Professional Information

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

LOSEC MUPS® 10, LOSEC MUPS® 20, LOSEC MUPS® 40, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LOSEC MUPS 10 tablet contains: Omeprazole magnesium equivalent to omeprazole 10 mg.

Contains sugar: sugar spheres (0,250 – 0,355) 22 mg per tablet.

Each LOSEC MUPS 20 tablet contains: Omeprazole magnesium equivalent to omeprazole 20 mg.

Contains sugar: sugar spheres (0,250 – 0,355) 22 mg per tablet

Each LOSEC MUPS 40 tablet contains: Omeprazole magnesium equivalent to omeprazole 40 mg.

Contains sugar: sugar spheres (0,250 – 0,355) 45 mg per tablet.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

LOSEC MUPS 10: Light-pink, oblong, biconvex, film-coated tablet engraved with  on one side and 10 mg on the other side.

LOSEC MUPS 20: Pink, oblong, biconvex, film-coated tablet engraved with  on one side and 20 mg on the other side.

LOSEC MUPS 40: Red-brown, oblong, biconvex, film-coated tablet engraved with  on one side and 40 mg and a score on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

LOSEC MUPS tablets are indicated for the treatment of duodenal ulcer including prevention of relapse, gastric ulcer, reflux oesophagitis, including long term management of patients with reflux oesophagitis, Zollinger-Ellison Syndrome, and for the symptomatic relief of heartburn in patients with gastroesophageal reflux disease and the short-term relief of functional dyspepsia.

LOSEC MUPS tablets are indicated for *H. pylori*-positive duodenal ulcers, as part of the eradication programme with appropriate antibiotics.

Treatment of NSAID associated gastric and/or duodenal ulcer and erosions and a reduction of the risk to develop gastric and/or duodenal ulcer/erosions and a risk of reduction for relapse of a previously healed gastric and/or duodenal ulcer/erosions in patients on NSAIDs treatment.

Children:

Short term (up to 3 months) treatment of severe ulcerative reflux oesophagitis resistant to previous medical treatment.

4.2 Posology and method of administration

Posology

Duodenal ulcer:

The recommended dosage is 20 mg once daily for two to four weeks.

In some duodenal ulcer patients, refractory to other treatment regimens, 40 mg once daily may be effective.

For the prevention of relapse in patients with duodenal ulcer the recommended dose is 10 mg once daily. If needed the dose can be increased to 20 – 40 mg once daily.

LOSEC MUPS tablets are indicated for *H. pylori*-positive duodenal ulcers, as part of the eradication

programme with appropriate antibiotics.

For NSAID associated duodenal ulcers, see “NSAID associated gastroduodenal lesions”.

Gastric ulcer and reflux oesophagitis:

The recommended dosage is 20 mg once daily for four to eight weeks.

In some patients with gastric ulcer or reflux oesophagitis refractory to other treatment regimens, 40 mg once daily may be effective.

For the long-term management of patients with reflux oesophagitis, the recommended dose is 10 mg once daily. If needed the dose can be increased to 20 – 40 mg once daily.

In patients with severe or symptomatic recurrent reflux oesophagitis treatment can be continued with LOSEC MUPS at a dosage of 20 mg once daily.

For NSAID associated gastric ulcers, see “NSAID associated gastroduodenal lesions”.

Severe ulcerative reflux oesophagitis in children from one year and older:

The recommended dosage regime is:

Weight:

10 – 20 kg	LOSEC MUPS 10 mg once daily
> 20 kg	LOSEC MUPS 20 mg once daily

If needed, dosage may be increased to 20 mg and 40 mg respectively.

NSAID associated gastroduodenal lesions:

NSAID associated gastric ulcers, duodenal ulcers or gastroduodenal erosions in patients with or without continued NSAID treatment, the recommended dosage of LOSEC MUPS is 20 mg once daily. Symptom

resolution is rapid and, in most patients, healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID associated gastric ulcers, duodenal ulcers, gastroduodenal erosions and dyspeptic symptoms, the recommended dosage of LOSEC MUPS is 20 mg once daily.

Symptomatic gastroesophageal reflux disease:

The recommended dosage is 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 20 mg daily, further investigation is recommended.

Functional dyspepsia:

For the relief of symptoms in patients with epigastric pain/discomfort with or without heartburn, the recommended dosage is 20 mg once daily.

Patients may respond adequately to 10 mg daily and therefore this dose could be considered as a starting dose.

