1. NAME OF THE MEDICINAL PRODUCT:

Product Name: Omeprazole (Gastro Resistant Omeprazole Capsules BP 20mg)

Strength: Omeprazole BP…20mg

Pharmaceutical Dosage Form: Hard Gelatin Capsule.

2. QUALITY AND QUANTITATIVE COMPOSITION:

Each Hard Gelatin Capsule Contains:
Omeprazole BP……20mg
(As enteric coated granules)
Excipients……q.s
Approved colour used in hard gelatin capsule

3. PHARMACEUTICAL FORM: Capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications:

Omeprazole capsules are indicated in:

Adults

Omeprazole delayed-release capsules are a proton pump inhibitor (PPI) indicated for the:
- Treatment of active duodenal ulcer in adults
- Eradication of Helicobacter pylori to reduce the risk of duodenal ulcer recurrence in adults
- Treatment of active benign gastric ulcer in adults
- Treatment of symptomatic gastroesophageal reflux disease (GERD) in patients 2 years of age and older
- Maintenance of healing of EE due to acid-mediated GERD in patients 2 years of age and older
- Pathologic hypersecretory conditions in adults

4.2 Posology and method of administration: DOSAGE AND ADMINISTRATION

*if ulcer present, continue Omeprazole 20 mg once daily for an additional 18 days.
†if ulcer present, continue Omeprazole 20 mg once daily for an additional 14 days.
‡an additional 4 weeks of treatment may be given if no response; if recurrence additional 4 to 8 week courses may be considered.

Indication	Recommended Adult (2.1) and Pediatric Dosage (2.2)	
Treatment of Active Duodenal Ulcer	20 mg once daily for 4 weeks; some patients may require an additional 4 weeks (2.1)	
H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence		
Triple Therapy:		
Omeprazole	20 mg	Each drug twice daily for 10 days (2.1)*
Amoxicillin	1000 mg	
Clarithromycin	500 mg	
Dual Therapy:		
Omeprazole	40 mg once daily for 14 days†	
Clarithromycin	500 mg three times daily for 14 days (2.1)	
Active Benign Gastric Ulcer	40 mg once daily for 4 to 8 weeks (2.1)	
Symptomatic GERD	20 mg once daily for up to 4 weeks (2.1) See full prescribing information for weight based dosing in pediatric patients 2 years of age and older (2.2)	
EE due to Acid-Mediated GERD	20 mg once daily for 4 to 8 weeks (2.1)‡ See full prescribing information for weight based dosing in pediatric patients 2 years of age and older (2.2)	
Maintenance of Healing of EE due to Acid-Mediated GERD	20 mg once daily (2.1)‡ See full prescribing information for weight based dosing in pediatric patients 2 years of age and older (2.2)	
Pathological Hypersecretory Conditions	Starting dose is 60 mg once daily (varies with individual patient, see full prescribing information) as long as clinically indicated (2.1)	

4.3 Contraindications:

Patients with known hypersensitivity to substituted benzimidazoles or any component of the formulation.

- Patients receiving rilpivirine-containing products.
- Refer to the Contraindications section of the prescribing information for clarithromycin and amoxicillin, when administered in combination with omeprazole.

4.4 Special warning and precaution for use:

Gastric Malignancy: In adults, symptomatic response does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing.

- Acute Interstitial Nephritis: Observed in patients taking PPIs.
- *Clostridium difficile*-Associated Diarrhea: PPI therapy may be associated with increased risk.
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.4)
- Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue omeprazole and refer to specialist for evaluation.
- Interaction with Clopidogrel: Avoid concomitant use of omeprazole.
- Cyanocobalamin (Vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin.
- Hypomagnesemia: Reported rarely with prolonged treatment with PPIs.

·Interaction with St. John's Wort or Rifampin: Avoid concomitant use of omeprazole.

·Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Increased Chromogranin A (CgA) levels may interfere with diagnostic investigations for neuroendocrine tumors; temporarily stop omeprazole at least 14 days before assessing CgA levels.

·Interaction with Methotrexate: Concomitant use with PPIs may elevate and/or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity. With high dose methotrexate administration, consider a temporary withdrawal of omeprazole.

·Fundic Gland Polyps: Risk increases with long-term use, especially beyond one year. Use the shortest duration of therapy

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

The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole.

Concomitant administration of omeprazole with nelfinavir is contraindicated (see section 4.3).

Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir exposure by ca. 40% and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75 –90%. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of omeprazole with atazanavir is not recommended (see section 4.4).

Concomitant administration of omeprazole (40 mg once daily) and atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a 75% decrease of the atazanavir exposure. Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared to 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. However caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily) resulting in a decreased exposure to the active metabolite of clopidogrel by an average of 46% and a decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Inconsistent data on the clinical implications of a PK/PD interaction of omeprazole in terms of major cardiovascular events have been reported from both

observational and clinical studies. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged (see section 4.4).

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

Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such medicinal products 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 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. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dose of tacrolimus adjusted if needed.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. 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. 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.

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

Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse events 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.

4.7 Effects on the 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 (see section 4.8). If affected, patients should not drive or operate machinery.

4.8 Undesirable effects:

Adults: Most common adverse reactions in adults (incidence ≥2%) are

- Headache, abdominal pain, nausea, diarrhea, vomiting, and flatulence.

Pediatric patients (2 to 16 years of age):

- Safety profile similar to that in adults, except that respiratory system events and fever were the most frequently reported reactions in pediatric studies.

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, diarrhoea 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 PARTICULARS:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid related disorders, drugs for peptic ulcer andgastro-oesophageal reflux disease (GORD), 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 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.

Dual therapies have been tested and found to be less effective than triple therapies. They could, however, be considered in cases 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 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 medicinal products may lead to slightly increased risk of gastrointestinal infections such as *Salmonella and Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile.*

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that 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.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients (both children and adults) during long term treatment with omeprazole. The findings are considered to be of no clinical significance.

Paediatric 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 the cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0–24 months with clinically diagnosed gastro-oesophageal reflux disease 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 the dose.

Eradication of *H. pylori* in children:

A randomised, double blind clinical study (Héliot study) concluded that omeprazole in combination with two antibiotics (amoxicillin and clarithromycin), was safe and effective in the treatment of *H. pylori* infection in children age 4 years old and above with gastritis: *H. pylori* eradication rate: 74.2% (23/31 patients) with omeprazole + amoxicillin + clarithromycin versus 9.4% (3/32 patients) with amoxicillin + clarithromycin. However, there was no evidence of any clinical benefit with respect to dyspeptic symptoms. This study does not support any information for children aged less than 4 years.

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. 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 in healthy subjects 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 sulphone. 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.

Linearity/non-linearity
The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose- dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone).
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).

Paediatric 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 metabolise omeprazole.

5.3 Pre-clinical Safety:
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:
EHCG Pink/clear Transparent Size 2

6.2 Incompatibilities: Nil.

6.3 Shelf Life: 36 months.

6.4 Special Precautions for storage:
Store below 30°C
Keep all medicine out of reach of children.

6.5 Nature and contents of container:
2x7's Alu-Alu blister pack, packed in a carton alongwith pack insert. 1x14's Alu-Alu Strip Pack, packed in a carton with pack insert

6.6 Special precautions for disposal and other handling
None

7. MARKETING AUTHORIZATION HOLDER:

ZOTA HEALTHCARE LIMITED

8- MARKETING AUTHORIZATION NUMBERS:

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9- Date of first authorization/renewal of the authorization:
.....

10- Date of revision of the text:
31.10.2022

11-Name and address of Manufacture Zota Healthcare Ltd.,

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