Omeprazole Delayed-Release Capsules USP 20 mg

Summary of Product Characteristics

1. Name of the Finished Pharmaceutical Product

Omeprazole Delayed-Release Capsules USP 20 mg

1.1 Strength

20 mg

2. Qualitative and Quantitative Composition

Sr. No.	Ingredients	Specification	Qty / Capsule (mg)	% Overages	Reason for inclusion
Active					
1	Omeprazole enteric coated pellets 7.5%	IHS	267.0	-	Proton Pump Inhibitor
2	Empty hard gelatin capsule size "2" Pink/Clear	IHS	1 Nos.	2%	Unit dose Holder
	Average fill Weight/Capsule		**267.00 mg/Capsule**	—	—

IHS: In House specification

3. Pharmaceutical form

Oral Capsules

4. Clinical particulars

4.1 Therapeutic indications

Omeprazole delayed-release capsules are indicated in:

Adults

- Treatment of duodenal ulcers
- Prevention of relapse of duodenal ulcers
- Treatment of gastric ulcers
- Prevention of relapse of gastric ulcers
- In combination with appropriate antibiotics, Helicobacter pylori (H. pylori) eradication in peptic ulcer disease
- Treatment of NSAID-associated gastric and duodenal ulcers

- Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk
- Treatment of reflux oesophagitis
- Long-term management of patients with healed reflux oesophagitis
- Treatment of symptomatic gastro-oesophageal reflux disease
- Treatment of Zollinger-Ellison syndrome

Pediatric use

Children over 1 year of age and ≥ 10 kg: - Treatment of reflux oesophagitis - Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease

Children and adolescents over 4 years of age: - In combination with antibiotics in treatment of duodenal ulcer caused by H. pylori

4.2 Posology and method of administration

Posology

Adults

Treatment of duodenal ulcers: The recommended dose in patients with an active duodenal ulcer is 20 mg once daily. In most patients healing occurs within two weeks.

Prevention of relapse of duodenal ulcers: For H. pylori negative patients or when eradication is not possible, the recommended dose is 20 mg once daily. In some patients a daily dose of 10 mg may be sufficient. In case of therapy failure, the dose can be increased to 40 mg.

Treatment of gastric ulcers: The recommended dose is 20 mg once daily. Healing occurs within four weeks in most patients; a further four weeks may be needed. In poorly responsive gastric ulcer, 40 mg once daily is recommended, with healing usually achieved within eight weeks.

Prevention of relapse of gastric ulcers: The recommended dose is 20 mg once daily, increased to 40 mg once daily if needed.

H. pylori eradication in peptic ulcer disease: Antibiotic selection should consider individual patient drug tolerance and local resistance patterns and guidelines.

- Omeprazole 20 mg + clarithromycin 500 mg + amoxicillin 1,000 mg, each twice daily for one week; or
- Omeprazole 20 mg + clarithromycin 250 mg (alternatively 500 mg) + metronidazole 400 mg (or 500 mg or tinidazole 500 mg), each twice daily for one week; or

- Omeprazole 40 mg once daily with amoxicillin 500 mg and metronidazole 400 mg (or 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.

Treatment of NSAID-associated gastric and duodenal ulcers: The recommended dose is 20 mg once daily; healing occurs within four weeks in most patients, with a further four weeks if needed.

Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk (age >60, previous history of gastric and duodenal ulcers, previous history of upper GI bleeding): the recommended dose is 20 mg once daily.

Treatment of reflux oesophagitis: The recommended dose is 20 mg once daily; healing occurs within four weeks in most patients, with a further four weeks if needed. In severe oesophagitis, 40 mg once daily is recommended, with healing usually achieved within eight weeks.

Long-term management of patients with healed reflux oesophagitis: The recommended dose is 10 mg once daily, increased to 20–40 mg once daily if needed.

Treatment of symptomatic gastro-oesophageal reflux disease: The recommended dose is 20 mg daily. Patients may respond adequately to 10 mg daily; individual dose adjustment should be considered. If symptom control has not been achieved after four weeks of 20 mg daily, further investigation is recommended.

