

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. Name of medicinal product

Omeprazole Capsules BP 20 mg

2. Composition:

Each Hard Gelatin capsule contains:

Omeprazole BP 20 mg

(As Enteric Coated Pellets)

Colour : Approved Colour used in Capsule Shells

3. Pharmaceutical Form:

Solid Oral

4. Clinical Particulars

Indication

Omeprazole gastro-resistant 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 esophagitis
- Long term management of patients with healed reflux esophagitis
- Treatment of symptomatic gastro-esophageal reflux disease
- Treatment of Zollinger-Ellison syndrome

Paediatric population:

Children over 1 year of age and ≥ 10 kg

- Treatment of reflux esophagitis,
- Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease

Children and adolescents over 4 years of age

- In combination with antibiotics in the treatment of duodenal ulcer caused by H. pylori

Posology and Administration

Posology in 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 a poorly responsive duodenal ulcer Omeprazole 40mg 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 20mg once daily. In some patients a daily dose of 10mg may be sufficient. In case of therapy failure, the dose can be increased to 40mg.

Treatment of gastric ulcers

The recommended dose is 20mg 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-week treatment period. In patients with a poorly responsive gastric ulcer Omeprazole 40mg 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 20mg once daily. If needed the dose can be increased to Omeprazole 40mg once daily.

H. pylori eradication in peptic ulcer disease

For the eradication of H. pylori the selection of antibiotics should consider the individual patient's drug tolerance, and should be undertaken in accordance with national, regional and local resistance patterns and treatment guidelines.

- Omeprazole 20 mg + clarithromycin 500 mg + amoxicillin 1000 mg, each twice daily for 1 week

or

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

or

- Omeprazole 40 mg once daily with amoxicillin 500 mg + metronidazole 400mg (or 500 mg or tinidazole 500mg) 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:

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 week treatment period.

Prevention of NSAID -associated gastric and duodenal ulcers in patients at risk

For the prevention of NSAID -associated gastric ulcers 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 omeprazole 20mg once daily.

Treatment of reflux esophagitis

The recommended dose is Omeprazole 20mg once daily. In most patients healing occurs within 4 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 esophagitis Omeprazole 40mg once daily is recommended and healing is usually achieved within eight weeks.

Long-term management of patients with healed reflux esophagitis

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

Treatment of symptomatic of gastro-esophageal reflux disease

The recommended dose is Omeprazole 20mg daily. Patients may respond adequately to 10mg daily, and therefore individual dose adjustments should be considered. If symptom control has not be achieved after four weeks treatment with Omeprazole 20mg 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 60mg 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 20-120mg daily. When the dose exceeds Omeprazole 80mg daily, the dose should be divided and given twice daily.

Patients with renal impairment

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

Patients with hepatic impairment

In patients with impaired hepatic function a daily dose of 10-20mg may be sufficient.

Older people (> 65 years)

Dose adjustment is not required in the elderly.

Method of administration:

It is recommended to take Omeprazole capsules in the morning, preferably without food, swallowed whole with half a glass of water.

The capsules must not be crushed or chewed.

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 apple sauce, 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.

Contraindication

- Hypersensitivity to the active substance(s) or to any of the excipients.
- Omeprazole like other proton pump inhibitors (PPIs) must not be used concomitantly with nelfinavir

Special Warning & precautions for use

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) 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 400mg with 100mg of ritonavir; omeprazole 20mg should not be exceeded.

Omeprazole as with 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.

Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with drugs metabolized through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole. The clinical relevance of this

interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with 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. In most affected patients, 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 other medicines 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. Observational studies suggest that proton pump inhibitors may increase the overall risk of fractures by 10-40%. Some of this increase may be due to other 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 healthcare 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 five 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.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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.

Paediatric population:

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

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 plasmas 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 (40mg 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 (40mg once daily) and atazanavir 300mg/ ritonavir 100mg to healthy volunteers resulted in a 75% decrease in atazanavir exposure. Increasing the atazanavir dose to 400mg did not compensate for the effect of omeprazole on atazanavir exposure. The co-administration of omeprazole (20mg once daily) with atazanavir 400mg/ritonavir 100mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared to atazanavir 300mg/ ritonavir 100mg once daily.

Digoxin

Concomitant treatment with omeprazole (20mg 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.

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 drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Cilostazol

Omeprazole, given in doses of 40mg to healthy subjects in a cross-over study, increased the 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 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 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 dosage 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 and 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 rifampacin and St John's Wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

Fertility, Pregnancy and lactation

Pregnancy

Results from three prospective epidemiologic 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.

Effects on ability to drive and use machines

Omeprazole has no or negligible influence on the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbance may occur. If affected, patients should not drive or operate machinery.

Undesirable effects

The most common side effects (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

Overdose

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

Pharmacodynamic properties

Pharmacotherapeutic group: 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 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.

Clinical Efficacy and Safety:**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 20mg, a mean decrease of at least 80% in 24-hour intragastric acidity is then maintained on 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 20mg 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 esophagus in patients with gastro-esophageal reflux disease. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not 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 have been found to be less effective than triple therapies. They could however be considered in cases where known hypersensitivity precludes the use of any triple combination.

Other effects related to acid inhibition

During long-term treatment gastric glandular cysts have been reported in 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 count 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 hospitalized 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 esophagitis, omeprazole at doses of 0.7 to 1.4 mg/kg improved esophagitis 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-esophageal 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 *Helicobacter pylori* in children

A randomised, double-blind clinical study (Heliot 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 of 4 years old and above with a gastritis: *H. pylori* eradication rate: 74 % (23/31 patients) with omeprazole + amoxicillin + clarithromycin versus 9.4 % (3/32 patients) with amoxicillin + clarithromycin. However, there was no evidence of clinical benefit demonstrated regarding dyspeptic symptoms. This study does not support any information for children aged less than 4 years old.

Pharmacokinetic properties

Absorption

Omeprazole is acid labile and is therefore administered orally as enteric-coated granules in hard-gelatin capsules. Absorption of omeprazole is rapid, with peak-plasma levels occurring 1-2 hours after the 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 0.31/kg body weight. Omeprazole is 97% protein bound.

Biotransformation

Omeprazole is completely metabolised, by the cytochrome P450 system (CYP). The major part of metabolism is dependent on the polymorphically expressed CYP 2C19 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 CYP 2C19, there is the potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP 2C19. 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 the Asian population lack a functional CYP 2C19 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 20mg 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.

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 it's metabolites (e.g. the sulphone).

No metabolite has been found to have any effect on gastric acid secretion.

Special Populations

Impaired hepatic function

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.

Impaired renal function

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 patients

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.

6. Shelf Life

24 months

7. Special precaution for Storage

Do not store above 25°C.

8. Nature and contents of container

10 X1x 14 pack in a carton along with insert.

9. Marketing Holder

ZADIP HEALTHCARE LTD

ONITSHA, ANAMBRA STATE, NIGERIA

10. Manufacturer

TOWA PHARMA PVT LTD

JALIYANAMATH VILLAGE, SURVEY, NO-17,

DEHGAM RAKHIYAL ROAD, TA.- DEHGAM,

DIST. GANDHINAGAR-382315 GUJARAT (INDIA)

OMEPRAZOLE CAPSULE 20 MG

Marketing Holder

ZADIP HEALTHCARE LTD

ONITSHA, ANAMBRA STATE, NIGERIA

11. Manufacturer

COMED CHEMICALS LIMITED

INDIA