ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Note: This SPC, labelling and package leaflet is the version valid at the time of Commission Decision.

After the Commission Decision the Member State Competent Authorities, in liaison with the Reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

For medicinal products available on prescription

1. NAME OF THE MEDICINAL PRODUCT

Losec and associated names (see Annex I) 10 mg hard capsules
Losec and associated names (see Annex I) 20 mg hard capsules
Losec and associated names (see Annex I) 40 mg hard capsules

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10 mg: Each capsule contains 10 mg omeprazole.
20 mg: Each capsule contains 20 mg omeprazole.
40 mg: Each capsule contains 40 mg omeprazole.

Excipient:
10 mg: Each capsule contains 4 mg lactose.
20 mg: Each capsule contains 8 mg lactose.
40 mg: Each capsule contains 9 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL form

Capsule, hard (capsule).

10 mg: hard gelatine capsules with an opaque pink body, marked 10 and an opaque pink cap marked A/OS, containing enteric coated pellets.

20 mg: hard gelatine capsules with an opaque pink body, marked 20 and an opaque reddish-brown cap marked A/OM, containing enteric coated pellets.

40 mg: hard gelatine capsules with an opaque reddish-brown body, marked 40 and an opaque reddish-brown cap marked A/OL, containing enteric coated pellets.

4. Clinical particulars

4.1 Therapeutic indications

Losec capsules 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 four 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:

Age	Weight	Posology
≥ 1 year of age	10-20 kg	10 mg once daily. The dose can be increased to 20 mg once daily if needed
≥ 2 years of age	> 20 kg	20 mg once daily. The dose 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	Posology
15–30 kg	Combination with two antibiotics: Losec 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight are all administrated together two times daily for one week.
31–40 kg	Combination with two antibiotics: Losec 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administrated two times daily for one week.
> 40 kg	Combination with two antibiotics: Losec 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administrated two times daily for one 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 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 omeprazole, substituted benzimidazoles or to any of the excipients.

Omeprazole 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; omeprazole 20 mg should not be exceeded.

Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} 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 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 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 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.

Effects of other active substances on the pharmacokinetics of omeprazole

Inhibitors CYP2C19 and/or CYP3A4
Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4
Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

4.6 Pregnancy and lactation

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
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
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 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 night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment. With omeprazole 20 mg, a mean decrease of at least 80% in 24-hour intragastric acidity is then maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70% 24 hours after dosing.

Oral dosing with omeprazole 20 mg maintains an intragastric pH of ≥ 3 for a mean time of 17 hours of the 24-hour period in duodenal ulcer patients.

As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the 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 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 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 H_2-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 hydrogen phosphate dihydrate,
hydroxypropylcellulose,
hydroxypropyl methylcellulose,
lactose anhydrous,
magnesium stearate,
mannitol,
methacrylic acid co-polymer,
microcrystalline cellulose,
macrogol (polyethylene glycol),
sodium lauryl sulphate,
iron oxide,
titanium dioxide,
gelatine,
printing ink (containing shellac, ammonium hydroxide, potassium hydroxide and black iron oxide)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.
Bottle: Keep the container tightly closed in order to protect from moisture.
Blister: Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

HDPE bottle: with a tight fitting polypropylene screw-cap equipped with a desiccant capsule.
10 mg: 5, 7, 10, 14, 15, 28, 30, 50, 56, 60, 100 capsules; hospital packs of 140, 280 or 700 capsules.
20 mg: 5, 7, 10, 14, 15, 28, 30, 50, 60, 100 capsules; hospital packs of 140, 280 or 700 capsules.
40 mg: 5, 7, 14, 15, 28, 30, 60 capsules; hospital packs of 140, 280 or 700 capsules.

Aluminium blister.
10 mg: 7, 14, 15, 28, 30, 35, 50, 56, 84 capsules.
20 mg 7, 14, 15, 28, 30, 50, 60, 84 capsules.
40 mg 7, 14, 15, 28, 30 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this product is available on the website of: {name of MS/Agency}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Losec and associated names (see Annex I) 10 mg gastro-resistant tablets
Losec and associated names (see Annex I) 20 mg gastro-resistant tablets
Losec and associated names (see Annex I) 40 mg gastro-resistant tablets

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10 mg: Each gastro-resistant tablet contains 10.3 mg omeprazole magnesium equivalent to 10 mg omeprazole..
20 mg: Each gastro-resistant tablet contains 20.6 mg omeprazole magnesium equivalent to 20 mg omeprazole.
40 mg: Each gastro-resistant tablet contains 41.3 mg omeprazole magnesium equivalent to 40 mg omeprazole.

Excipient:
10 mg: Each gastro-resistant tablet contains 19–20 mg sucrose.
20 mg: Each gastro-resistant tablet contains 19–20 mg sucrose.
40 mg: Each gastro-resistant tablet contains 39–41 mg sucrose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL form

Gastro-resistant tablet.

Losec 10 mg gastro-resistant tablets: Light-pink, oblong, biconvex, film-coated tablets engraved with  or  on one side and 10 mg on the other side containing enteric coated pellets.

Losec 20 mg gastro-resistant tablets: Pink, oblong, biconvex, film-coated tablets, engraved with  or  on one side and 20 mg on the other side containing enteric coated pellets.

Losec 40 mg gastro-resistant tablets: Dark red-brown, oblong, biconvex, film-coated tablets, engraved with  or  on one side and 40 mg and a score 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:

Age	Weight	Posology
≥ 1 year of age	10-20 kg	10 mg once daily. The dose can be increased to 20 mg once daily if needed
≥ 2 years of age	> 20 kg	20 mg once daily. The dose 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	Posology
15-30 kg	Combination with two antibiotics: Losec 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight are all administrated together two times daily for one week
31-40 kg	Combination with two antibiotics: Losec 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administrated two times daily for one week
> 40 kg	Combination with two antibiotics: Losec 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administrated two times daily for one 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 B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} 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.

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 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.

Effects of other active substances on the pharmacokinetics of omeprazole

Inhibitors of CYP2C19 and/or CYP3A4
Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4
Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

4.6 Pregnancy and lactation

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
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
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, ATC code: A02BC01

Mechanism of action
Omeprazole, a racemic mixture of two enantiomers reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H^+ K^+-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

Pharmacodynamic effects
All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.

Effect on gastric acid secretion
Oral dosing with omeprazole once daily provides for rapid and effective inhibition of daytime and night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment. With omeprazole 20 mg, a mean decrease of at least 80% in 24-hour intragastric acidity is then maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70% 24 hours after dosing.

Oral dosing with omeprazole 20 mg maintains an intragastric pH of ≥ 3 for a mean time of 17 hours of the 24-hour period in duodenal ulcer patients.

As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the 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 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 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 (C_{max}) 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 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 H_2-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,
glyceryl monostearate,
hydroxypropylcellulose,
hydroxypropyl methylcellulose,
magnesium stearate,
methacrylic 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

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

HDPE bottle: with a tight fitting polypropylene screw-cap equipped with a desiccant capsule.
10 mg: 7, 14, 15, 28, 30, 50, 100 tablets; hospital pack of 140 tablets.
20 mg: 7, 14, 15, 28, 30, 50, 56, 100 tablets; hospital packs of 140, 200, 280 tablets.
40 mg: 7, 14, 15, 28, 30, 100 tablets.

Aluminium blister.
10 mg: 5, 7, 10, 14, 15, 25, 28, 30, 50, 56, 60, 84, 90, 100 tablets; hospital pack of 560 tablets.
20 mg: 5, 7, 14, 15, 25, 28, 30, 50, 56, 60, 84, 90, 98, 100 tablets; hospital pack of, 560 tablets.
40 mg: 5, 7, 14, 15, 28, 30, 50, 56, 60, 100 tablets; hospital pack of 560 tablets.

Perforated unit dose blister (hospital pack):
10 mg: 25 x 1, 28 x 1, 50 x 1, 56 x 1 tablets.
20 mg: 25 x 1, 28 x 1, 50 x 1, 56 x 1, 100 x 1 tablets.
40 mg: 25 x 1, 28 x 1, 50 x 1 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this product is available on the website of: {name of MS/Agency}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Losec and associated names (see Annex I) 40 mg powder for solution for infusion

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains omeprazole sodium 42.6 mg, equivalent to omeprazole 40 mg. After reconstitution, 1 ml contains omeprazole sodium 0.426 mg, equivalent to omeprazole 0.4 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL form

Powder for solution for infusion (Powder for infusion)

pH interval in glucose is approximately 8.9-9.5 and in sodium chloride 0.9%, 9.3-10.3

4. Clinical particulars

4.1 Therapeutic indications

Losec for intravenous use is indicated as an alternative to oral therapy for the following indications i.e.

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

4.2 Posology and method of administration

Posology
Alternative to oral therapy
In patients where the use of oral medicinal products is inappropriate, Losec IV 40 mg once daily is recommended. In patients with Zollinger-Ellison Syndrome the recommended initial dose of Losec given intravenously is 60 mg daily. Higher daily doses may be required and the dose should be adjusted individually. When doses exceed 60 mg daily, the dose should be divided and given twice daily.

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

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

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).

Paediatric patients
There is limited experience with Losec for intravenous use in children.

4.3 Contraindications

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

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 symptoms (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_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} 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).

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 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 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.

Effects of other active substances on the pharmacokinetics of omeprazole

Inhibitors of CYP2C19 and/or CYP3A4
Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4
Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

4.6 Pregnancy and lactation

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
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
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

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.

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, 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
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.*

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.

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
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

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).

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_2-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

This medicinal product should not be mixed with other medicinal products than those mentioned in section 6.6.

6.3 Shelf life

Unopened packs: 2 years.

