LOSEC® 20 mg
Omeprazole
Capsules

Composition
Each capsule contains: Omeprazole 20 mg

Pharmaceutical form
LOSEC capsules 20 mg : hard gelatine capsules with an opaque pink body, marked 20 and an opaque reddish-brown cap marked A/OM. Each capsule contains omeprazole 20 mg as enteric coated pellets.

Theurapeutic indication
LOSEC is indicated for the treatment of

- Duodenal ulcer
- Gastric ulcer
- NSAID associated gastric and duodenal ulcers or erosions
- *Helicobacter pylori* eradication in peptic ulcer disease
- Reflux oesophagitis
- Zollinger-Ellison syndrome

Posology and method of administration

LOSEC capsules are recommended to be given in the morning and swallowed whole with half a glass of water.

Duodenal ulcer
The recommended dosage in patients with an active duodenal ulcer is LOSEC 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 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 10 mg once daily. If needed the dose can be increased to LOSEC 20 mg once daily.

Gastric ulcer
The recommended dosage is LOSEC 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 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 20 mg once daily. If needed the dose can be increased to LOSEC 40 mg once daily.

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

Helicobacter pylori (Hp) eradication regimens in peptic ulcer disease: LOSEC 40 mg daily with amoxicillin 1.5 g daily in divided doses for two weeks.
In clinical studies daily doses of 1.5-2 g of amoxicillin have been used with or without metronidazole 400 mg three times daily. LOSEC 40 mg once daily and clarithromycin 500 mg three times a day for 2 weeks.

Reflux oesophagitis
The recommended dosage is LOSEC 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 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 10 mg once daily. If needed the dose can be increased to LOSEC 20 mg once daily.

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 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 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.

Children
There is a limited experience with LOSEC in children.

Contraindications
Known hypersensitivity to omeprazole.

Special warnings and special precautions for use
In the presence of any alarm symptom (eg, significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.

Interactions with other medicinal products and other forms of interaction
The absorption of some drugs might be altered due to the increased intragastric acidity. Thus it can be predicted that the absorption of ketoconazole and itraconazole can decrease during omeprazole treatment, as it does during treatment with other acid secretion inhibitors or antacids.

No interaction with food or concomitantly administered antacids has been found.

As omeprazole is metabolised in the liver through cytochrome P450 2C19 (CYP2C19), it can prolong the elimination of diazepam, phenytoin, warfarin (R-warfarin) and other vitamin K antagonists, which are in part substrates for this enzyme. Monitoring of patients receiving warfarin or phenytoin is recommended and a reduction of phenytoin or warfarin 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 drug. 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.

Plasma concentrations of omeprazole and clarithromycin are increased during concomitant administration but there is no interaction with metronidazole or amoxicillin. These antimicrobials are used together with omeprazole for eradication of *Helicobacter pylori*.

Concomitant administration of omeprazole has been reported to reduce the plasma levels of atazanavir.

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more that doubling of the omeprazole exposure. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or greater, it is recommended that the omeprazole dose be reduced by one-half.

Pregnancy and lactation
Pregnancy
LOSEC can be used during pregnancy only if clearly needed.

Lactation
Omeprazole passes into breast milk. The possible effect on the child in unknown.

Effect on ability to drive and use machines
LOSEC is not likely to affect the ability to drive or use machines.

Undesirable effects
LOSEC is well-tolerated and adverse reactions have generally been mild and reversible. The following events have been reported as adverse events in clinical trials or reported from routine use, but in many cases a relationship to treatment with omeprazole has not been established.
The following definitions of frequencies are used :
Common ≥1/100
Uncommon ≥1/1,000 to <1/100
Rare <1/1,000

Common	*Central and peripheral nervous system :* *Gastrointestinal :*	Headache Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting.

