Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Losec Control 20 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 20.6 mg omeprazole magnesium equivalent to 20 mg omeprazole.
Excipients with known effect:
Each gastro-resistant tablet contains 19–20 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet.
Pink, oblong, biconvex, film-coated tablets engraved with on one side and 20 mg on the other side, containing enteric coated pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Losec Control gastro-resistant tablets is 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 Control (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 Control tablets in the morning, preferably on an empty stomach, 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 listed in section 6.1.

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 Control 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.

Subacute cutaneous lupus erythematosus (SCLE)
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Losec Control. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

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.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, Losec Control treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Renal impairment
Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

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 then be reinforced.

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

Other active substances
The absorption of posaconazole, erlotinib, ketoconazole and itraconazole is significantly reduced and thus clinical efficacy may be impaired. For 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.

Methotrexate
When given together with proton-pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Effects of other active substances on the pharmacokinetics of omeprazole

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy.

Breastfeeding
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 Control 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, nausea/vomiting and fundic gland polyps (benign).
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, severe hypomagnesaemia may result in hypocalcemia. Hypomagnesaemia may also result in hypokalemia
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, fundic gland polyps (benign)
Rare:	Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
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)
Not known	Subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal and connective tissue disorders	
Rare:	Arthralgia, myalgia
Very rare:	Muscular weakness
Renal and urinary disorders	
Rare:	Tubulointerstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders	

Very rare:	Gynaecomastia
General disorders and administration site conditions	
Uncommon:	Malaise, peripheral oedema
Rare:	Increased sweating

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

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 inhibitor, ATC code: A02BC01.

Mechanism of action
Omeprazole, a racemic mixture of two enantiomers is an inactive pro-drug and requires nonenzymatic, proton-catalyzed conversion to an active sulphenamide intermediate in the secretory canaliculi of the parietal cell. It is rapidly acting and provides control through irreversible inhibition of gastric acid secretion with once-daily dosing.

Omeprazole highly lipophilic and is a weak base so after absorption it concentrates in the acidic secretory canaliculi of the parietal cells of the gastric mucosa and it's transformed into the active form, the sulphenamide. The sulphenamide covalently binds to the extracellular domain of the H^+K^+-ATPase, also known as 'proton pump', and thereby irreversibly blocks its activity.
This effect on the final step of the gastric acid production process is dose-dependent and ensures 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.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

5.2 Pharmacokinetic properties

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. The time of administration and concomitant intake of food has minimal 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 65%.

Distribution
The mean apparent volume of distribution in healthy subjects given 20 mg orally, was reported to be approximately 0.3 l/kg body weight.
Omeprazole is 97% plasma protein bound, principally albumin and α1-acid glycoprotein. It subsequently becomes preferentially concentrated within parietal cells of stomach mucosa.

Metabolism
Omeprazole is almost completely metabolised by the cytochrome P450 system (CYP) so that virtually no unchanged drug is excreted. 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.

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 H2-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these changes are not from a direct effect of any individual active substance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Glycerol monostearate 40-55
Hydroxypropylcellulose
Hypromellose
Macrogol 6000
Magnesium stearate
Methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30 percent
Polysorbate 80
Crospovidone (type A)
Sodium hydroxide (for pH-adjustment),
Sodium stearyl fumarate
Sugar spheres (contains sucrose and corn starch)
Synthetic paraffin
Talc
Triethyl citrate
Iron oxide reddish-brown (E172)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Polyamide/Aluminium/PVC blister containing 7 or 14 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

MA639/03401

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Date of first authorisation: 14th February 2022

10. DATE OF REVISION OF THE TEXT

March 2023