If symptom control has not been achieved after 2 weeks treatment with 20 mg daily, further investigation is recommended.

Zollinger-Ellison Syndrome:

The recommended initial dosage is 60 mg once daily. The dosage should be adjusted individually, and treatment continued as long as is clinically indicated. Patients with severe disease have been effectively controlled on LOSEC MUPS with more than 90 % maintained on doses of 20 mg to 120 mg daily. With doses above 80 mg daily, the dose should be divided and given twice daily.

Special populations

Elderly:

No dose adjustment is necessary in the elderly.

Impaired renal function:

No dose adjustment is required in patients with impaired renal function.

Impaired hepatic function:

As bioavailability and plasma half-life of omeprazole are increased in patients with impaired hepatic function, a daily dose of 10 – 20 mg is generally sufficient.

The long-term safety of LOSEC MUPS in patients with renal and hepatic impairment has not been established.

Paediatric population

Children:

There is very limited experience with LOSEC MUPS in children.

Method of administration

Oral administration:

LOSEC MUPS tablets are recommended to be given in the morning and swallowed whole with half a glass of liquid. The tablets should not be chewed or crushed.

For patients with swallowing difficulties the tablets may be dispersed in half a glass of non-carbonated water or fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of fluid and drink. The pellets must not be chewed or crushed.

4.3 Contraindications

- Known hypersensitivity to omeprazole, substituted benzimidazoles or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

LOSEC MUPS is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

Prior to treatment the possibility of malignancy or gastric ulcer or a malignant disease of the oesophagus should be excluded as the treatment with LOSEC MUPS may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Concomitant administration with omeprazole and medicines such as atazanavir and nelfinavir is not recommended (see section 4.5).

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e., four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46 % and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16 %. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see section 4.5).

Some published observational studies suggest that the use of the use of LOSEC may be associated with a small increased risk for osteoporosis related fractures. However, in other similar observational studies no such increased risk was found.

In randomized, double-blind and controlled clinical studies on omeprazole and esomeprazole (including two open long-term studies of up to more than 12 years) there are no indications that proton pump inhibitors (PPIs) are associated with osteoporotic fractures.

Although a causal relationship between omeprazole/esomeprazole and osteoporotic fractures has not been established, patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

PPIs, especially if used in high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that PPIs may increase the overall risk of fracture by 10 – 40 %. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Subacute cutaneous lupus erythematosus (SCLE)

PPIs 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 healthcare provider should consider stopping LOSEC. SCLE after previous treatment with a PPI may increase the risk of SCLE with other PPIs.

Renal impairment

Acute interstitial nephritis (AIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms ranging from those of hypersensitivity reactions to nonspecific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia). Discontinue LOSEC and evaluate patients with suspected AIN.

Severe hypomagnesaemia has been reported in patients treated with PPIs like LOSEC for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur, but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare providers should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Omeprazole, as in LOSEC MUPS, is a CYP2C19 inhibitor. When starting or ending treatment with LOSEC MUPS, the potential for interactions with medicines 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.

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported very rarely and rarely, respectively in association with omeprazole treatment.

Interference with laboratory tests

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

Some children with chronic illnesses may require long-term treatment although it is not recommended.

Treatment with PPIs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile* (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.

Sugar spheres

LOSEC MUPS contain sugar spheres which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Effects of omeprazole on the pharmacokinetics of other medicines

Active substances with pH dependant absorption

The gastric acid suppression during treatment with LOSEC might decrease or increase the absorption of medicines with a gastric pH dependent absorption.

Nelfinavir, atazanavir

Omeprazole has been reported to interact with some antiretroviral medicines. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral medicine. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral medicines, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Concomitant administration with omeprazole and medicines such as atazanavir and nelfinavir is therefore not recommended. For other antiretroviral medicines, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral medicines of which unchanged serum levels have been reported when given with omeprazole.

Digoxin

Absorption of medicines such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10 % (up to 30 % in two out of ten subjects). Digoxin toxicity has rarely been reported. However, caution should be exercised when omeprazole is given at high doses in elderly patients.

Therapeutic monitoring of digoxin should be reinforced.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/ pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46 % and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16 %. It is, however, uncertain to what extent this interaction is clinically important.

Inconsistent data on the clinical implications of a PK/PD interaction of omeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged (see section 4.4).

Other active substances

The absorption of medicines, such as posaconazole, ketoconazole, itraconazole, erlotinib is significantly reduced and thus clinical efficacy may be impaired. For posaconazole and erlotinib concomitant use should be avoided.

