1.6 Product Information

1.6.1 Prescribing Information (Summary of Product Characteristics)

1. Name of the Medicinal Product

1.1 Trade Name : PRAZIM 20 (Gastro-resistant Omeprazole Capsules BP 20 mg)

1.2 Strength : 20 mg

1.3 Pharmaceutical Form : Hard gelatin capsule

2. Qualitative and Quantitative Composition

S. No	Name of Ingredients	Quantity/ Capsule (mg)
Active Substance		
1	Omeprazole	20.00
Inactive Substance		
2	Mannitol	65.55
3	Sucrose	61.20
4	Disodium Hydrogen Phosphate	2.70
5	Calcium Carbonate	7.05
6	Sodium Lauryl Sulphate	0.85
7	Hypromellose	18.85
8	Methacrylic Acid and ethyl Acrylate copolymer dispersion	47.05
9	Diethyl Phthalate	4.70
10	Titanium Dioxide	2.35
11	Purified Talc	4.70
12	N.P. Seeds	60.00
13	Purified Water*	Q.S.
14	Empty Hard Gelatin Capsule Size “2”	1 Nos. (65.00 mg)
	Total	**360.00 mg**

*Get evaporated during manufacturing process and does not remains in the final products.

3. Pharmaceutical Form

"Hard gelatin capsule"

Pink transparent/ clear transparent, size '2', hard gelatin capsules filled with white to off white enteric coated pellets.

4. Clinical Particulars

4.1 Therapeutic indications

Omeprazole 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

Paediatric 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 Omeprazole 20 mg once daily. In most patients healing occurs within two weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further two weeks treatment period. In patients with poorly responsive duodenal ulcer Omeprazole 40 mg once daily is recommended and healing is usually achieved within four weeks.

Prevention of relapse of duodenal ulcers: For the prevention of relapse of duodenal ulcer in *H. pylori* negative patients or when *H. pylori* eradication is not possible the recommended dose is

Omeprazole 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 Omeprazole 20 mg once daily. In most patients healing occurs within four weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further four weeks treatment period. In patients with poorly responsive gastric ulcer Omeprazole 40 mg once daily is recommended and healing is usually achieved within eight weeks.

Prevention of relapse of gastric ulcers: For the prevention of relapse in patients with poorly responsive gastric ulcer the recommended dose is Omeprazole 20 mg once daily. If needed the dose can be increased to Omeprazole 40 mg once daily.

Treatment of NSAID-associated gastric and duodenal ulcers: For the treatment of NSAID-associated gastric and duodenal ulcers, the recommended dose is Omeprazole 20 mg once daily. In most patients healing occurs within four weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further four weeks treatment period.

Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk: For the prevention of NSAID-associated gastric ulcers or 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 Omeprazole 20 mg once daily.

Treatment of reflux oesophagitis: The recommended dose is Omeprazole 20 mg once daily. In most patients healing occurs within four weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further four weeks treatment period. In patients with severe oesophagitis Omeprazole 40 mg once daily is recommended and healing is usually achieved within eight weeks.

Long-term management of patients with healed reflux oesophagitis: For the long-term management of patients with healed reflux oesophagitis the recommended dose is Omeprazole 10 mg once daily. If needed, the dose can be increased to Omeprazole 20-40 mg once daily.

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

Treatment of Zollinger-Ellison syndrome: In patients with Zollinger-Ellison syndrome the dose should be individually adjusted and treatment continued as long as clinically indicated. The recommended initial dose is Omeprazole 60 mg daily. All patients with severe disease and inadequate response to other therapies have been effectively controlled and more than 90% of the patients maintained on doses of Omeprazole 20-120 mg daily. When dose exceed Omeprazole 80 mg daily, the dose should be divided and given twice daily.

Paediatric population

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
The posology recommendations are as follows:

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: The treatment time is 4-8 weeks.
Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease: The 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: When selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents.
The treatment should be supervised by a specialist.
The posology recommendations are as follows:

Weight	Posology
15-30 kg	Combination with two antibiotics: Omeprazole 10mg, amoxicillin 25mg/kg body weight and clarithromycin 7.5mg/kg body weight are all administrated together two times daily for one week.
31-40 kg	Combination with two antibiotics: Omeprazole 20mg, amoxicillin 750mg and clarithromycin 7.5mg/kg body weight are all administrated two times daily for one week.
>40 kg	Combination with two antibiotics: Omeprazole 20mg, amoxicillin 1g and clarithromycin 500mg are all administrated two times 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
Oral Administration
It is recommended to take Omeprazole 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. Patients should be advised that 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.