Reconstituted solution:
Chemical and physical in-use stability has been demonstrated for 12 hours at 25°C after reconstitution with sodium chloride 9 mg/ml (0.9%) solution for infusion and for 6 hours at 25°C after reconstitution with glucose 50 mg/ml (5%) solution for infusion.

From a microbiological point of view, the product should be used immediately unless it has been reconstituted under controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25^{o}C.

Keep the vial in the outer carton in order to protect from light. Vials can however be stored exposed to normal indoor light out side the box for up to 24 hours.

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

6.5 Nature and contents of container

Vial of 10 ml made of colourless borosilicate glass, type I. Stopper made of bromobutyl rubber, cap made of aluminium and a plastic polypropylene lid.

Pack sizes: Vials 1x40 mg, 5x40 mg, 10x40 mg.
Not all pack sizes may be marketed.

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 administrered in an intravenous infusion for 20-30 minutes.

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

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this product is available on the website of: {name of MS/Agency}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Losec and associated names (see Annex I) 40 mg powder and solvent for solution for injection

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder for solution for injection contains omeprazole sodium 42.6 mg, equivalent to omeprazole 40 mg. After reconstitution, 1 ml contains omeprazole sodium 4.26 mg, equivalent to omeprazole 4 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL form

Powder and solvent for solution for injection (Powder for injection; and Solvent for injection)

pH 8.8 to 9.2

4. Clinical particulars

4.1 Therapeutic indications

Losec for intravenous use is indicated as an alternative to oral therapy for the following indications:

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

4.2 Posology and method of administration

Posology
Alternative to oral therapy
In patients where the use of oral medicinal products is inappropriate, Losec IV 40 mg once daily is recommended. In patients with Zollinger-Ellison Syndrome the recommended initial dose of Losec given intravenously is 60 mg daily. Higher daily doses may be required and the dose should be adjusted individually. When doses exceed 60 mg daily, the dose should be divided and given twice daily.

Losec solution for injection must be given only as an intravenous injection and it must not be added to infusion solutions. After reconstitution the injection should be given slowly over a period of at least 2.5 minutes at a maximum rate of 4 ml per minute. For instructions on reconstitution of the product before administration, see section 6.6.

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).

Paediatric patients
There is limited experience with Losec for intravenous use in children.

4.3 Contraindications

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

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 symptoms (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_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} 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).

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
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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
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Clopidogrel
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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.

Effects of other active substances on the pharmacokinetics of omeprazole

Inhibitors of CYP2C19 and/or CYP3A4
Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4
Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

4.6 Pregnancy and lactation

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
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
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

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.

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, 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
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.*

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.

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
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. 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 due to a decrease of 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).

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_2-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

Vial of active substance
Sodium hydroxide (for pH adjustment)

Ampoule of solvent
Citric acid monohydrate (for pH adjustment),
macrogol 400,
water for injection

6.2 Incompatibilities

This medicinal product should not be mixed with other medicinal products than those mentioned in section 6.6.

6.3 Shelf life

Unopened packs: 2 years.

Reconstituted solution:
Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C after reconstitution.

From a microbiological point of view, the product should be used immediately unless it has been reconstituted under controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the containers in the outer carton in order to protect from light. Vials can however be stored exposed to normal indoor light out side the box for up to 24 hours.

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

6.5 Nature and contents of container

Combination pack (I+II):
I: Dry substance in a 10 ml vial made of colourless borosilicate glass, type I. Stopper made of bromobutyl rubber, cap made of aluminium and a plastic polypropylene lid.
II: 10 ml solvent in an ampoule (colourless borosilicate glass).

Pack sizes: 1x40 mg (I+II), 5x40 mg (I+II) and 10x40 mg (I+II).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Losec solution for injection is obtained by dissolving the freeze-dried substance in the accompanying solvent. No other solvent should be used.

The stability of omeprazole is influenced by the pH of the solution for injection, which is why no other solvents or quantities should be used for dilution. Improperly prepared solutions can be identified by their yellow to brown discolouration and must not be used. Use only clear, colourless or pale yellowish-brown solutions.

Preparation
NOTE: Steps 1 to 5 must be performed in immediate sequence:
1. With a syringe draw all of the solvent from the ampoule (10 ml).
2. Add approximately 5 ml of the solvent to the vial with freeze-dried omeprazole.
3. Withdraw as much air as possible from the vial back into the syringe. This will make it easier to add the remaining solvent.
4. Add the remaining solvent into the vial, make sure the syringe is empty.
5. Rotate and shake the vial to ensure all the freeze-dried omeprazole has dissolved.

Losec solution for injection must be given only as an intravenous injection and it must not be added to infusion solutions. After reconstitution the injection should be given slowly over a period of at least 2.5 minutes at a maximum rate of 4 ml per minute.

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

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this product is available on the website of: {name of MS/Agency}

[To be completed nationally]

SUMMARY OF PRODUCT CHARACTERISTICS

For medicinal products available without prescription

1. NAME OF THE MEDICINAL PRODUCT

Losec and associated names (see Annex I) 10 mg gastro-resistant tablets
Losec and associated names (see Annex I) 20 mg gastro-resistant tablets

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10 mg: Each gastro-resistant tablet contains 10.3 mg omeprazole magnesium equivalent to 10 mg omeprazole.
20 mg: Each gastro-resistant tablet contains 20.6 mg omeprazole magnesium equivalent to 20 mg omeprazole.

Excipient:
10 mg: Each gastro-resistant tablet contains 19–20 mg sucrose.
20 mg: Each gastro-resistant tablet contains 19–20 mg sucrose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL form

Gastro-resistant tablet.

Losec 10 mg gastro-resistant tablets: Light-pink, oblong, biconvex, film-coated tablets engraved with  or  on one side and 10 mg on the other side containing enteric coated pellets.

Losec 20 mg gastro-resistant tablets: Pink, oblong, biconvex, film-coated tablets, engraved with  or  on one side and 20 mg on the other side containing enteric coated pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Losec gastro-resistant tablets are indicated for the treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults

4.2 Posology and method of administration

Posology in adults
The recommended dose is 20 mg once daily for 14 days.

It might be necessary to take the tablets for 2-3 consecutive days to achieve improvement of symptoms.

The majority of patients achieve complete relief of heartburn within 7 days. Once complete relief of symptoms has occurred, treatment should be discontinued.

Special populations

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

Impaired hepatic function
Patients with impaired hepatic function should be advised by a doctor before taking Losec (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
Break the tablet and disperse it in a spoonful of non-carbonated water - if so wished, mix with some fruit juices or applesauce. The dispersion should be taken immediately (or within 30 minutes). The dispersion should 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 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.

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).

Patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Especially, patients over 55 years taking any ‘over-the-counter’ (OTC, non-prescription) indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor.

Patients should be instructed to consult a doctor if:

- They have had previous gastric ulcer or gastrointestinal surgery
- They are on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks
- They have jaundice or severe liver disease.
- They are aged over 55 years with new or recently changed symptoms.

Patients should not take omeprazole as a preventative medication.

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 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.

Effects of other active substances on the pharmacokinetics of omeprazole

Inhibitors of CYP2C19 and/or CYP3A4
Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4
Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

4.6 Pregnancy and lactation

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
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
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

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, 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 sustained inhibition of daytime and night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment. With omeprazole 20 mg, a mean decrease of at least 80% in 24-hour intragastric acidity is then maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70% 24 hours after dosing.

Oral dosing with omeprazole 20 mg maintains an intragastric pH of ≥ 3 for a mean time of 17 hours of the 24-hour period in duodenal ulcer patients.

As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the 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.

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.*

Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} absorption on long-term therapy.

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).

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_2-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,
glyceryl monostearate,
hydroxypropylcellulose,
hydroxypropyl methylcellulose,
magnesium stearate,
methacrylic 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

Not applicable.

6.3 Shelf life

3 years.

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

Aluminium blister.
10 mg: 7, 14, 28 tablets
20 mg: 7, 14 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON FOR BLISTER
CARTON FOR BOTTLE
BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Losec and associated names (see Annex I) 10 mg hard capsules
Losec and associated names (see Annex I) 20 mg hard capsules
Losec and associated names (see Annex I) 40 mg hard capsules
[See Annex I - To be completed nationally]
omeprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 10 mg omeprazole.
Each capsule contains 20 mg omeprazole.
Each capsule contains 40 mg omeprazole.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules

Blister:
7 capsules
14 capsules
15 capsules
28 capsules
30 capsules
35 capsules (10 mg only)
50 capsules (10 mg and 20 mg only)
56 capsules (10 mg only)
60 capsules (20 mg only)
84 capsules (10 mg and 20 mg only)

HDPE bottle:
5 capsules
7 capsules
10 capsules (10 mg and 20 mg only)
14 capsules
15 capsules
28 capsules
30 capsules
50 capsules (10 mg and 20 mg only)

56 capsules (10 mg only)
60 capsules
100 capsules (10 mg and 20 mg only)
140 capsules
280 capsules
700 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

Carton for blister: Store in the original package in order to protect from moisture.
Carton for bottle and label: Keep the container tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Losec and associated names (see Annex I) 10 mg
Losec and associated names (see Annex I) 20 mg
Losec and associated names (see Annex I) 40 mg

Hospital pack: Justification for not including Braille accepted

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Losec and associated names (see Annex I) 10 mg capsules
Losec and associated names (see Annex I) 20 mg capsules
Losec and associated names (see Annex I) 40 mg capsules
[See Annex I - To be completed nationally]
omeprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON FOR BOTTLE
CARTON FOR BLISTER
WALLET
BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Losec and associated names (see Annex I) 10 mg gastro-resistant tablets
Losec and associated names (see Annex I) 20 mg gastro-resistant tablets
Losec and associated names (see Annex I) 40 mg gastro-resistant tablets
[See Annex I - To be completed nationally]
omeprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 10 mg omeprazole.
Each gastro-resistant tablet contains 20 mg omeprazole.
Each gastro-resistant tablet contains 40 mg omeprazole.

