Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Losec MUPS 20 mg Gastro-resistant Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

20mg: Each gastro- resistant tablet contains 20.6mg omeprazole magnesium equivalent to 20mg omeprazole.

Excipients

20mg: each gastro-resistant tablet contains sucrose (contained in sugar spheres)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

Product imported from UK and Holland: Pink, oblong, biconvex, film-coated tablets engraved with  on one side and '20mg' on the other side containing enteric coated pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Losec gastro-resistant tablets are indicated for:
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 use
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 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 Losec 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 Losec 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 Losec 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 Losec 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 Losec 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 Losec 20 mg once daily. If needed the dose can be increased to Losec 40 mg 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.

- Losec 20 mg + clarithromycin 500 mg + amoxicillin 1,000 mg, each twice daily for one week, or

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

- Losec 40 mg once daily with amoxicillin 500 mg and metronidazole 400 mg (or 500 mg or tinidazole 500 mg), 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 Losec 20 mg once daily. In most patients healing occurs within four weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further four weeks treatment period.

Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk
For the prevention of NSAID associated gastric ulcers or duodenal ulcers in patients at risk (age> 60, previous history of gastric and duodenal ulcers, previous history of upper GI bleeding) the recommended dose is Losec 20 mg once daily.

Treatment of reflux esophagitis
The recommended dose is Losec 20 mg once daily. In most patients healing occurs within four weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further four weeks treatment period.
In patients with severe esophagitis Losec 40 mg 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 Losec 10 mg once daily. If needed, the dose can be increased to Losec 20-40 mg once daily.

Treatment of symptomatic gastro-esophageal reflux disease
The recommended dose is Losec 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 4 weeks treatment with Losec 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 Losec 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 Losec 20–120 mg daily. When dose exceed Losec 80 mg daily, the dose should be divided and given twice daily.

Posology in children
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
The posology recommendations are as follows:

The dosage recommendations are as follows:

Age	Weight	Dosage
≥ 1 year of age	10-20 kg	10 mg once daily. The dosage can be increased to 20 mg once daily if needed.
≥ 2 years of age	> 20 kg	20 mg once daily. The dosage can be increased to 40 mg once daily if needed.

Reflux esophagitis: The treatment time is 4–8 weeks.
Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease: The treatment time is 2–4 weeks. If symptom control has not been achieved after 2–4 weeks the patient should be investigated further.

Children and adolescents over 4 years of age
Treatment of duodenal ulcer caused by H. pylori
When selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents.

The treatment should be supervised by a specialist.
The posology recommendations are as follows:

Weight	**Dosage**
15-30 kg	Combination with two antibiotics: Losec Mups 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight are all administered together, 2 times daily for 1 week.
30-40 kg	Combination with two antibiotics: Losec Mups 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered 2 times daily for 1 week.
> 40 kg	Combination with two antibiotics: Losec Mups 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered 2 times daily for 1 week.

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 Losec tablets in the morning, swallowed whole with half a glass of water. The tablets must not be chewed or crushed.

For patients with swallowing difficulties and for children who can drink or swallow semi-solid food
Patients can break the tablet and disperse it in a spoonful of non-carbonated water and if so wished, mix with some fruit juices or applesauce. 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. **DO NOT USE** milk or carbonated water. The enteric-coated pellets must not be chewed

4.3 Contraindications

Hypersensitivity to omeprazole, substituted benzimidazoles or to any of the excipients.
Omeprazole like other proton pump inhibitors 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; omeprazole 20 mg should not be exceeded.
Omeprazole, 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.
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.
Some children with chronic illnesses may require long-term treatment although it is not recommended.
Losec gastro-resistant tablets contain sucrose. 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* (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.

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 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.

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 manisfestations 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.

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 nelvinavir 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, ketoconazol 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 subjects in a cross-over study, increased 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 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.

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

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

Losec 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 (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

SOC/frequency	Adverse reaction
Blood and lymphatic system disorders	
Rare:	Leukopenia, thrombocytopenia
Very rare:	Agranulocytosis, pancytopenia
Immune system disorders	
Rare:	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders	
Rare:	Hyponatraemia
Very rare:	Hypomagnesaemia
Frequency not known:	Hypomagnesaemia. [See Special warnings and precautions for use (4.4)]
Psychiatric disorders	
Uncommon:	Insomnia
Rare:	Agitation, confusion, depression
Very rare:	Aggression, hallucinations
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness, paraesthesia, somnolence
Rare:	Taste disturbance
Eye disorders	
Rare:	Blurred vision
Ear and labyrinth disorders	
Uncommon:	Vertigo
Respiratory, thoracic and mediastinal disorders	
Rare:	Bronchospasm
Gastrointestinal disorders	
Common:	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Rare:	Dry mouth, stomatitis, gastrointestinal candidiasis
Hepatobiliary disorders	
Uncommon:	Increased liver enzymes
Rare:	Hepatitis with or without jaundice
Very rare:	Hepatic failure, encephalopathy in patients with pre-existing liver disease
Skin and subcutaneous tissue disorders	
Uncommon:	Dermatitis, pruritus, rash, urticaria
Rare:	Alopecia, photosensitivity
Very rare:	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	
Rare:	Arthralgia, myalgia
Very rare:	Muscular weakness
Uncommon:	Fracture of the hip, wrist or spine (see section 4.4)
Renal and urinary disorders	
Rare:	Interstitial nephritis
Reproductive system and breast disorders	
Very rare:	Gynaecomastia
General disorders and administration site conditions	
Uncommon:	Malaise, peripheral oedema
Rare:	Increased sweating

Paediatric population
The safety of omeprazole has been assessed in a total of 310 children aged 0 to 16 years with acid-related disease. There are limited long term safety data from 46 children who received maintenance therapy of omeprazole during a clinical study for severe erosive esophagitis for up to 749 days. The adverse event profile was generally the same as for adults in short- as well as in long-term treatment. There are no long term data regarding the effects of omeprazole treatment on puberty and growth.

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 in connection to omeprazole overdose have been transient, and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses. Treatment, if needed, is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 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
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 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 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 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*.

Paediatric use
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 gastroesophageal 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.
Bioequivalence between Losec capsules and Losec gastro-resistant tablets, based on both area under the omeprazole plasma concentration-time curve (AUC) and maximum plasma concentration (Cmax) of omeprazole, has been demonstrated for all doses, 10 mg, 20 mg and 40 mg.

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 drugdrug 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 dosedependency 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

Microcrystalline Cellulose
Glycerol monostearate
Hydroxypropylcellulose
Hydroxypropyl methylcellulose
Magnesium Stearate
Methcrylic acid co-polymer
Sugar spheres
Paraffin
Macrogol (polyethylene glycol)
Polysorbate
Polyvinylpyrrolidone crosslinked
Sodium hydroxide (for pH-adjustment)
Sodium stearyl fumarate
Talc
Triethyl citrate
Iron oxide
Titanium dioxide

6.2 Incompatibilities

None applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.
Blister: Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Product imported from the UK: Opaque blister packs of 7 tablets per blister available in pack size of 28 tablets.

Product imported from Holland: Opaque blister packs of 5 tablets per blister available in pack size of 30 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

B&S Healthcare,
Unit 4,
Bradfield Road,
Ruislip,
Middlesex,
HA4 ONU,
United Kingdom.

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1328/15/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation : 31st August 2007

10 DATE OF REVISION OF THE TEXT

June 2012