4.3 Contraindication

• Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients in this formulation.
• Omeprazole like other proton pump inhibitors (PPIs) must not be used concomitantly with nelfinavir.

4.4 Special warnings and special 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 the combination of atazanavir with a proton pump inhibitor is judged 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 B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12}absorption on long-term therapy.
Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.
Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like omeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. Hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Patients at risk of osteoporosis should receive care

according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Subacute cutaneous lupus erythematosus (SCLE): Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping omeprazole.

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.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

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: Concomitant administration of omeprazole with nelfinavir is contraindicated. Concomitant administration of omeprazole with atazanavir is not recommended.

Digoxin: Caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should be then be reinforced.

Clopidogrel: As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

Other active substances: 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.

Active substances metabolised by CYP2C19: The metabolism of concomitant active substances metabolised 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 may 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 should occur upon ending omeprazole treatment.

Unknown mechanism

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

Tacrolimus: Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate: In high-dose methotrexate administration a 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: 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.

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

4.6 Pregnancy and lactation

Pregnancy: 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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most common side effects are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

The frequency categories are defined according to the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

Common: Headache, Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign).

Uncommon: Insomnia, Dizziness, paraesthesia, somnolence, Vertigo, Increased liver enzymes, Dermatitis, pruritus, rash, urticaria, Fracture of the hip, wrist or spine, Malaise, peripheral oedema.

Rare: Leukopenia, thrombocytopenia, Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock, Hyponatraemia, Agitation, confusion, depression, Taste disturbance, Blurred vision, Bronchospasm, Dry mouth, stomatitis, gastrointestinal candidiasis, Hepatitis with or without jaundice, Alopecia, photosensitivity, Arthralgia, myalgia, Interstitial nephritis, Increased sweating.
Very Rare: Agranulocytosis, pancytopenia, Aggression, hallucinations, Hepatic failure, encephalopathy in patients with pre-existing liver disease, Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), Muscular weakness, Gynaecomastia.
Not Known: Microscopic colitis, Subacute cutaneous lupus erythematosus.

4.9 Overdose
When single oral doses have been reached of up to 2,400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported. Also apathy, depression and confusion have been described in single cases.

The symptoms described in connection with omeprazole overdose 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 Pharmacodynamics properties
Pharmacotherapeutic group: Proton pump inhibitors, Drugs for acid-related disorders;
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:
Effect on gastric acid secretion: Oral dosing with omeprazole once daily provides for rapid and effective inhibition of daytime and night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment. With omeprazole 20 mg, a mean decrease of at least 80% in 24-hour intragastric acidity is then maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being 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. *H. pylori* is a major factor in the development of gastritis. *H. pylori* together with gastric acid are major factors in the development 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.
Other effects related to acid inhibition: During long-term treatment gastric glandular cysts have been reported in 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 proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile.* Proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

5.2 Pharmacokinetic Properties

Absorption: Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. Concomitant intake of food has no influence on the bioavailability. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.
Distribution: The apparent volume of distribution is approximately 0.3 l/kg body weight. Omeprazole is 97% plasma protein bound.
Biotransformation: 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. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates. In addition, omeprazole lacks an inhibitory effect on the main CYP enzymes.

Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also higher, by 3 to 5 times. These findings have no implications for the posology of omeprazole.
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 of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

5.3 Preclinical safety data
Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition. Similar findings have been made after treatment with H2-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these changes are not from a direct effect of any individual active substance.

6. Pharmaceutical Particulars
6.1 List of excipients
Mannitol E421
Sucrose E473
Disodium hydrogen phosphate E339 (ii)
Calcium Carbonate E170
Sodium Lauryl Sulphate E487
Hypromellose E464
Methacrylic acid and ethyl acrylate copolymer dispersion E1207
Diethyl phthalate
Titanium Dioxide E171
Purified Talc E553b
N.P. Seeds
Empty hard gelatin capsule size'2'

6.2 Incompatibilities
None

6.3 Shelf life
3 years from the date of manufacture

6.4 Special precautions for storage
Store at a temperature not exceeding 30°C, protect from moisture.
Keep out of the reach of children.

6.5 Nature and contents of container
10 × 10 hard gelatin capsule pack in Alu-Alu strip.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder
ZIM Laboratories Limited
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 441501
Maharashtra State,
India.

8. Number(S) In the National Register of Finished pharmaceutical products
NA

9. Date of First Authorization/Renewal of the Authorization
NA

10. Date of Revision of the Text
01 April 2019