3. LIST OF EXCIPIENTS

Contains sucrose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Gastro-resistant tablets

Blister:
5 tablets
7 tablets
10 tablets (10 mg only)
14 tablets
15 tablets
25 tablets
28 tablets
30 tablets
50 tablets
56 tablets
60 tablets
84 tablets (10 mg and 20 mg only)
90 tablets (10 mg and 20 mg only)
98 tablets (20 mg only)
100 tablets
560 tablets

Perforated unit dose blister:
25 x 1 tablets
28 x 1 tablets
50 x 1 tablets
56 x 1 tablets (10 mg and 20 mg only)
100 x 1 (20 mg only)

HDPE bottle:
7 tablets
14 tablets
15 tablets
28 tablets
30 tablets
50 tablets (10 mg and 20 mg only)
56 tablets (20 mg only)
100 tablets
140 tablets (10 mg and 20 mg only)
200 tablets (20 mg only)
280 tablets (20 mg only)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

Carton for blister and wallet: Store in the original package in order to protect from moisture.
Carton for bottle and label: Keep the container tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Losec and associated names (see Annex I) 10 mg
Losec and associated names (see Annex I) 20 mg
Losec and associated names (see Annex I) 40 mg

Hospital pack: Justification for not including Braille accepted

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Losec and associated names (see Annex I) 10 mg gastro-resistant tablets
Losec and associated names (see Annex I) 20 mg gastro-resistant tablets
Losec and associated names (see Annex I) 40 mg gastro-resistant tablets
[See Annex I - To be completed nationally]
omeprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Losec and associated names (see Annex I) 40 mg powder for solution for infusion
[See Annex I - To be completed nationally]
omeprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains omeprazole sodium equivalent to 40 mg omeprazole

3. LIST OF EXCIPIENTS

Each vial contains disodium edetate and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial x40 mg
5 vials x40 mg
10 vials x40 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hospital pack: Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Losec and associated names (see Annex I) 40 mg powder for infusion
[See Annex I - To be completed nationally]
omeprazole
iv

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Losec and associated names (see Annex I) 40 mg powder and solvent for solution for injection (I+II)
[See Annex I - To be completed nationally]
omeprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains omeprazole sodium equivalent to 40 mg omeprazole

3. LIST OF EXCIPIENTS

I. Powder for injection
Each vial contains sodium hydroxide.

II. Solvent for injection
Each ampoule contains citric acid monohydrate, macrogol 400 and water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

1x40 mg
5x40 mg
10x40 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hospital pack: Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Losec and associated names (see Annex I) 40 mg powder for injection
[See Annex I - To be completed nationally]
omeprazole
iv

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for reconstitution of Losec and associated names (see Annex I) solution for injection
[See Annex I - To be completed nationally]
iv

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OTC CARTON FOR BOTTLE CARTON FOR BLISTER
WALLET
BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Losec and associated names (see Annex I) 10 mg gastro-resistant tablets
Losec and associated names (see Annex I) 20 mg gastro-resistant tablets
[See Annex I - To be completed nationally]
omeprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 10 mg omeprazole.
Each gastro-resistant tablet contains 20 mg omeprazole.

3. LIST OF EXCIPIENTS

Contains sucrose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Gastro-resistant tablets

Blister:
7 tablets
14 tablets
28 tablets (10 mg only)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

Carton for blister: Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product not subject to medical prescription.

15. INSTRUCTIONS ON USE

For short – term treatment of reflux symptoms (for example, heartburn, acid regurgitation) in adults.

Take one 20 mg tablet or two 10 mg tablets once a day for 14 days. Contact your doctor if you are not free from symptoms after this period.
Read the package leaflet before use.

16. INFORMATION IN BRAILLE

Losec and associated names (see Annex I) 10 mg
Losec and associated names (see Annex I) 20 mg

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Losec and associated names (see Annex I) 10 mg gastro-resistant tablets
Losec and associated names (see Annex I) 20 mg gastro-resistant tablets
[See Annex I - To be completed nationally]
omeprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PACKAGE LEAFLETs

For medicinal products available on prescription

PACKAGE LEAFLET: INFORMATION FOR THE USER

Losec and associated names (see Annex I) 10 mg hard capsules
Losec and associated names (see Annex I) 20 mg hard capsules
Losec and associated names (see Annex I) 40 mg hard capsules
[See Annex I - To be completed nationally]
Omeprazole

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Losec is and what it is used for
2. Before you take Losec
3. How to take Losec
4. Possible side effects
5. How to store Losec
6. Further information

1. WHAT LOSEC IS AND WHAT IT IS USED FOR

Losec contains the active substance omeprazole. It belongs to a group of medicines called 'proton pump inhibitors'. They work by reducing the amount of acid that your stomach produces.

Losec is used to treat the following conditions:

In adults:
- 'Gastro-esophageal reflux disease' (GERD). This is where acid from the stomach escapes into the gullet (the tube which connects your throat to your stomach) causing pain, inflammation and heartburn.
- Ulcers in the upper part of the intestine (duodenal ulcer) or stomach (gastric ulcer).
- Ulcers which are infected with bacteria called '*Helicobacter pylori'*. If you have this condition, your doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.
- Ulcers caused by medicines called NSAIDs (Non-Steroidal Anti-Inflammatory Drugs). Losec can also be used to stop ulcers from forming if you are taking NSAIDs.
- Too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome).

In children:
Children over 1 year of age and ≥ 10 kg
- 'Gastro-esophageal reflux disease' (GERD). This is where acid from the stomach escapes into the gullet (the tube which connects your throat to your stomach) causing pain, inflammation and heartburn.
  In children, the symptoms of the condition can include the return of stomach contents into the mouth (regurgitation), being sick (vomiting) and poor weight gain.

Children and adolescents over 4 years of age
- Ulcers which are infected with bacteria called '*Helicobacter pylori'*. If your child has this condition, your doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.

2. BEFORE YOU TAKE LOSEC

Do not take Losec
- if you are allergic (hypersensitive) to omeprazole or any of the other ingredients of Losec.
- if you are allergic to medicines containing other proton pump inhibitors (eg pantoprazole, lansoprazole, rabeprazole, esomeprazole).
- if you are taking a medicine containing nelfinavir (used for HIV infection)

If you are not sure, talk to your doctor or pharmacist before taking Losec.

Take special care with Losec
Losec may hide the symptoms of other diseases. Therefore, if any of the following happen to you before you start taking Losec or while you are taking it, talk to your doctor straight away:
- You lose a lot of weight for no reason and have problems swallowing.
- You get stomach pain or indigestion.
- You begin to vomit food or blood.
- You pass black stools (blood-stained faeces).
- You experience severe or persistent diarrhoea, as omeprazole has been associated with a small increase in infectious diarrhoea.
- You have severe liver problems.

If you take Losec on a long-term basis (longer than 1 year) your doctor will probably keep you under regular surveillance. You should report any new and exceptional symptoms and circumstances whenever you see your doctor.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because Losec can affect the way some medicines work and some medicines can have an effect on Losec.

Do not take Losec if you are taking a medicine containing **nelfinavir** (used to treat HIV infection).

Tell your doctor or pharmacist if you are taking any of the following medicines:
- Ketoconazole, itraconazole or voriconazole (used to treat infections caused by a fungus)
- Digoxin (used to treat heart problems)
- Diazepam (used to treat anxiety, relax muscles or in epilepsy)
- Phenytoin (used in epilepsy). If you are taking phenytoin, your doctor will need to monitor you when you start or stop taking Losec
- Medicines that are used to thin your blood, such as warfarin or other vitamin K blockers. Your doctor may need to monitor you when you start or stop taking Losec
- Rifampicin (used to treat tuberculosis)
- Atazanavir (used to treat HIV infection)
- Tacrolimus (in cases of organ transplantation)
- St John's wort (*Hypericum perforatum*) (used to treat mild depression)
- Cilostazol (used to treat intermittent claudication)
- Saquinavir (used to treat HIV infection)
- Clopidogrel (used to prevent blood clots (thrombi))

If your doctor has prescribed the antibiotics amoxicillin and clarithromycin as well as Losec to treat ulcers caused by *Helicobacter pylori* infection, it is very important that you tell your doctor about any other medicines you are taking.

Taking Losec with food and drink
You can take your capsules with food or on an empty stomach.

Pregnancy and breast-feeding
Before taking Losec, tell your doctor if you are pregnant or trying to get pregnant. Your doctor will decide whether you can take Losec during this time.

Your doctor will decide whether you can take Losec if you are breastfeeding.

Driving and using machines
Losec is not likely to affect your ability to drive or use any tools or machines. Side effects such as dizziness and visual disturbances may occur (see section 4). If affected, you should not drive or operate machinery.

Important information about some of the ingredients of Losec
Losec capsules contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE LOSEC

Always take Losec exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will tell you how many capsules to take and how long to take them for. This will depend on your condition and how old you are.
The usual doses are given below.

Adults:

To treat symptoms of GERD such as **heartburn and acid regurgitation**:
- If your doctor has found that your food pipe (gullet) has been slightly damaged, the usual dose is 20 mg once a day for 4-8 weeks. Your doctor may tell you to take a dose of 40 mg for a further 8 weeks if your gullet has not yet healed.
- The usual dose once the gullet has healed is 10 mg once a day.
- If your gullet has not been damaged, the usual dose is 10 mg once a day.

