LOSEC® MUPS® 10 MG AND 20 MG

omeprazole

Tablets

Composition

Each tablet contains: Omeprazole magnesium 10.3 mg and 20.6 mg (corresponding to omeprazole 10 mg and 20 mg).

For excipients see "List of excipients".

Pharmaceutical form

LOSEC MUPS tablets 10 mg : Light-pink, oblong, biconvex, film-coated tablets engraved with ⓐ on one side and 10 mg on the other side. Each tablet contains omeprazole magnesium 10.3 mg as enteric coated pellets.

LOSEC MUPS tablets 20 mg: Pink, oblong, biconvex, film-coated tablets, engraved with ⓐ on one side and 20 mg on the other side. Each tablet contains omeprazole magnesium 20.6 mg as enteric coated pellets.

Therapeutic indications

- LOSEC MUPS is indicated for the treatment of:
- Duodenal ulcer
- Gastric ulcer
- NSAID associated gastric and duodenal ulcers or erosions
- In combination with antibiotics for treatment of duodenal ulcer caused by Helicobacter pylori
- Reflux oesophagitis
- Symptomatic gastro-oesophageal reflux disease
- Acid related dyspepsia
- Zollinger-Ellison syndrome

Posology and method of administration

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

For patients with swallowing difficulties

Break the MUPS 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). Always stir just before drinking. Rinse it down with half a glass of water. DO NOT USE milk or carbonated water. Ingest without chewing the enteric-coated pellets.

Duodenal ulcer

The recommended dosage in patients with an active duodenal ulcer is LOSEC MUPS 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 2 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 2 week treatment period.

In patients with poorly responsive duodenal ulcer LOSEC MUPS 40 mg once daily is recommended and healing is usually achieved within 4 weeks. For the prevention of relapse in patients with duodenal ulcer disease the recommended dose is LOSEC MUPS 10 mg once daily. If needed the dose can be increased to LOSEC MUPS 20-40mg once daily.

Gastric ulcer

The recommended dosage is LOSEC MUPS 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.

In patients with poorly responsive gastric ulcer LOSEC MUPS 40 mg once daily is recommended and healing is usually achieved within 8 weeks. For the prevention of relapse in patients with poorly responsive gastric ulcer the recommended dose is LOSEC MUPS 20 mg once daily. If needed the dose can be increased to LOSEC MUPS 40 mg once daily.

NSAID associated ulcers or gastroduodenal erosions

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.

Helicobacter pylori (Hp) eradication

There are many treatment regimens for eradication of Helicobacter pylori. Success rates vary and the regimens are evolving. Currently acceptable regimens include the following:

Dual therapy regimens

LOSEC MUPS 20 mg twice daily with amoxicillin 1.5-2g daily for two weeks

Triple therapy regimens

LOSEC MUPS 20 mg, amoxicillin 1 g and clarithromycin 500 mg, all twice a day for one week

or

LOSEC MUPS 20 mg, clarithromycin 250 mg and metronidazole 400 mg (or tinidazole 500 mg) all twice a day for one week

Reflux oesophagitis

The recommended dosage is LOSEC MUPS 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.

In patients with severe reflux oesophagitis LOSEC MUPS 40 mg once daily is recommended and healing is usually achieved within 8 weeks.

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

Severe reflux oesophagitis in children from one year and older

The recommended dosage for healing is:

Weight	Dosage
10-20 kg	10 mg once daily
>20 kg	20 mg once daily

If needed the dosage may be increased to 20 mg and 40 mg respectively. The duration of treatment in these patients should be between 2 to 8 weeks.

***Symptomatic gastro-oesophageal reflux* disease**

The recommended dosage is LOSEC MUPS 20 mg daily. Symptom relief is rapid. 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 MUPS 20 mg daily, further investigation is recommended.

Acid related dyspepsia

In the relief of symptoms in patients with epigastric pain/discomfort with or without heartburn the recommended dosage is LOSEC MUPS 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 4 weeks treatment with LOSEC MUPS 20 mg daily, further investigation is recommended.

Zollinger-Ellison syndrome

In patients with Zollinger-Ellison syndrome the dosage should be individually adjusted and treatment continued as long as is clinically indicated. The recommended initial dosage is LOSEC MUPS 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 doses exceed LOSEC MUPS 80 mg daily, the dose should be divided and given twice daily.

Impaired renal function

Dose adjustment is not needed 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 may be sufficient.

Elderly

Dose adjustment is not needed in the elderly.