Treatment of 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. More than 90% of patients with severe disease are effectively controlled on doses of 20–120 mg daily. When the dose exceeds 80 mg daily, it should be divided and given twice daily.

Pediatric population

Children over 1 year of age and ≥ 10 kg (treatment of reflux oesophagitis; symptomatic treatment of heartburn and acid regurgitation in GERD):

Age	Weight	Posology
≥ 1 year of age	10–20 kg	10 mg once daily. The dose can be increased to 20 mg once daily if needed
≥ 2 years of age	> 20 kg	20 mg once daily. The dose can be increased to 40 mg once daily if needed

Reflux oesophagitis: treatment time is 4–8 weeks. Symptomatic treatment of heartburn and acid regurgitation in GERD: treatment time is 2–4 weeks; if

symptom control has not been achieved after 2–4 weeks the patient should be investigated further.

Children and adolescents over 4 years of age – treatment of duodenal ulcer caused by H. pylori: consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents. Treatment should be supervised by a specialist.

Weight	Posology
15–30 kg	Combination with two antibiotics: Omeprazole 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight, all administered together twice daily for one week
31–40 kg	Combination with two antibiotics: Omeprazole 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight, administered twice daily for one week
> 40 kg	Combination with two antibiotics: Omeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg, administered twice daily for one week

Special populations

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

Hepatic impairment: In patients with impaired hepatic function a daily dose of 10–20 mg may be sufficient.

Elderly: Dose adjustment is not needed in the elderly.

Method of administration

It is recommended to take the capsules in the morning, swallowed whole with half a glass of water. The capsules must not be chewed or crushed.

For patients with swallowing difficulties and for children who can drink or swallow semi-solid food: patients can open the capsule and swallow the contents with half a glass of water or after mixing the contents in a slightly acidic fluid, e.g. fruit juice or applesauce, or in non-carbonated water. The dispersion should be taken immediately (or within 30 minutes) and always be stirred just before drinking and rinsed down with half a glass of water. Alternatively, patients can suck the capsule and swallow the pellets with half a glass of water. The enteric-coated pellets must not be chewed.

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles. Omeprazole, like other proton pump inhibitors (PPIs), must not be used concomitantly with nelfinavir.

4.4 Special warnings and precautions for use

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.

Co-administration of atazanavir with proton pump inhibitors is not recommended. If unavoidable, close clinical monitoring (e.g. virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; omeprazole 20 mg should not be exceeded.

Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (Cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

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 omeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests: Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, omeprazole treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Some children with chronic illnesses may require long-term treatment although it is not recommended.

Paediatric population: Not applicable.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of omeprazole on the pharmacokinetics of other active substances

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, atazanavir: Plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole. Concomitant administration with nelfinavir is contraindicated (omeprazole 40 mg once daily reduced mean nelfinavir exposure by ca. 40% and exposure of the active metabolite M8 by ca. 75–90%; the interaction may also involve CYP2C19 inhibition). Concomitant administration with atazanavir is not recommended (omeprazole 40 mg once daily with atazanavir 300 mg/ritonavir 100 mg resulted in a 75% decrease of atazanavir exposure; increasing atazanavir to 400 mg did not compensate. Omeprazole 20 mg once daily with atazanavir 400 mg/ritonavir 100 mg resulted in an approximate 30% decrease in atazanavir exposure compared with atazanavir 300 mg/ritonavir 100 mg once daily).

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; caution should be exercised at high omeprazole doses in elderly patients, and therapeutic drug monitoring of digoxin should be reinforced.

Clopidogrel: Studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel 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 platelet aggregation by an average of 16%.

Other active substances: The absorption of posaconazole, erlotinib, ketoconazole and itraconazole is significantly reduced and clinical efficacy may be impaired. Concomitant use of posaconazole and erlotinib with omeprazole should be avoided.