To treat **ulcers in the upper part of the intestine** (duodenal ulcer):
- The usual dose is 20 mg once a day for 2 weeks. Your doctor may tell you to take the same dose for a further 2 weeks if your ulcer has not yet healed.
- If the ulcer do not fully heal, the dose can be increased to 40 mg once a day for 4 weeks.

To treat **ulcers in the stomach** (gastric ulcer):
- The usual dose is 20 mg once a day for 4 weeks. Your doctor may tell you to take the same dose for a further 4 weeks if your ulcer has not yet healed.
- If the ulcer do not fully heal, the dose can be increased to 40 mg once a day for 8 weeks.

To **prevent the duodenal and stomach ulcers** from coming back:
- The usual dose is 10 mg or 20 mg once a day. Your doctor may increase the dose to 40 mg once a day.

To treat duodenal and stomach **ulcers caused by NSAIDs** (Non-Steroidal Anti-Inflammatory Drugs):

- The usual dose is 20 mg once a day for 4–8 weeks.

To **prevent duodenal and stomach ulcers** if you are taking **NSAIDs:**
- The usual dose is 20 mg once a day.

To treat **ulcers caused by *Helicobacter pylori*** infection and to stop them coming back:
- The usual dose is 20 mg Losec twice a day for one week.
- Your doctor will also tell you to take two antibiotics among amoxicillin, clarithromycin and metronidazole.

To treat too much acid in the stomach caused by a **growth in the pancreas (Zollinger-Ellison syndrome)**:
- The usual dose is 60 mg daily.
- Your doctor will adjust the dose depending on your needs and will also decide how long you need to take the medicine for.

Children:

To treat symptoms of GERD such as **heartburn and acid regurgitation**:
- Children over 1 year of age and with a body weight of more than 10 kg may take Losec. The dose for children is based on the child's weight and the doctor will decide the correct dose.

To treat **ulcers caused by *Helicobacter pylori*** infection and to stop them coming back:
- Children aged over 4 years may take Losec. The dose for children is based on the child's weight and the doctor will decide the correct dose.
- Your doctor will also prescribe two antibiotics called amoxicillin and clarithromycin for your child.

Taking this medicine
- It is recommended that you take your capsules in the morning.
- You can take your capsules with food or on an empty stomach.
- Swallow your capsules whole with half a glass of water. Do not chew or crush the capsules. This is because the capsules contain coated pellets which stop the medicine from being broken down by the acid in your stomach. It is important not to damage the pellets.

What to do if you or your child have trouble swallowing the capsules
- If you or your child have trouble swallowing the capsules:
  - Open the capsules and swallow the contents directly with half a glass of water or put the contents into a glass of still (non-fizzy) water, any acidic fruit juice (e.g. apple, orange or pineapple) or apple sauce.
  - Always stir the mixture just before drinking it (the mixture will not be clear). Then drink the mixture straight away or within 30 minutes.
  - To make sure that you have drunk all of the medicine, rinse the glass very well with half a glass of water and drink it. The solid pieces contain the medicine - do not chew or crush them.

If you take more Losec than you should
If you take more Losec than prescribed by your doctor, talk to your doctor or pharmacist straight away.

If you forget to take Losec
If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Losec can cause side effects, although not everybody gets them.

If you notice any of the following rare but serious side effects, stop taking Losec and contact a doctor immediately:

- Sudden wheezing, swelling of your lips, tongue and throat or body, rash, fainting or difficulties in swallowing (severe allergic reaction).
- Reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be 'Stevens-Johnson syndrome' or 'toxic epidermal necrolysis'.
- Yellow skin, dark urine and tiredness which can be symptoms of liver problems.

Side effects may occur with certain frequencies, which are defined as follows:

Very common:	affects more than 1 user in 10
Common:	affects 1 to 10 users in 100
Uncommon:	affects 1 to 10 users in 1,000
Rare:	affects 1 to 10 users in 10,000
Very rare:	affects less than 1 user in 10,000
Not known:	frequency cannot be estimated from the available data

Other side effects include:

Common side effects

- Headache.
- Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).

Uncommon side effects

- Swelling of the feet and ankles.
- Disturbed sleep (insomnia).
- Dizziness, tingling feelings such as "pins and needles", feeling sleepy.
- Spinning feeling (vertigo).
- Changes in blood tests that check how the liver is working.
- Skin rash, lumpy rash (hives) and itchy skin.
- Generally feeling unwell and lacking energy.

Rare side effects

- Blood problems such as a reduced number of white cells or platelets. This can cause weakness, bruising or make infections more likely.
- Allergic reactions, sometimes very severe, including swelling of the lips, tongue and throat, fever, wheezing.
- Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps.
- Feeling agitated, confused or depressed.
- Taste changes.
- Eyesight problems such as blurred vision.
- Suddenly feeling wheezy or short of breath (bronchospasm).
- Dry mouth.
- An inflammation of the inside of the mouth.
- An infection called "thrush" which can affect the gut and is caused by a fungus.
- Liver problems, including jaundice which can cause yellow skin, dark urine, and tiredness.
- Hair loss (alopecia).
- Skin rash on exposure to sunshine.
- Joint pains (arthralgia) or muscle pains (myalgia).
- Severe kidney problems (interstitial nephritis).

- Increased sweating.

Very rare side effects
- Changes in blood count including agranulocytosis (lack of white blood cells).
- Aggression.
- Seeing, feeling or hearing things that are not there (hallucinations).
- Severe liver problems leading to liver failure and inflammation of the brain.
- Sudden onset of a severe rash or blistering or peeling skin. This may be associated with a high fever and joint pains (Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Muscle weakness.
- Enlarged breasts in men.
- Hypomagnesaemia

Losec may in very rare cases affect the white blood cells leading to immune deficiency. If you have an infection with symptoms such as fever with a **severely** reduced general condition or fever with symptoms of a local infection such as pain in the neck, throat or mouth or difficulties in urinating, you must consult your doctor as soon as possible so that a lack of white blood cells (agranulocytosis) can be ruled out by a blood test. It is important for you to give information about your medicine at this time.

Do not be concerned by this list of possible side effects. You may not get any of them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE LOSEC

- Keep out of the reach and sight of children.

- Do not use Losec after the expiry date which is stated on the pack after EXP. The expiry date refers to the last day of that month.

- Do not store above 30°C.

- Store this blister in the original package or keep the bottle tightly closed in order to protect from moisture.

- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Losec contains
- The active substance is omeprazole. Losec capsules contain 10 mg, 20 mg or 40 mg of omeprazole.
- The other ingredients are disodium hydrogen phosphate dihydrate, hydroxypropylcellulose, hydroxypropyl methylcellulose, lactose anhydrous, magnesium stearate, mannitol, methacrylic acid co-polymer, microcrystalline cellulose, macrogol (polyethylene glycol), sodium lauryl sulphate, iron oxide, titanium dioxide, gelatine, printing ink (containing shellac, ammonium hydroxide, potassium hydroxide and black iron oxide).

What Losec looks like and contents of the pack
- Losec 10 mg capsules have a pink body, marked 10 and a pink cap marked A/OS.
- Losec 20 mg capsules have a pink body, marked 20 and a reddish-brown cap marked A/OM.

- Losec 40 mg capsules have a reddish-brown body marked 40 and a reddish-brown cap marked A/OL.

Pack sizes:

- 10 mg:
  - HDPE bottles of 5, 7, 10, 14, 15, 28, 30, 50, 56, 60 or 100 capsules; hospital packs of 140, 280 or 700 capsules.
  - Blisters of 7, 14, 15, 28, 30, 35, 50, 56 and 84 capsules.

- 20 mg:
  - HDPE bottles of 5, 7, 10, 14, 15, 28, 30, 50, 60 or 100 capsules; hospital packs of 140, 280 , or 700 capsules.
  - Blisters of 7, 14, 15, 28, 30, 50, 60 or 84 capsules.

- 40 mg:
  - HDPE bottles of 5, 7, 14, 15, 28, 30 or 60 capsules; hospital packs of 140, 280, or 700 capsules.
  - Blisters of 7, 14, 15, 28 or 30 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

PACKAGE LEAFLET: INFORMATION FOR THE USER

Losec and associated names (see Annex I) 10 mg gastro-resistant tablets
Losec and associated names (see Annex I) 20 mg gastro-resistant tablets
Losec and associated names (see Annex I) 40 mg gastro-resistant tablets
[See Annex I - To be completed nationally]
Omeprazole

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Losec is and what it is used for
2. Before you take Losec
3. How to take Losec
4. Possible side effects
5. How to store Losec
6. Further information

1. WHAT LOSEC IS AND WHAT IT IS USED FOR

Losec gastro-resistant tablets contains the active substance omeprazole. It belongs to a group of medicines called 'proton pump inhibitors'. They work by reducing the amount of acid that your stomach produces.

Losec is used to treat the following conditions:

In adults:
- 'Gastro-esophageal reflux disease' (GERD). This is where acid from the stomach escapes into the gullet (the tube which connects your throat to your stomach) causing pain, inflammation and heartburn.
- Ulcers in the upper part of the intestine (duodenal ulcer) or stomach (gastric ulcer).
- Ulcers which are infected with bacteria called '*Helicobacter pylori*'. If you have this condition, your doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.
- Ulcers caused by medicines called NSAIDs (Non-Steroidal Anti-Inflammatory Drugs). Losec can also be used to stop ulcers from forming if you are taking NSAIDs.
- Too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome).

In children:
Children over 1 year of age and ≥ 10 kg
- 'Gastro-esophageal reflux disease' (GERD). This is where acid from the stomach escapes into the gullet (the tube which connects your throat to your stomach) causing pain, inflammation and heartburn.
  In children, the symptoms of the condition can include the return of stomach contents into the mouth (regurgitation), being sick (vomiting) and poor weight gain.

