



For instructions on reconstitution of the medicinal product before administration, see section 6.6.

#### **4.3 Contraindications**

Hypersensitivity to omeprazole, substituted benzimidazoles or to any of the excipients listed in section 6.1.

Omeprazole like other proton pump inhibitors (PPIs) should not be used concomitantly with nelfinavir (see section 4.5).

#### **4.4 Special warnings and precautions for use**

In the presence of any alarm symptom (eg, 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 (see section 4.5). 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<sub>12</sub> (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B<sub>12</sub> 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. An interaction is

observed between clopidogrel and omeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* (see section 5.1).

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. 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 drugs that may cause hypomagnesaemia (e.g., diuretics), health care 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 recognized risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture 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 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 (see section 5.1). 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.

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

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium free".

### **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 be then be reinforced.

#### *Clopidogrel*

In a crossover clinical study, clopidogrel (300 mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) was diminished by 47% (24 hours) and 30% (Day 5) when clopidogrel and omeprazole were administered together. In another study it was shown that administering clopidogrel and omeprazole at different times did not prevent their interaction that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19.

Inconsistent data on the clinical implications of this PK/PD interaction in terms of major cardiovascular events have been reported from observational and clinical studies.

#### *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 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 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 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 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.

**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 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**

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

The following adverse drug reactions have been identified or suspected in the clinical trials programme for omeprazole and post-marketing. None was found to be dose-related. Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency categories are defined according to the following convention: Very common ( $\geq 1/10$ ), Common ( $\geq 1/100$  to  $< 1/10$ ), Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), Very rare ( $< 1/10,000$ ), Not known (cannot be estimated from the available data).

SOC/frequency	Adverse reaction
<b>Blood and lymphatic system disorders</b>	
Rare:	Leukopenia, thrombocytopenia
Very rare:	Agranulocytosis, pancytopenia
<b>Immune system disorders</b>	
Rare:	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
<b>Metabolism and nutrition disorders</b>	
Rare:	Hyponatraemia
Not known:	Hypomagnesaemia



<b>Psychiatric disorders</b>	
Uncommon:	Insomnia
Rare:	Agitation, confusion, depression
Very rare:	Aggression, hallucinations
<b>Nervous system disorders</b>	
Common:	Headache
Uncommon:	Dizziness, paraesthesia, somnolence
Rare:	Taste disturbance
<b>Eye disorders</b>	
Rare:	Blurred vision
<b>Ear and labyrinth disorders</b>	
Uncommon:	Vertigo
<b>Respiratory, thoracic and mediastinal disorders</b>	
Rare:	Bronchospasm
<b>Gastrointestinal disorders</b>	
Common:	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)
Rare:	Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
<b>Hepatobiliary disorders</b>	
Uncommon:	Increased liver enzymes
Rare:	Hepatitis with or without jaundice
Very rare:	Hepatic failure, encephalopathy in patients with pre-existing liver disease
<b>Skin and subcutaneous tissue disorders</b>	
Uncommon:	Dermatitis, pruritus, rash, urticaria
Rare:	Alopecia, photosensitivity

Very rare:	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
Not known	Subacute cutaneous lupus erythematosus (see section 4.4)
<b>Musculoskeletal and connective tissue disorders</b>	
Uncommon	Fracture of the hip, wrist or spine
Rare:	Arthralgia, myalgia
Very rare:	Muscular weakness
<b>Renal and urinary disorders</b>	
Rare:	Interstitial nephritis
<b>Reproductive system and breast disorders</b>	
Very rare:	Gynaecomastia
<b>General disorders and administration site conditions</b>	
Uncommon:	Malaise, peripheral oedema
Rare:	Increased sweating

Irreversible visual impairment has been reported in isolated cases of critically ill patients who have received omeprazole intravenous injection, especially at high doses, but no causal relationship has been established.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

#### **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.

Intravenous doses of up to 270 mg on a single day and up to 650 mg over a three-day period have been given in clinical trials without any dose-related adverse reactions.

## **5. Pharmacological properties**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Proton pump inhibitors.

#### 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*

Intravenous omeprazole produces a dose dependent inhibition of gastric acid secretion in humans. In order to immediately achieve a similar reduction of intragastric acidity as after repeated dosing with 20 mg orally, a first dose of 40 mg intravenously is recommended. This results in an immediate decrease in intragastric acidity and a mean decrease over 24 hours of approximately 90% for both iv injection and iv infusion.

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*.

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.

## **5.2 Pharmacokinetic properties**

### 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

Total plasma clearance is about 30-40 l/h after a single dose.

The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. Almost 80% of a 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 its metabolites (e.g. the sulphone). No metabolite has been found to have any effect on gastric acid secretion.

### Special populations

#### *Patients with 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.

#### *Patients with renal impairment*

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

#### *Older people*

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

### **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 H<sub>2</sub>-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**

Disodium edetate, sodium hydroxide (for pH adjustment).

### **6.2 Incompatibilities**

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### **6.3 Shelf life**

Before opening: 18 months

After reconstitution:

Chemical and physical in-use stability has been demonstrated for 12 hours after reconstitution in 0.9% sodium chloride and for 6 hours after reconstitution in 5% glucose at 25°C.

However, from a microbiological point of view, the product should be used immediately after reconstitution.

### **6.4 Special precautions for storage**

Do not store above 25°C.

Store in the original package in order to protect from light.

For storage conditions after the reconstitution of the medicinal product, see section 6.3.

### **6.5 Nature and contents of container**

Powder in 6 ml vial (type I colourless glass) with a stopper (Bromobutyl) and a flip-off type capsule (Aluminium). Box of 5 or 10 vials.

### **6.6 Special precautions for disposal and other handling**

The entire contents of each vial is to be dissolved in approximately 5 ml and then immediately diluted to 100 ml. Sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose 50 mg/ml (5%) solution for infusion must be used. The stability of omeprazole is influenced by the pH of the solution for infusion, which is why no other



solvent or quantities should be used for dilution.

#### Preparation

1. With a syringe draw 5 ml of infusion solution from the 100 ml infusion bottle or bag.
2. Add this volume to the vial with the freeze-dried omeprazole, mix thoroughly making sure all omeprazole is dissolved.
3. Draw the omeprazole solution back into the syringe.
4. Transfer the solution into the infusion bag or bottle.
5. Repeat steps 1-4 to make sure all omeprazole is transferred from the vial into the infusion bag or bottle.

#### Alternative preparation for infusions in flexible containers

1. Use a double-ended transfer needle and attach to the injection membrane of the infusion bag. Connect the other needle-end from the vial with freeze-dried omeprazole.
2. Dissolve the omeprazole substance by pumping the infusion solution back and forward between the infusion bag and the vial.
3. Make sure all omeprazole is dissolved.

The solution for infusion is to be administered in an intravenous infusion for 20-30 minutes.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

#### **7.Manufactured in India by: TAJ PHARMACEUTICALS LTD.**

Mumbai, India  
Unit No. 214.Old Bake House,  
Maharashtra chambers of Commerce Lane,

Fort, Mumbai - 400001

at:Gujarat, INDIA.

Customer Service and Product Inquiries:

1-800-TRY-FIRST (1-800-222-434 & 1-800-222-825)

Monday through Saturday 9:00 a.m. to 7:00 p.m. EST

E-mail: [tajgroup@tajpharma.com](mailto:tajgroup@tajpharma.com)