gastrokinetic properties.

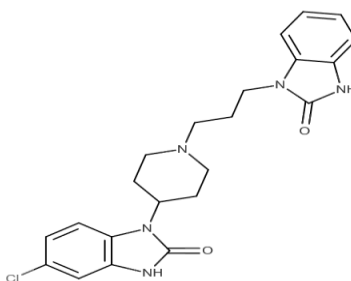
Domperidone is white or almost white powder which is slightly soluble in water.

Molecular Weight: 425.9 g/mol.

Molecular Formula: C₂₂H₂₄ClN₅O₂.

Chemical Name: 6-chloro-3-[1-[3-(2-oxo-3H-benzimidazol-1-yl)propyl]piperidin-4-yl]-1H-benzimidazol-2-one.

Structural Formula:



Inactive ingredients (excipients) of pellets contain Hypromellose, Mannitol, Sucrose, Croscopvidone, HPMC Phthalate, Diethyl Phthalate, Isopropyl Alcohol, Dicloromethane, PVP K 30, Ethyl Cellulose, Sunset Yellow Supra, Talcum, 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-D Capsules if they are allergic to omeprazole or to any other Proton Pump Inhibitor (PPI) medicine or to domperidone.
- Instruct patients to take OMEPREN-D Capsules exactly as prescribed by doctor. Do not change the dose or stop therapy without consulting to doctor.
- Instruct patients to take OMEPREN-D Capsules at least 1 hour before meal, preferably in the morning.
- Instruct patients to swallow OMEPREN-D 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: 10/03/2005.

Manufacturing License No: 31/UA/2013.

Date of Product Permission: 13/02/2019.

12. Date of Revision

February 2021.



Marketed by:

BLUE CROSS LABORATORIES PVT LTD.

A-12, M.I.D.C., NASHIK-422 010.

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