Contraindications

Known hypersensitivity to omeprazole, substituted benzimidazoles or any other constituent of the formulation.
Omeprazole like other proton pump inhibitors must not be used concomitantly with nelfinavir (see Interactions).

Special warnings and special 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 Interactions). 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 Interactions).
The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like omeprazole 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 drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may need to be considered in some patients (see section Interactions).

Some published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with a small increased risk for osteoporosis related fractures. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). However, in other similar observational studies no such increased risk was found.

In AstraZeneca's 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 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.

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.

Interference with laboratory tests

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.

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 and, in hospitalised patients, possibly also Clostridium difficile (see section Pharmacological Properties).

As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Cutaneous lupus erythematosus and Systemic lupus erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE. The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving LOSEC MUPS, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., Antinuclear antibody) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Interactions

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 Posology and method of administration). 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 Special warnings and special precautions for use). Concomitant administration of omeprazole (40 mg once daily) and atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a 75% decrease of the atazanavir exposure. Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared to atazanavir 300 mg/ritonavir 100 mg once daily.

Digoxin

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10%. Digoxin toxicity has been rarely reported. However caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should be then be reinforced.

Clopidogrel

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

Other active substances

The absorption of posaconazole, erlotinib, ketoconazole and itraconazole 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 is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Cilostazol

Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Phenytoin

Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating omeprazole treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending omeprazole treatment.

Unknown mechanism

Saquinavir

Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70% for saquinavir associated with good tolerability in HIV-infected patients.

Tacrolimus

Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

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.

Pregnancy and lactation

Results from three prospective epidemiological studies indicate no adverse effects of omeprazole on pregnancy or on the health of the fetus/newborn child. LOSEC/LOSEC MUPS can be used during pregnancy.

Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

Effects on ability to drive and use machines

LOSEC MUPS is not likely to affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see Undesirable effects). If affected, patients should not drive or operate machinery.

Undesirable effects

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. The reactions are classified according to frequency (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).

Blood and lymphatic system disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
Not known: Systemic lupus erythematosus

Metabolism and nutrition disorders

Rare: Hyponatraemia
Very Rare: Hypomagnesaemia, severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia.

Psychiatric disorders

Uncommon: Insomnia
Rare: Agitation, aggression, confusion, depression, 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, microscopic colitis

Hepatobiliary disorders

Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritus, rash, urticaria
Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalized exant-hematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: Cutaneous lupus erythematosus

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Reproductive system and breast disorders

Rare: Gynaecomastia

General disorders and administration site conditions

Uncommon: Malaise
Rare: Increased sweating, peripheral oedema

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 to 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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.

Site and mechanism of action

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.

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

Effect on gastric acid secretion

Oral dosing with LOSEC/LOSEC MUPS 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 LOSEC/LOSEC MUPS 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% twenty-four hours after dosing.

Oral dosing with LOSEC/LOSEC MUPS 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 oesophagus in patients with gastrooesophageal 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 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 treatment with antisecretory drugs 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 measurement. 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. No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.

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 and, in hospitalised patients, possibly also Clostridium difficile.

Pharmacokinetics

Absorption

The absorption of omeprazole takes place in the small intestine, and is usually completed within 3-6 hours. The bioavailability of omeprazole after repeated oral administration is approximately 60%. Concomitant intake of food does not affect the bioavailability. The systemic availability (bioavailability) of omeprazole from a single oral dose of LOSEC is approximately 40%.

Binding to plasma proteins is approximately 95 % and the volume of distribution is 0.3 L/kg.

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.

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. 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 (eg, the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once daily administration.

No metabolite has been found to have any effect on gastric acid secretion. 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. Poor metabolisers: 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 LOSEC.

Elimination

The half-life in plasma in the elimination phase is approximately 40 minutes (30-90 minutes) after multiple doses. Approximately 80% of the metabolites are excreted via the urine and the remainder in the faeces.

Special patient 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).

Children: Available data from children (1 year and older) suggests that the pharmacokinetics, within the recommended dosages (see Posology and method of administration), are similar to what has been reported in adults.

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 drug.

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 stearyl fumarate, talc, triethyl citrate, iron oxide (E 172), titanium dioxide (E 171).

Incompatibilities

None known when instructions in method of administration are followed.

Special precautions for storage

Do not store above 25°C.

Shelf Life

Please refer to expiry date on outer carton.

Pack Size

Please refer to outer pack for pack size.
Not all strength/presentation may be available locally.

Date of revision

November 2021

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Losec MUPS tbl	smer vlákna kolmo na text		
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