Active substances metabolized by CYP2C19: Omeprazole is a moderate inhibitor of CYP2C19; metabolism of concomitant active substances also metabolized by CYP2C19 may be decreased and systemic exposure increased. Examples: R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Cilostazol: Omeprazole 40 mg increased Cmax 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, with further monitoring/adjustment upon ending omeprazole treatment.

Unknown mechanism

Saquinavir: Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels of up to approximately 70% for saquinavir, associated with good tolerability in HIV-infected patients.

Tacrolimus: Concomitant administration of omeprazole has been reported to increase serum levels of tacrolimus. Reinforced monitoring of tacrolimus concentrations and renal function (creatinine clearance) should be performed, with dosage adjustment if needed.

Methotrexate: When given together with PPIs, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration, temporary withdrawal of omeprazole may need to be considered.

Effects of other active substances on the pharmacokinetics of omeprazole

Inhibitors of CYP2C19 and/or CYP3A4: Active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated, dose adjustment is not generally required, but should be considered in patients with severe hepatic impairment and long-term treatment.

Inducers of CYP2C19 and/or CYP3A4: Active substances known to induce CYP2C19 or CYP3A4 (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels.

Paediatric population: Not applicable.

4.6 Fertility, pregnancy and lactation

Pregnancy: Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy.

Breast-feeding: Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

Fertility: Animal studies with the racemic mixture omeprazole, given by oral administration, do not indicate effects with respect to fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Metabolism and nutrition disorders: Hyponatraemia, Hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also be associated with hypokalemia.

Psychiatric disorders: Insomnia, Agitation, confusion, depression, Aggression, hallucinations.

Nervous system disorders: Headache, Dizziness, paraesthesia, somnolence, Taste disturbance.

Eye disorders: Blurred vision.

Ear and labyrinth disorders: Vertigo.

Respiratory, thoracic and mediastinal disorders: Bronchospasm.

Gastrointestinal disorders: Abdominal pain, constipation, diarrhea, flatulence, nausea/vomiting, fundic gland polyps (benign), Dry mouth, stomatitis, gastrointestinal candidiasis, Microscopic colitis.

Hepatobiliary disorders: Increased liver enzymes, Hepatitis with or without jaundice, Hepatic failure, encephalopathy in patients with pre-existing liver disease.

Skin and subcutaneous tissue disorders: Dermatitis, pruritus, rash, urticaria, Alopecia, photosensitivity, Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), Subacute cutaneous lupus erythematosus.

Musculoskeletal and connective tissue disorders: Fracture of the hip, wrist or spine, Arthralgia, myalgia, Muscular weakness.

Renal and urinary disorders: Interstitial nephritis.

Reproductive system and breast disorders: Gynaecomastia.

General disorders and administration site conditions: Malaise, peripheral oedema, increased sweating.

Reporting of suspected adverse reactions: Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is limited information available on the effects of overdoses of omeprazole in humans. In the literature, doses of up to 560 mg have been described, and occasional reports have been received when single oral doses have reached up to 2,400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhea and headache have been reported. Also apathy, depression and confusion have been described in single cases.

The symptoms described have been transient, and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses. Treatment, if needed, is symptomatic.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitors

ATC Code: A02BC01

Mechanism of action: Omeprazole, a racemic mixture of two enantiomers, reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H+K+-ATPase — the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

Pharmacodynamic effects: All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.

Effect on gastric acid secretion: Oral dosing with omeprazole once daily provides rapid and effective inhibition of daytime and night-time gastric acid secretion, with maximum effect achieved within 4 days of treatment. With omeprazole 20 mg, a mean decrease of at least 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients, with a mean decrease in peak acid output after pentagastrin stimulation of about 70% 24 hours after dosing. Oral dosing with omeprazole 20 mg maintains an intragastric pH of ≥3 for a mean time of 17 hours of the 24-hour period in duodenal ulcer patients. As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the oesophagus in patients with gastro-oesophageal reflux disease. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time. No tachyphylaxis has been observed during treatment with omeprazole.

