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 in adults

*Treatment of duodenal ulcers*

The recommended dose in patients with an active duodenal ulcer is Omепrex 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 Omепrex 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 Omепrex 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 Omепrex 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 Omепrex 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 Omепrex 20 mg once daily. If needed the dose can be increased to Omепrex 40 mg once daily.

*Helicobacter pylori* eradication in peptic ulcer disease

For the eradication of *Helicobacter pylori* the selection of antibiotics should consider the individual patient’s drug

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2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20 mg omeprazole.

Excipient:

For a full list of excipients, see section 6.1.
Treatment of symptomatic gastro-oesophageal reflux disease
The recommended dose is Omeprex 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 Omeprex 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 Omeprex 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 Omeprex 20-120 mg daily. When dose exceed Omeprex 80 mg daily, the dose should be divided and given twice daily.

Posology in children

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Posology</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 year of age</td>
<td>10-20 kg</td>
<td>10 mg once daily. The dose can be increased to 20 mg once daily if needed</td>
</tr>
<tr>
<td>≥2 years of age</td>
<td>&gt;20 kg</td>
<td>20 mg once daily. The dose can be increased to 40 mg once daily if needed</td>
</tr>
</tbody>
</table>

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
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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:

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Posology</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–30 kg</td>
<td>Combination with two antibiotics: Omeprazol 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight are all administered together two times daily for one week.</td>
</tr>
<tr>
<td>31–40 kg</td>
<td>Combination with two antibiotics: Omeprazol 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered two times daily for one week.</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>Combination with two antibiotics: Omeprazol 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered two times daily for one week.</td>
</tr>
</tbody>
</table>

**Special populations**

*Impaired renal function*

Dose adjustment is not needed in patients with impaired renal function (see section 5.2).

*Impaired hepatic function*

In patients with impaired hepatic function a daily dose of 10–20 mg may be sufficient (see section 5.2).

*Elderly (>65 years old)*

Dose adjustment is not needed in the elderly (see section 5.2).

**Method of administration**

It is recommended to take Omeprazol capsules in the morning, preferably without food, 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 Contraindications**

Hypersensitivity to omeprazol, substituted benzimidazoles or to any of the excipients.

Omeprazol like other proton pump inhibitors (PPIs) must 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 (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 (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; omeprazol 20 mg should not be exceeded.

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

Omeprazol, as a CYP2C19 inhibitor. When starting or ending treatment with omeprazol, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazol (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazol and clopidogrel should be discouraged.

**Interference with laboratory tests**

Increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the omeprazol treatment should be temporarily stopped five days before CgA measurements.

Some children with chronic illnesses may require long-term treatment although it is not recommended.
Omeprazole contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

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

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 itraconazol is significantly reduced and thus clinical efficacy may be impaired. For posaconazol 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
4.6 Pregnancy and lactation
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.

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
Omeprox 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).

<table>
<thead>
<tr>
<th>SOC/ frequency</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Rare: Leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Very rare: Agranulocytosis, pancytopenia</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Rare: Hyponatraemia</td>
</tr>
<tr>
<td>Very rare: Hypomagnesaemia</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Uncommon: Insomnia</td>
</tr>
<tr>
<td>Rare: Agitation, confusion, depression</td>
<td></td>
</tr>
<tr>
<td>Very rare: Aggression, hallucinations</td>
<td></td>
</tr>
</tbody>
</table>
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4.8 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 PROPERTIES

5.1 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 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 nighttime 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 20mg maintains an intra gastric 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 intra gastric 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 drugs may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter. Chromogranin A (CgA) also increases due to decreased gastric acidity. This CgA modifying effect cannot be demonstrated five days after stopping treatment with PPIs..

**Paediatric use**

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.

**Metabolism**

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.

**Excretion**

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 its 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.

**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**

Manitol, Lactose, Sucrose, Hydroxypropyl methyl Cellulose, Methacrylic acid copolymer, Empty Gelatin Capsule.
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
4 years

6.4 Special precautions for storage
Store below 25°C.
Store in the original package

6.5 Nature and contents of container
Forming Aluminium / aluminium blister pack.
Packs of 14 or 28 capsules

6.6 Special precautions for disposal and other handling
No special requirements.

7. MARKETING AUTHORISATION HOLDER
SAJA Pharmaceuticals
Saudi Arabian Japanese pharmaceutical company limited
Jeddah – Saudi Arabia

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Jeddah – Saudi Arabia
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Tel: + 96612 6515909
Fax: +966126574688
www.sajapharma.com

8. MARKETING AUTHORISATION NUMBER(S)
Omeprex 20 mg 14 cap 7/370/03
Omeprex 20 mg 28 cap 8/370/03

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02-07-2014

10. DATE OF REVISION OF THE TEXT
April 2012