Children and adolescents over 4 years of age
- Ulcers which are infected with bacteria called '*Helicobacter pylori'*. If your child has this condition, your doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.

2. BEFORE YOU TAKE LOSEC

Do not take Losec
- if you are allergic (hypersensitive) to omeprazole or any of the other ingredients of Losec.
- if you are allergic to medicines containing other proton pump inhibitors (e.g. pantoprazole, lansoprazole, rabeprazole, esomeprazole).
- if you are taking a medicine containing nelfinavir (for HIV infection).

If you are not sure, talk to your doctor or pharmacist before taking Losec.

Take special care with Losec
Losec may hide the symptoms of other diseases. Therefore, if any of the following happen to you before you start taking Losec or while you are taking it, talk to your doctor straight away:
- You lose a lot of weight for no reason and have problems swallowing.
- You get stomach pain or indigestion.
- You begin to vomit food or blood.
- You pass black stools (blood-stained faeces).
- You experience severe or persistent diarrhoea, as omeprazole has been associated with a small increase in infectious diarrhoea.
- You have severe liver problems.

If you take Losec on a long-term basis (longer than 1 year) your doctor will probably keep you under regular surveillance. You should report any new and exceptional symptoms and circumstances whenever you see your doctor.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because Losec can affect the way some medicines work and some medicines can have an effect on Losec.

Do not take Losec if you are taking a medicine containing **nelfinavir** (used to treat HIV infection).

Tell your doctor or pharmacist if you are taking any of the following medicines:
- Ketoconazole, itraconazole or voriconazole (used to treat infections caused by a fungus).
- Digoxin (used to treat heart problems)
- Diazepam (used to treat anxiety, relax muscles or in epilepsy).
- Phenytoin (used in epilepsy). If you are taking phenytoin, your doctor will need to monitor you when you start or stop taking Losec
- Medicines that are used to thin your blood, such as warfarin or other vitamin K blockers. Your doctor may need to monitor you when you start or stop taking Losec.
- Rifampicin (used to treat tuberculosis)
- Atazanavir (used to treat HIV infections)
- Tacrolimus (in cases of organ transplantation)
- St John's wort (*Hypericum perforatum*) (used to treat mild depression)
- Cilostazol (used to treat intermittent claudication)
- Saquinavir (used to treat HIV infection)
- Clopidogrel (used to prevent blood clots (thrombi))

If your doctor has prescribed the antibiotics amoxicillin and clarithromycin as well as Losec to treat ulcers caused by *Helicobacter pylori* infection, it is very important that you tell your doctor about any other medicines you are taking.

Taking Losec with food and drink
You can take your tablets with food or on an empty stomach.

Pregnancy and breast-feeding
Before taking Losec, tell your doctor if you are pregnant or trying to get pregnant. Your doctor will decide whether you can take Losec during this time.

Your doctor will decide whether you can take Losec if you are breastfeeding.

Driving and using machines
Losec is not likely to affect your ability to drive or use any tools or machines. Side effects such as dizziness and visual disturbances may occur (see section 4). If affected, you should not drive or operate machinery.

Important information about some of the ingredients of Losec
Losec gastro-resistant tablets contain sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product

3. HOW TO TAKE LOSEC

Always take Losec exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will tell you how many tablets to take and how long to take them for. This will depend on your condition and how old you are.
The usual doses are given below.

Adults:

To treat symptoms of GERD such as **heartburn and acid regurgitation**:
- If your doctor has found that your food pipe (gullet) has been slightly damaged, the usual dose is 20 mg once a day for 4-8 weeks. Your doctor may tell you to take a dose of 40 mg for a further 8 weeks if your gullet has not yet healed.
- The usual dose once the gullet has healed is 10 mg once a day.
- If your gullet has not been damaged, the usual dose is 10 mg once a day.

To treat **ulcers in the upper part of the intestine** (duodenal ulcer):
- The usual dose is 20 mg once a day for 2 weeks. Your doctor may tell you to take the same dose for a further 2 weeks if your ulcer has not yet healed.
- If the ulcer do not fully heal, the dose can be increased to 40 mg once a day for 4 weeks.

To treat **ulcers in the stomach** (gastric ulcer):
- The usual dose is 20 mg once a day for 4 weeks. Your doctor may tell you to take the same dose for a further 4 weeks if your ulcer has not yet healed.
- If the ulcer do not fully heal, the dose can be increased to 40 mg once a day for 8 weeks.

To **prevent the duodenal and stomach ulcers** from coming back:
- The usual dose is 10 mg or 20 mg once a day. Your doctor may increase the dose to 40 mg once a day.

To treat duodenal and stomach **ulcers caused by NSAIDs** (Non-Steroidal Anti-Inflammatory Drugs):
- The usual dose is 20 mg once a day for 4 to 8 weeks.

To **prevent duodenal and stomach ulcers** if you are taking **NSAIDs**:
- The usual dose is 20 mg once a day.

To treat **ulcers caused by *Helicobacter pylori*** infection and to stop them coming back:
- The usual dose is 20 mg Losec twice a day for one week.
- Your doctor will also tell you to take two antibiotics among amoxicillin, clarithromycin and metronidazole.

To treat too much acid in the stomach caused by a **growth in the pancreas (Zollinger-Ellison syndrome)**:
- The usual dose is 60 mg daily.
- Your doctor will adjust the dose depending on your needs and will also decide how long you need to take the medicine for.

Children:

To treat symptoms of GERD such as **heartburn and acid regurgitation**:
- Children over 1 year of age and with a body weight of more than 10 kg may take Losec. The dose for children is based on the child's weight and the doctor will decide the correct dose.

To treat **ulcers caused by *Helicobacter pylori* infection** and to stop them coming back:
- Children aged over 4 years may take Losec. The dose for children is based on the child's weight and the doctor will decide the correct dose.
- Your doctor will also prescribe two antibiotics called amoxicillin and clarithromycin for your child.

Taking this medicine
- It is recommended that you take your tablets in the morning.
- You can take your tablets with food or on an empty stomach.
- Swallow your tablets whole with half a glass of water. Do not chew or crush the tablets. This is because the tablets contain coated pellets which stop the medicine from being broken down by the acid in your stomach. It is important not to damage the pellets.

What to do if you or your child have trouble swallowing the tablets
- If you or your child have trouble swallowing the tablets:
  - Break the tablet and disperse it in a spoonful of water (non-fizzy), any acidic fruit juice (e.g. apple, orange or pineapple) or apple sauce.
  - Always stir the mixture just before drinking (the mixture will not be clear). Then drink the mixture straight away or within 30 minutes.
  - To make sure that you have drunk all of the medicine, rinse the glass very well with half a glass of water and drink it. **Do not use** milk or fizzy water. The solid pieces contain the medicine - do not chew or crush them.

If you take more Losec than you should
If you take more Losec than prescribed by your doctor, talk to your doctor or pharmacist straight away.

If you forget to take Losec
If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Losec can cause side effects, although not everybody gets them.

If you notice any of the following rare but serious side effects, stop taking Losec and contact a doctor immediately:

- Sudden wheezing, swelling of your lips, tongue and throat or body, rash, fainting or difficulties in swallowing (severe allergic reaction).
- Reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be 'Stevens-Johnson syndrome' or 'toxic epidermal necrolysis'.
- Yellow skin, dark urine and tiredness which can be symptoms of liver problems.

Side effects may occur with certain frequencies, which are defined as follows:

Very common:	affects more than 1 user in 10
Common:	affects 1 to 10 users in 100
Uncommon:	affects 1 to 10 users in 1,000
Rare:	affects 1 to 10 users in 10,000
Very rare:	affects less than 1 user in 10,000
Not known:	frequency cannot be estimated from the available data

Other side effects include:

Common side effects

- Headache.
- Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).

Uncommon side effects

- Swelling of the feet and ankles.
- Disturbed sleep (insomnia).
- Dizziness, tingling feelings such as "pins and needles", feeling sleepy.
- Spinning feeling (vertigo).
- Changes in blood tests that check how the liver is working.
- Skin rash, lumpy rash (hives) and itchy skin.
- Generally feeling unwell and lacking energy.

Rare side effects

- Blood problems such as a reduced number of white cells or platelets. This can cause weakness, bruising or make infections more likely.
- Allergic reactions, sometimes very severe, including swelling of the lips, tongue and throat, fever, wheezing.
- Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps.
- Feeling agitated, confused or depressed.
- Taste changes.
- Eyesight problems such as blurred vision.
- Suddenly feeling wheezy or short of breath (bronchospasm).
- Dry mouth.
- An inflammation of the inside of the mouth.
- An infection called "thrush" which can affect the gut and is caused by a fungus.
- Liver problems, including jaundice which can cause yellow skin, dark urine, and tiredness.
- Hair loss (alopecia).
- Skin rash on exposure to sunshine.
- Joint pains (arthralgia) or muscle pains (myalgia).
- Severe kidney problems (interstitial nephritis).
- Increased sweating.

Very rare side effects
- Changes in blood count including agranulocytosis (lack of white blood cells)
- Aggression.
- Seeing, feeling or hearing things that are not there (hallucinations).
- Severe liver problems leading to liver failure and inflammation of the brain.
- Sudden onset of a severe rash or blistering or peeling skin. This may be associated with a high fever and joint pains (Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)
- Muscle weakness.
- Enlarged breasts in men.
- Hypomagnesaemia

Losec may in very rare cases affect the white blood cells leading to immune deficiency. If you have an infection with symptoms such as fever with a **severely** reduced general condition or fever with symptoms of a local infection such as pain in the neck, throat or mouth or difficulties in urinating, you must consult your doctor as soon as possible so that a lack of white blood cells (agranulocytosis) can be ruled out by a blood test. It is important for you to give information about your medicine at this time.