Active substances metabolised by CYP2C19

Omeprazole inhibits CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant medicines also metabolised by CYP2C19, such as diazepam, phenytoin, warfarin (R-warfarin) or other vitamin K antagonists and cilostazol, may be delayed. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. However, concomitant treatment with LOSEC 20 mg daily did not change the blood concentration of phenytoin in patients on continuous treatment with this medicine. In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary. Concomitant treatment with LOSEC 20 mg daily did, however, not change coagulation time in patients on continuous treatment with warfarin.

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.

Omeprazole is partly metabolised also by CYP3A4, but omeprazole does not inhibit this enzyme. Thus, omeprazole does not affect the metabolism of medicines metabolised by CYP3A4, such as cyclosporin, lidocaine, quinidine, estradiol, erythromycin, and budesonide.

Results from a range of interaction studies with omeprazole versus other medicines demonstrate that omeprazole, 20 – 40 mg daily, has no significant influence on any other CYP enzymes relevant for medicine metabolism, as shown by the lack of metabolic interaction with substrates for CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as S-warfarin, piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol, propranolol), CYP2E1 (such as ethanol).

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 medicines on the pharmacokinetics of omeprazole

Inhibitors of CYP2C19 and/or CYP3A4

Since omeprazole is metabolised by CYP2C19 and CYP3A4, medicines known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of omeprazole's metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. Since high doses of omeprazole have been well-tolerated, adjustment of the omeprazole dose is not generally required during temporary concomitant use. 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

Medicines 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 indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/ newborn child. LOSEC 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.

Fertility

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

4.7 Effects on ability to drive and 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

a. Summary of the safety profile

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

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) have been reported in association with omeprazole treatment (see section 4.4).

b. Tabulated list of adverse reactions

The following events have been reported as adverse events in clinical trials or reported adverse reactions from post marketing surveillance. None was found to be dose related.

The reactions are classified according to frequency (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).

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia
Immune system disorders	Rare	Hypersensitivity reactions e.g. fever,

MedDRA system organ class	Frequency	Adverse reactions
		angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders	Rare	Hyponatraemia
	Very Rare	Hypomagnesaemia, severe hypomagnesaemia may result in hypocalcaemia
	Not known	Hypomagnesaemia may also be associated with hypokalaemia
Psychiatric disorders	Uncommon	Insomnia
	Rare	Agitation, confusion, depression, hallucinations, aggression
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, paraesthesia, light-headedness, 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, hepatic

MedDRA system organ class	Frequency	Adverse reactions
		failure, encephalopathy in patients with pre-existing liver disease
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, pruritus, urticaria, rash
	Rare	Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), bullous eruption, acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
	Not known	Subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal and connective tissue and bone disorders	Uncommon	Fracture of the hip, wrist or spine
	Rare	Arthralgia, myalgia, muscular weakness
Renal and urinary disorders	Rare	Interstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders	Rare	Gynaecomastia
General disorders and administration site conditions	Uncommon	Malaise
	Rare	Increased sweating~~,~~ peripheral oedema

c. Description of selected adverse reactions

Other effects related to acid inhibition:

During long term treatment gastric glandular cysts have been reported in 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 increases gastric counts of bacteria normally present in the gastrointestinal tract.

Treatment with omeprazole may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Rare reports have been received of overdosage with omeprazole. 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 from overdosage with omeprazole. Also, apathy, depression and confusion have been described in single cases.

The symptoms described in connection with omeprazole overdosage have been transient, and no serious outcome due to omeprazole has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses and no specific treatment has been needed.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitors

ATC code: A02BC01

LOSEC (omeprazole) reduces gastric acid secretion. It is a specific inhibitor of the gastric proton pump in the parietal cell. It provides control through reversible inhibition of gastric acid secretion with once daily dosing.

Mechanism of action

Omeprazole, a racemic mixture of two active 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 acid environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H^+, K^+-ATPase – the proton pump. This effect on the final step of the gastric acid formation process is dose-dependant and provides for effective inhibition of both basal acid secretion and stimulated acid secretion irrespective of the secretagogue.

Omeprazole has no effect on acetylcholine, histamine or gastrin receptors.