Effect on H. pylori: H. pylori is associated with peptic ulcer disease, including duodenal and gastric ulcer disease, and is a major factor in the development of gastritis and, together with gastric acid, of peptic ulcer disease. H. pylori is a major factor in the development of atrophic gastritis, which is associated with an increased risk of developing gastric cancer. Eradication of H. pylori with

omeprazole and antimicrobials is associated with high rates of healing and long-term remission of peptic ulcers. Dual therapies have been tested and found to be less effective than triple therapies; they could however be considered where known hypersensitivity precludes use of any triple combination.

Other effects related to acid inhibition: During long-term treatment, gastric glandular cysts have been reported at a somewhat increased frequency; these changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible. Decreased gastric acidity due to any means, including PPIs, increases gastric counts of bacteria normally present in the gastrointestinal tract; treatment with acid-reducing drugs may lead to a slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter, and in hospitalized patients possibly also Clostridium difficile. During treatment with antisecretory medicinal products, serum gastrin increases in response to decreased acid secretion; CgA also increases due to decreased gastric acidity, which may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that PPIs should be discontinued between 5 days and 2 weeks prior to CgA measurements. An increased number of ECL cells, possibly related to the increased serum gastrin levels, have been observed in some patients during long-term treatment with omeprazole.

Pediatric population: In a non-controlled study in children (1 to 16 years of age) with severe reflux oesophagitis, omeprazole at doses of 0.7 to 1.4 mg/kg improved oesophagitis level in 90% of cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0–24 months with clinically diagnosed GERD were treated with 0.5, 1.0 or 1.5 mg omeprazole/kg; the frequency of vomiting/regurgitation episodes decreased by 50% after 8 weeks of treatment irrespective of dose.

5.2 Pharmacokinetic properties

Absorption: Omeprazole and omeprazole magnesium are acid labile and are therefore administered orally as enteric-coated granules in capsules or tablets. Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1–2 hours after dose, and is usually completed within 3–6 hours. Concomitant intake of food has no influence on bioavailability. The systemic availability (bioavailability) from a single oral dose is approximately 40%; after repeated once-daily administration, bioavailability increases to about 60%.

Distribution: The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight. Omeprazole is 97% plasma protein bound.

Biotransformation: Omeprazole is completely metabolized 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 CYP3A4, responsible for the formation of omeprazole sulfone.

Because of high affinity of omeprazole to CYP2C19, there is potential for competitive inhibition and metabolic drug-drug interactions with other substrates of CYP2C19.

Elimination: The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. Almost 80% of an oral dose is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

Linearity/non-linearity: The AUC of omeprazole increases with repeated administration, in a dose-dependent, non-linear manner, due to a decrease of first pass metabolism and systemic clearance probably caused by inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulfone). No metabolite has been found to have any effect on gastric acid secretion.

Special populations

Hepatic impairment: The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased AUC; omeprazole has not shown any tendency to accumulate with once daily dosing.

Renal impairment: The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.

Elderly: The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75–79 years of age).

Pediatric population: During treatment with the recommended doses to children from the age of 1 year, similar plasma concentrations were obtained as compared to adults. In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolize omeprazole.

5.3 Pre-clinical safety data

Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients

Empty hard gelatin capsule size “2” Pink/Clear.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and contents of container

10 capsules are in Alu-Alu strip pack. Such 03 Alu-Alu strips are packed in a printed carton along with packing insert.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder and manufacturing site addresses

DEN MARK PHARMACEUTICALS PVT. LTD.

First Floor Harish Textiles, Parsi Panchayat Road, Andheri East, Mumbai-400069, India

Manufacturing Site: RATNATRIS PHARMACEUTICALS PVT. LTD., Survey No. 416, At. – Indrad, Ta. – Kadi, Dist. – Mehsana, Pin-382715, Gujarat, India.

8. Marketing authorisation number

H2022/CTD10579/22879

9. Date of first registration/renewal of the registration

2023 November 01

10. Date of revision of the text

2023 November 01