Do not be concerned by this list of possible side effects. You may not get any of them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE LOSEC

- Keep out of the reach and sight of children.

- Do not use Losec after the expiry date which is stated on the outer and inner pack after EXP. The expiry date refers to the last day of that month.

- Do not store above 25°C.

- Store this blister in the original package or keep the bottle tightly closed in order to protect from moisture.

- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Losec contains
- The active substance is omeprazole. Losec gastro-resistant tablets contain omeprazole magnesium corresponding to 10 mg, 20 mg or 40 mg omeprazole.
- The other ingredients are microcrystalline cellulose, glyceryl monostearate, hydroxypropylcellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic 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.

What Losec looks like and contents of the pack
- Losec 10 mg gastro-resistant tablets are light-pink with  or  on one side and 10 mg on the other side.
- Losec 20 mg gastro-resistant tablets are pink with  or  on one side and 20 mg on the other side.

- Losec 40 mg gastro-resistant tablets are dark red-brown with  or  on one side and 40 mg on the other side.

Pack sizes:

- 10 mg:
  - HDPE bottles of 7, 14, 15, 28, 30, 50, 100 tablets; hospital pack of 140 tablets.
  - Blisters of 5, 7, 10, 14, 15, 25, 28, 30, 50, 56, 60, 84, 90, 100 tablets; hospital pack of 560 tablets.
  - Perforated unit dose blisters (hospital packs) of 25 x 1, 28 x 1, 50 x 1, 56 x 1 tablets.

- 20 mg:
  - HDPE bottles of 7, 14, 15, 28, 30, 50, 56, 100 tablets; hospital packs of 140 , 200, 280 tablets.
  - Blisters of 5, 7, 14, 15, 25, 28, 30, 50, 56, 60, 84, 90, 98, 100 tablets; hospital pack of 560 tablets.
  - Perforated unit dose blisters (hospital packs) of 25 x 1, 28 x 1, 50 x 1, 56 x 1, 100 x 1 tablets.

- 40 mg:
  - HDPE bottles of 7, 14, 15, 28, 30, 100 tablets.
  - Blisters of 5, 7, 14, 15, 25, 28, 30, 50, 56, 60, 100 tablets; hospital pack of 560 tablets.
  - Perforated unit dose blisters (hospital packs) of 25 x 1, 28 x 1, 50 x 1 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

PACKAGE LEAFLET: INFORMATION FOR THE USER

Losec and associated names (see Annex I) 40 mg powder for solution for infusion
[See Annex I - To be completed nationally]
Omeprazole

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

In this leaflet:

1. What Losec is and what it is used for
2. Before Losec is given to you
3. How Losec is given to you
4. Possible side effects
5. How to store Losec
6. Further information

1. WHAT LOSEC IS AND WHAT IT IS USED FOR

Losec contains the active substance omeprazole. It belongs to a group of medicines called 'proton pump inhibitors'. They work by reducing the amount of acid that your stomach produces.

Losec powder for solution for infusion can be used as an alternative to oral therapy.

2. BEFORE LOSEC IS GIVEN TO YOU

You must not be given Losec
- if you are allergic (hypersensitive) to omeprazole or any of the other ingredients of Losec.
- if you are allergic to other proton pump inhibitor medicines (e.g. pantoprazole, lansoprazole, rabeprazole, esomeprazole).
- if you are taking a medicine containing nelfinavir (used for HIV infection).

If you are not sure, talk to your doctor, nurse or pharmacist before you are given this medicine.

Take special care with Losec
Losec may hide the symptoms of other diseases. Therefore, if any of the following happen to you before you are given Losec or after you are given it, talk to your doctor straight away:
- You lose a lot of weight for no reason and have problems swallowing.
- You get stomach pain or indigestion.
- You begin to vomit food or blood.
- You pass black stools (blood-stained faeces).
- You experience severe or persistent diarrhoea, as omeprazole has been associated with a small increase in infectious diarrhoea.
- You have severe liver problems.

Using other medicines
Please tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because Losec can affect the way some medicines work and some medicines can have an effect on Losec.

You must not be given Losec if you are taking a medicine containing **nelfinavir** (used to treat HIV infection).

Tell your doctor or pharmacist if you are taking any of the following medicines:
- Ketoconazole, itraconazole or voriconazole (used to treat infections caused by a fungus).
- Digoxin (used to treat heart problems)
- Diazepam (used to treat anxiety, relax muscles or in epilepsy)
- Phenytoin (used in epilepsy). If you are taking phenytoin, your doctor will need to monitor you when you start or stop taking Losec.
- Medicines that are used to thin your blood, such as warfarin or other vitamin K blockers. Your doctor may need to monitor you when you start or stop taking Losec
- Rifampicin (used to treat tuberculosis)
- Atazanavir (used to treat HIV infection)
- Tacrolimus (in cases of organ transplantation)
- St John's wort (*Hypericum perforatum*) (used to treat mild depression)
- Cilostazol (used to treat intermittent claudication)
- Saquinavir (used to treat HIV infection)
- Clopidogrel (used to prevent blood clots (thrombi))

If your doctor has prescribed the antibiotics amoxicillin and clarithromycin as well as Losec to treat ulcers caused by *Helicobacter pylori* infection, it is very important that you tell your doctor about any other medicines you are taking.

Pregnancy and breast-feeding
Before you are given Losec, tell your doctor if you are pregnant or trying to get pregnant. Your doctor will decide whether you can be given Losec during this time.

Your doctor will decide whether you can take Losec if you are breastfeeding.

Driving and using machines
Losec is not likely to affect your ability to drive or use any tools or machines. Side effects such as dizziness and visual disturbances may occur (see section 4). If affected, you should not drive or operate machinery.

3. HOW LOSEC IS GIVEN TO YOU

- Losec can be given to adults including the elderly.
- There is limited experience with Losec for intravenous use in children.

Being given Losec
- Losec will be given to you by a doctor who will decide how much you need.
- The medicine will be given to you as an infusion into one of your veins.

If you are given more Losec than you should
If you think you have been given too much Losec, talk to your doctor straight away.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Losec can cause side effects, although not everybody gets them.

If you notice any of the following rare but serious side effects, stop using Losec and contact a doctor immediately:

- Sudden wheezing, swelling of your lips, tongue and throat or body, rash, fainting or difficulties to swallow (severe allergic reaction).
- Reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be 'Stevens-Johnson syndrome' or 'toxic epidermal necrolysis'.
- Yellow skin, dark urine and tiredness which can be symptoms of liver problems.

Side effects may occur with certain frequencies, which are defined as follows:

Very common:	affects more than 1 user in 10
Common:	affects 1 to 10 users in 100
Uncommon:	affects 1 to 10 users in 1,000
Rare:	affects 1 to 10 users in 10,000
Very rare:	affects less than 1 user in 10,000
Not known:	frequency cannot be estimated from the available data

Other side effects include:

Common side effects

- Headache.
- Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).

Uncommon side effects

- Swelling of the feet and ankles.
- Disturbed sleep (insomnia).
- Dizziness, tingling feelings such as "pins and needles", feeling sleepy.
- Spinning feeling (vertigo).
- Changes in blood tests that check how the liver is working.
- Skin rash, lumpy rash (hives) and itchy skin.
- Generally feeling unwell and lacking energy.

Rare side effects

- Blood problems such as a reduced number of white cells or platelets. This can cause weakness, bruising or make infections more likely.
- Allergic reactions, sometimes very severe, including swelling of the lips, tongue and throat, fever, wheezing.
- Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps.
- Feeling agitated, confused or depressed.
- Taste changes.
- Eyesight problems such as blurred vision.
- Suddenly feeling wheezy or short of breath (bronchospasm).
- Dry mouth.
- An inflammation of the inside of the mouth.
- An infection called "thrush" which can affect the gut and is caused by a fungus.
- Liver problems, including jaundice which can cause yellow skin, dark urine, and tiredness.
- Hair loss (alopecia).
- Skin rash on exposure to sunshine.
- Joint pains (arthralgia) or muscle pains (myalgia).
- Severe kidney problems (interstitial nephritis).
- Increased sweating.

Very rare side effects
- Changes in blood count including agranulocytosis (lack of white blood cells).
- Aggression.
- Seeing, feeling or hearing things that are not there (hallucinations).
- Severe liver problems leading to liver failure and inflammation of the brain.
- Sudden onset of a severe rash or blistering or peeling skin. This may be associated with a high fever and joint pains (Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)
- Muscle weakness.
- Enlarged breasts in men.
- Hypomagnesaemia

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.

Losec may in very rare cases affect the white blood cells leading to immune deficiency. If you have an infection with symptoms such as fever with a **severely** reduced general condition or fever with symptoms of a local infection such as pain in the neck, throat or mouth or difficulties in urinating, you must consult your doctor as soon as possible so that a lack of white blood cells (agranulocytosis) can be ruled out by a blood test. It is important for you to give information about your medicine at this time.

Do not be concerned by this list of possible side effects. You may not get any of them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE LOSEC

- Keep out of the reach and sight of children.

- Do not use Losec after the expiry date which is stated on the vial and carton after EXP. The expiry date refers to the last day of that month.

- Do not store above 25°C. Store in the original package in order to protect from light.

- *Shelf life after reconstitution:*
  Solution for infusion reconstituted with sodium chloride 9 mg/ml (0.9%) should be used within 12 hours after preparation.
  Solution for infusion reconstituted with glucose 50 mg/ml (5%) should be used within 6 hours after preparation.