Pharmacodynamic effects

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

Effect on gastric secretion

Oral dosing with omeprazole, as in LOSEC MUPS, once daily provides inhibition of gastric acid secretion with maximum effect being achieved within four days of treatment. In duodenal ulcer patients, a mean decrease of approximately 80 % in twenty-four-hour intragastric acidity is then maintained, with the mean decrease in peak acid output after pentagastrin stimulation being about 70 %, twenty-four hours after dosing with LOSEC MUPS.

Effect on Helicobacter pylori

Helicobacter 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 rapid symptom relief, high rates of healing of any mucosal lesions, and long-term remission of peptic ulcer disease thus reducing complications such as gastrointestinal bleeding as well as the need for prolonged antisecretory treatment.

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 medicines may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile.*

During treatment with antisecretory medicines, serum gastrin increases in response to the decreased acid secretion. Also, chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurements. Measurements should be repeated if levels have not normalised by this time.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in both children and adults during long term treatment with omeprazole. The findings are

considered to be of no clinical significance.

Paediatric population

In a non-controlled study in children (1 to 16 years of age) with severe reflux oesophagitis, omeprazole at doses of 0,7 to 1,4 mg/kg improved oesophagitis levels in 90 % of the cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0 – 24 months with clinically diagnosed gastro-oesophageal reflux disease were treated with 0,5, 1,0 or 1,5 mg omeprazole/kg. The frequency of vomiting/regurgitation episodes decreased by 50 % after 8 weeks of treatment irrespective of the dose.

Eradication of H. pylori in children

A randomised, double blind clinical study (Hé liot 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 aged 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 less than 4 years old.

5.2 Pharmacokinetic properties

Absorption

Omeprazole and omeprazole magnesium is acid labile and is therefore administered orally as enteric-coated granules in 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 three to six hours. Concomitant intake of food has no influence on the bioavailability. The systemic bioavailability of omeprazole from a single oral dose of LOSEC MUPS 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 litres/kg and a similar value is also seen in patients with renal insufficiency The plasma protein binding of omeprazole is 97 %. In elderly and in patients with hepatic insufficiency, the volume of distribution is slightly decreased.

Biotransformation

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. Identified metabolites in plasma are the sulphone, the sulphide and hydroxyomeprazole, these metabolites having no significant effect on acid secretion. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulfone. 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.

Elimination

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

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 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 excrete as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion. The two main urinary metabolites are hydroxyomeprazole and the corresponding carboxylic acid.

The average half-life of the terminal phase of the plasma concentration-time curve is approximately forty minutes. There is no change in half-life during treatment. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at a given time.

Linearity/non-linearity

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 sulfone).

No metabolite has been found to have any effect on gastric acid secretion.

Special populations

Hepatic impairment

The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased AUC. Omeprazole has not shown any tendency to accumulate with once daily dosing.

Renal impairment

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 population

Limited data from children (1 year and older), do not suggest significant differences in the pharmacokinetics of omeprazole within the recommended dosages between children and adults. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol monostearate 40-55

Hydrogen peroxide 30 %

Hydroxypropylcellulose, (E463)

Hydroxypropylmethylcellulose, (E464)

Iron oxide reddish brown CI 77491 (10 mg, 20 mg, 40 mg tablets), (E172)

Iron oxide yellow CI 77492 (10 mg tablets), (E172)

Magnesium stearate

Methacrylic acid copolymer type C

Microcrystalline cellulose

Paraffin, synthetic

Polyethylene glycol 6000

Polysorbate 80, (E434)

Polyvinylpyrrolidone crosslinked, (E1202)

Sodium hydroxide, (E524)

Sodium stearyl fumarate

Sugar spheres 0,250 – 0,355

Talc

Titanium dioxide CI 77891, (E171)

Triethyl citrate, (E1505)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 ºC.

Replace cap firmly after use.

6.5 Nature and contents of container

LOSEC MUPS 10 in plastic containers of 7, 14, 28 and 30.

LOSEC MUPS 20 in plastic containers of 7, 14, 28 and 30.

LOSEC MUPS 40 in plastic containers of 7, 14, 28 and 30.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBERS

LOSEC MUPS 10: 32/11.4.3/0222

LOSEC MUPS 20: 32/11.4.3/0223

LOSEC MUPS 40: 32/11.4.3/0224

9 DATE OF FIRST AUTHORISATION

LOSEC MUPS 10: 11 March 1999

LOSEC MUPS 20: 11 March 1999

LOSEC MUPS 40: 11 March 1999

10 DATE OF REVISION OF THE TEXT

14 March 2025