Uncommon	*Central and peripheral nervous system :*	Dizziness, paraesthesia, somnolence, Insomnia and Vertigo.
	Hepatic :	Increased liver enzymes
	Skin :	Rash, dermatitis and/or pruritis, urticaria.
	Other :	Malaise.
Rare	*Central and peripheral nervous system :*	Reversible mental confusion, agitation, aggregasion, depression and hallucinations, predominantly in severely ill patients.
	Endocrine :	Gynaecomastia
	Gastrointestinal :	Dry mouth, stomatitis and gastrointestinal candidiasis.
	Haematological:	Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia
	Hepatic :	Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing severe liver disease
	Musculoskeletal :	Arthralgia, myalgia, muscular weakness
	Skin :	Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome,

	Other :	toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) Hypersensitivity reactions e.g. fever, angioedema, Bronchospasm. Interstitial nephritis and anaphylactic reaction/shock, Increased sweating, peripheral oedema , Blurred vision, taste disturbance and Hyponatraemia.

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 2400 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

Pharmacotherapeutic group : ATC-code: A02BC01
Substance reducing gastric acid secretion – proton pump inhibitor

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 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 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 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 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 gastro-oesophageal 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, in ehich about 95% and 70% of patients respectively are infected with this bacterium *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. Eradication of *H. pylori* with omeprazole and antimicrobials is also associated with regression of atrophic gastritis, and a reduced risk for development of gastric cancer.

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.*

Pharmacokinetic properties

Absorption and distribution
Omeprazole is acid labile and are therefore administered orally as enteric-coated granules in capsules. Absorption takes place in the small intestine and is usually completed within 3-6 hours. The systemic availability (bioavailability) of omeprazole from a single oral dose of LOSEC is approximately 35%. After repeated once-daily administration, the bioavailability increases to about 60%. The apparent volume of distribution in healthy subjects is approximately 0.3 L/kg and a similar value is also seen in patients with renal insufficiently. In elderly and in patients with hepatic insufficientcy, the volume of distribution is slightly decreased. Concomitant intake of food has no influence on the bioavailability. The plasma protein binding of omeprazole is about 95%.

Metabolism and excretion

The plasma elimination half-life of omeprazole is usually shorter than one hour and there is no change in half-life during long-term treatment.

Omeprazole is completely metabolised by the cytochrome P450 system (CYP). Mainly in the liver. The major part of its metabolism is dependent on the polymorphically expressed specific isoform CYP2C19 (S-mephenytoin hydroxylase) , responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. In accordance with this, as a consequence of competitive inhibition, there is a potential for metabolic drug-drug interactions between omeprazole and other substrates for CYP2C19. Results from a range of interaction studies with LOSEC versus other drugs indicate however that omeprazole , 20-40 m daily, has no influence on any other relevant isoform of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (Ethanol) and CYP3A (cyclosporin, lidocaine, quinidine, estradiol, erythromycin, budesonide).

No metabolite has been found to have any effect on gastric acid secretion. Almost 80% of an orally given dose is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

The systemic bioavailability and elimination of omeprazole is unchanged in patients with reduced renal function. The area under plasma concentration-time curve is increased in patients with impaired liver function, but omeprazole has not shown any tendency to accumulate with once daily dosing.

List of excipients

Mannitol, lactose anhydrous, hydroxypropyl cellulose, sodium lauryl sulphate**,** disodium hydrogen phosphate dihydrate, microcrystalline cellulose, hydroxypropyl methylcellulose, methacrylic acid co-polymer type C, polyethylene glycol, magnesium stearate, water purified.

Incompatibilities

None known when instructions in Method of administration are followed.

Special precautions for storage

Store in a cool (15°C - 25°C) and dry place.

Shelf life

Please refer to expiry date on the outer carton.

Packsize

Please refer to outer carton for pack size.

HARUS DENGAN RESEP DOKTER

Registration Numbers

LOSEC 20 mg, aluminium blister of 14 capsules, Reg. No.:DKI9551300701A1

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AstraZeneca AB, Sodertalje, Sweden

Imported by :

PT. AstraZeneca Indonesia
Cikarang, Bekasi – Indonesia

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