  From a microbiological point of view, the product should be used immediately unless it has been reconstituted under controlled and validated aseptic conditions.

- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Losec contains
- The active substance is omeprazole. Each vial of powder for solution for infusion contains omeprazole sodium equivalent to 40 mg of omeprazole. - The other ingredients are disodium edetate and sodium hydroxide.

What Losec looks like and contents of the pack

Losec 40 mg powder for solution for infusion (powder for infusion) comes in a vial.

The dry powder in the vial is made into a solution before it is given to you.

Pack sizes: Vials 1x40 mg, 5x40 mg and 10x40 mg.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

The following information is intended for medical or healthcare professionals only:

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 administrered in an intravenous infusion for 20-30 minutes.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Losec and associated names (see Annex I) 40 mg powder and solvent for solution for injection

[See Annex I - To be completed nationally]
Omeprazole

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

In this leaflet:

1. What Losec is and what it is used for
2. Before Losec is given to you
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6. Further information

1. WHAT LOSEC IS AND WHAT IT IS USED FOR

Losec contains the active substance omeprazole. It belongs to a group of medicines called 'proton pump inhibitors'. They work by reducing the amount of acid that your stomach produces.

Losec powder and solvent for solution for injection can be used as an alternative to oral therapy.

2. BEFORE LOSEC IS GIVEN TO YOU

You must not be given Losec
- if you are allergic (hypersensitive) to omeprazole or any of the other ingredients of Losec.
- if you are allergic to other proton pump inhibitor medicines (e.g. pantoprazole, lansoprazole, rabeprazole, esomeprazole).
- if you are taking a medicine containing nelfinavir (used for HIV infection).

If you are not sure, talk to your doctor, nurse or pharmacist before you are given this medicine.

Take special care with Losec
Losec may hide the symptoms of other diseases. Therefore, if any of the following happen to you before you are given Losec or after you are given it, talk to your doctor straight away:
- You lose a lot of weight for no reason and have problems swallowing.
- You get stomach pain or indigestion.
- You begin to vomit food or blood.
- You pass black stools (blood-stained faeces).
- You experience severe or persistent diarrhoea, as omeprazole has been associated with a small increase in infectious diarrhoea.
- You have severe liver problems.

Using other medicines
Please tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because Losec can affect the way some medicines work and some medicines can have an effect on Losec.

You must not be given Losec if you are taking a medicine containing **nelfinavir** (used to treat HIV infection).

Tell your doctor or pharmacist if you are taking any of the following medicines:
- Ketoconazole, itraconazole or voriconazole (used to treat infections caused by a fungus).
- Digoxin (used to treat heart problems)
- Diazepam (used to treat anxiety, relax muscles or in epilepsy).
- Phenytoin (used in epilepsy). If you are taking phenytoin, your doctor will need to monitor you when you start or stop taking Losec
- Medicines that are used to thin your blood, such as warfarin or other vitamin K blockers. Your doctor may need to monitor you when you start or stop taking Losec
- Rifampicin (used to treat tuberculosis)
- Atazanavir (used to treat HIV infection)
- Tacrolimus (in cases of organ transplantation)
- St John's wort (*Hypericum perforatum*) (used to treat mild depression)
- Cilostazol (used to treat intermittent claudication)
- Saquinavir (used to treat HIV infection)
- Clopidogrel (used to prevent blood clots (thrombi))

If your doctor has prescribed the antibiotics amoxicillin and clarithromycin as well as Losec to treat ulcers caused by *Helicobacter pylori* infection, it is very important that you tell your doctor about any other medicines you are taking.

Pregnancy and breast-feeding
Before you are given Losec, tell your doctor if you are pregnant or trying to get pregnant. Your doctor will decide whether you can be given Losec during this time.

Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used. Your doctor will decide whether you can take Losec if you are breastfeeding.

Driving and using machines
Losec is not likely to affect your ability to drive or use any tools or machines. Side effects such as dizziness and visual disturbances may occur (see section 4). If affected, you should not drive or operate machinery.

3. HOW LOSEC IS GIVEN TO YOU

- Losec can be given to adults including the elderly.
- There is limited experience with Losec for intravenous use in children.

Being given Losec
- Losec will be given to you by a doctor who will decide how much you need.
- The medicine will be given to you as an injection into one of your veins.

If you are given more Losec than you should
If you think you have been given too much Losec, talk to your doctor straight away.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Losec can cause side effects, although not everybody gets them.

If you notice any of the following rare but serious side effects, stop using Losec and contact a doctor immediately:
- Sudden wheezing, swelling of your lips, tongue and throat or body, rash, fainting or difficulties to swallow (severe allergic reaction).
- Reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be 'Stevens-Johnson syndrome' or 'toxic epidermal necrolysis'.
- Yellow skin, dark urine and tiredness which can be symptoms of liver problems.

Side effects may occur with certain frequencies, which are defined as follows:

Very common:	affects more than 1 user in 10
Common:	affects 1 to 10 users in 100
Uncommon:	affects 1 to 10 users in 1,000
Rare:	affects 1 to 10 users in 10,000
Very rare:	affects less than 1 user in 10,000
Not known:	frequency cannot be estimated from the available data.

Other side effects include:
Common side effects
- Headache.
- Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).

Uncommon side effects
- Swelling of the feet and ankles.
- Disturbed sleep (insomnia).
- Dizziness, tingling feelings such as "pins and needles", feeling sleepy.
- Spinning feeling (vertigo).
- Changes in blood tests that check how the liver is working.
- Skin rash, lumpy rash (hives) and itchy skin.
- Generally feeling unwell and lacking energy.

Rare side effects
- Blood problems such as a reduced number of white cells or platelets. This can cause weakness, bruising or make infections more likely.
- Allergic reactions, sometimes very severe, including swelling of the lips, tongue and throat, fever, wheezing.
- Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps.
- Feeling agitated, confused or depressed.
- Taste changes.
- Eyesight problems such as blurred vision.
- Suddenly feeling wheezy or short of breath (bronchospasm).
- Dry mouth.
- An inflammation of the inside of the mouth.
- An infection called "thrush" which can affect the gut and is caused by a fungus.
- Liver problems, including jaundice which can cause yellow skin, dark urine, and tiredness.
- Hair loss (alopecia).
- Skin rash on exposure to sunshine.
- Joint pains (arthralgia) or muscle pains (myalgia).

- Severe kidney problems (interstitial nephritis).
- Increased sweating.

Very rare side effects
- Changes in blood count including agranulocytosis (lack of white blood cells).
- Aggression.
- Seeing, feeling or hearing things that are not there (hallucinations).
- Severe liver problems leading to liver failure and inflammation of the brain.
- Sudden onset of a severe rash or blistering or peeling skin. This may be associated with a high fever and joint pains (Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Muscle weakness.
- Enlarged breasts in men.
- Hypomagnesaemia

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

Losec may in very rare cases affect the white blood cells leading to immune deficiency. If you have an infection with symptoms such as fever with a **severely** reduced general condition or fever with symptoms of a local infection such as pain in the neck, throat or mouth or difficulties in urinating, you must consult your doctor as soon as possible so that a lack of white blood cells (agranulocytosis) can be ruled out by a blood test. It is important for you to give information about your medicine at this time.

Do not be concerned by this list of possible side effects. You may not get any of them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE LOSEC

- Keep out of the reach and sight of children.

- Do not use Losec after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

- Do not store above 25°C. Store in the original package in order to protect from light.

- *Shelf life after reconstitution:*
  The reconstituted solution should not be stored at temperatures above 25°C and should be used within 4 hours after preparation. From a microbiological point of view, the product should be used immediately unless it has been reconstituted under controlled and validated aseptic conditions.

- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Losec contains
- The active substance is omeprazole. Each vial of powder for solution for injection contains omeprazole sodium equivalent to 40 mg of omeprazole.
- The other ingredients are:
  Powder for injection: sodium hydroxide (for pH adjustment).

Solvent for injection: citric acid monohydrate (for pH adjustment), macrogol 400, and water for injection.

What Losec looks like and contents of the pack

Losec 40 mg powder and solvent for solution for injection (Powder for injection; and Solvent for reconstitution of solution for injection) comes in a combination pack consisting of a vial containing dry substance (I) and an ampoule containing solvent (II).

The dry powder in the vial is made into a solution before it is given to you.

Pack sizes: 1x40 mg(I+II), 5x40 mg(I+II), 10x40 mg (I+II).
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

The following information is intended for medical or healthcare professionals only:

Losec solution for injection is obtained by dissolving the freeze-dried substance in the accompanying solvent. No other solvent should be used.

The stability of omeprazole is influenced by the pH of the solution for injection, which is why no other solvents or quantities should be used for dilution. Improperly prepared solutions can be identified by their yellow to brown discolouration and must not be used. Use only clear, colourless or pale yellowish-brown solutions.

Preparation
NOTE: Steps 1 to 5 must be performed in immediate sequence:
1. With a syringe draw all of the solvent from the ampoule (10 ml).
2. Add approximately 5 ml of the solvent to the vial with freeze-dried omeprazole.
3. Withdraw as much air as possible from the vial back into the syringe. This will make it easier to add the remaining solvent.
4. Add the remaining solvent into the vial, make sure the syringe is empty.
5. Rotate and shake the vial to ensure all the freeze-dried omeprazole has dissolved.

Losec solution for injection must be given only as an intravenous injection and it must not be added to infusion solutions. After reconstitution the injection should be given slowly over a period of at least 2.5 minutes at a maximum rate of 4 ml per minute.

PACKAGE LEAFLET

For medicinal products available without prescription

PACKAGE LEAFLET: INFORMATION FOR THE USER

Losec and associated names (see Annex I) 10 mg gastro-resistant tablets
Losec and associated names (see Annex I) 20 mg gastro-resistant tablets
[See Annex I - To be completed nationally]
Omeprazole

Read all of this leaflet carefully because it contains important information for you.
This medicine is available without prescription. However, you still need to take Losec carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve after 14 days.
- If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Losec is and what it is used for
2. Before you take Losec
3. How to take Losec
4. Possible side effects
5. How to store Losec
6. Further information

1. WHAT LOSEC IS AND WHAT IT IS USED FOR

Losec gastro-resistant tablets contains the active substance omeprazole. It belongs to a group of medicines called 'proton pump inhibitors'. They work by reducing the amount of acid that your stomach produces.

Losec is used in adults for the short-term treatment of reflux symptoms (for example, heartburn, acid regurgitation).

Reflux is the backflow of acid from the stomach into the gullet "foodpipe", which may become inflamed and painful. This may cause you symptoms such as a painful burning sensation in the chest rising up to the throat (heartburn) and a sour taste in the mouth (acid regurgitation).
It might be necessary to take the tablets for 2-3 consecutive days to achieve improvement of symptoms.

2. BEFORE YOU TAKE LOSEC

Do not take Losec
- if you are allergic (hypersensitive) to omeprazole or any of the other ingredients of Losec.
- if you are allergic to medicines containing other proton pump inhibitors (e.g. pantoprazole, lansoprazole, rabeprazole, esomeprazole).
- if you are taking a medicine containing nelfinavir (for HIV infection).

If you are not sure, talk to your doctor or pharmacist before taking Losec.

Take special care with Losec
Do not take Losec for more than 14 days without consulting a doctor. If you do not experience relief, or if you experience a worsening of symptoms, consult your doctor.

Losec may hide the symptoms of other diseases. Therefore, if any of the following happen to you before you start taking Losec or while you are taking it, talk to your doctor straight away:
- You lose a lot of weight for no reason and have problems swallowing.
- You get stomach pain or indigestion.
- You begin to vomit food or blood.
- You pass black stools (blood-stained faeces).
- You experience severe or persistent diarrhoea, as omeprazole has been associated with a small increase in infectious diarrhoea.
- You have had previous gastric ulcer or gastrointestinal surgery.
- You are on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks.
- You continuously suffer from indigestion or heartburn for 4 or more weeks.
- You have jaundice or severe liver disease.
- You are aged over 55 years with new or recently changed symptoms.

Patients should not take omeprazole as a preventative medication.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because Losec can affect the way some medicines work and some medicines can have an effect on Losec.

Do not take Losec if you are taking a medicine containing **nelfinavir** (used to treat HIV infection).

You should specifically tell your doctor or pharmacist if you are taking clopidogrel (used to prevent blood clots (thrombi)).

Tell your doctor or pharmacist if you are taking any of the following medicines:
- Ketoconazole, itraconazole or voriconazole (used to treat infections caused by a fungus).
- Digoxin (used to treat heart problems)
- Diazepam (used to treat anxiety, relax muscles or in epilepsy).
- Phenytoin (used in epilepsy). If you are taking phenytoin, your doctor will need to monitor you when you start or stop taking Losec.
- Medicines that are used to thin your blood, such as warfarin or other vitamin K blockers. Your doctor may need to monitor you when you start or stop taking Losec.
- Rifampicin (used to treat tuberculosis)
- Atazanavir (used to treat HIV infection)
- Tacrolimus (in cases of organ transplantation)
- St John's wort (*Hypericum perforatum*) (used to treat mild depression)
- Cilostazol (used to treat intermittent claudication)
- Saquinavir (used to treat HIV infection)

Taking Losec with food and drink
You can take your tablets with food or on an empty stomach.

Pregnancy and breast-feeding
Before taking Losec, tell your doctor or pharmacist if you are pregnant or trying to get pregnant. Your doctor will decide whether you can take Losec during this time.

Your doctor will decide whether you can take Losec if you are breastfeeding.

Driving and using machines
Losec is not likely to affect your ability to drive or use any tools or machines. Side effects such as dizziness and visual disturbances may occur (see section 4). If affected, you should not drive or operate machinery.

Important information about some of the ingredients of Losec
Losec gastro-resistant tablets contain sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product

3. HOW TO TAKE LOSEC

Always take Losec exactly as described in this leaflet. You should check with your doctor or pharmacist if you are not sure.

The usual dose is one 20 mg tablet or two 10 mg tablets once a day for 14 days. Contact your doctor if you are not free from symptoms after this period.

It might be necessary to take the tablets for 2-3 consecutive days to achieve improvement of symptoms.

Taking this medicine
- It is recommended that you take your tablets in the morning.
- You can take your tablets with food or on an empty stomach.
- Swallow your tablets whole with half a glass of water. Do not chew or crush the tablets. This is because the tablets contain coated pellets which stop the medicine from being broken down by the acid in your stomach. It is important not to damage the pellets. These micro-pellets contain the active substance omeprazole and are enteric coated which protects them from being broken down during passage through the stomach. The pellets release the active ingredient in the intestine, where it is absorbed by your body to give an effect.

What to do if you have trouble swallowing the tablets
- If you have trouble swallowing the tablets:
  - Break the tablet and disperse it in a spoonful of water (non-fizzy), any acidic fruit juice (e.g. apple, orange or pineapple) or apple sauce.
  - Always stir the mixture just before drinking (the mixture will not be clear). Then drink the mixture straight away or within 30 minutes.
  - To make sure that you have drunk all of the medicine, rinse the glass very well with half a glass of water and drink it. **Do not use** milk or fizzy water. The solid pieces contain the medicine - do not chew or crush them.

If you take more Losec than you should
If you take more Losec than recommended, talk to your doctor or pharmacist straight away.

If you forget to take Losec
If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Losec can cause side effects, although not everybody gets them.

If you notice any of the following rare but serious side effects, stop taking Losec and contact a doctor immediately:
- Sudden wheezing, swelling of your lips, tongue and throat or body, rash, fainting or difficulties in swallowing (severe allergic reaction).

- Reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be 'Stevens-Johnson syndrome' or 'toxic epidermal necrolysis'.
- Yellow skin, dark urine and tiredness which can be symptoms of liver problems.

Side effects may occur with certain frequencies, which are defined as follows:

Very common:	affects more than 1 user in 10
Common:	affects 1 to 10 users in 100
Uncommon:	affects 1 to 10 users in 1,000
Rare:	affects 1 to 10 users in 10,000
Very rare:	affects less than 1 user in 10,000
Not known:	frequency cannot be estimated from the available data

Other side effects include:

Common side effects
- Headache.
- Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).

Uncommon side effects
- Swelling of the feet and ankles.
- Disturbed sleep (insomnia).
- Dizziness, tingling feelings such as "pins and needles", feeling sleepy.
- Spinning feeling (vertigo).
- Changes in blood tests that check how the liver is working.
- Skin rash, lumpy rash (hives) and itchy skin.
- Generally feeling unwell and lacking energy.

Rare side effects
- Blood problems such as a reduced number of white cells or platelets. This can cause weakness, bruising or make infections more likely.
- Allergic reactions, sometimes very severe, including swelling of the lips, tongue and throat, fever, wheezing.
- Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps.
- Feeling agitated, confused or depressed.
- Taste changes.
- Eyesight problems such as blurred vision.
- Suddenly feeling wheezy or short of breath (bronchospasm).
- Dry mouth.
- An inflammation of the inside of the mouth.
- An infection called "thrush" which can affect the gut and is caused by a fungus.
- Liver problems, including jaundice which can cause yellow skin, dark urine, and tiredness.
- Hair loss (alopecia).
- Skin rash on exposure to sunshine.
- Joint pains (arthralgia) or muscle pains (myalgia).
- Severe kidney problems (interstitial nephritis).
- Increased sweating.

Very rare side effects
- Changes in blood count including agranulocytosis (lack of white blood cells).
- Aggression.
- Seeing, feeling or hearing things that are not there (hallucinations).

- Severe liver problems leading to liver failure and inflammation of the brain.
- Sudden onset of a severe rash or blistering or peeling skin. This may be associated with a high fever and joint pains (Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)
- Muscle weakness.
- Enlarged breasts in men.
- Hypomagnesaemia

Losec may in very rare cases affect the white blood cells leading to immune deficiency. If you have an infection with symptoms such as fever with a **severely** reduced general condition or fever with symptoms of a local infection such as pain in the neck, throat or mouth or difficulties in urinating, you must consult your doctor as soon as possible so that a lack of white blood cells (agranulocytosis) can be ruled out by a blood test. It is important for you to give information about your medicine at this time.

Do not be concerned by this list of possible side effects. You may not get any of them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE LOSEC

- Keep out of the reach and sight of children.

- Do not use Losec after the expiry date which is stated on the outer and inner pack after EXP. The expiry date refers to the last day of that month.

- Do not store above 25°C.

- Store this blister in the original package in order to protect from moisture.

- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Losec contains
- The active substance is omeprazole. Losec gastro-resistant tablets contain omeprazole magnesium corresponding to 10 mg or 20 mg omeprazole.
- The other ingredients are microcrystalline cellulose, glyceryl monostearate, hydroxypropylcellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic 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.

What Losec looks like and contents of the pack
- Losec 10 mg gastro-resistant tablets are light-pink with  or  on one side and 10 mg on the other side.
- Losec 20 mg gastro-resistant tablets are pink with  or  on one side and 20 mg on the other side.

Pack sizes:
- 10 mg:
    - Blisters of 7, 14, 28 tablets

- 20 mg:
    - Blisters of 7, 14 tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]