

NEW ZEALAND DATA SHEET

NAME OF MEDICINE

LOSIVA®
Omeprazole 10 mg, 20 mg, 40 mg capsules

PRESENTATION

LOSIVA capsules 10 mg: hard gelatine size 3 capsules with an opaque pink body, **marked 10**, and an opaque pink cap marked A/OS. Each capsule contains omeprazole 10 mg as enteric coated pellets.

LOSIVA capsules 20 mg: hard gelatine size 2 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.

LOSIVA capsules 40 mg: hard gelatine size 1 capsules with an opaque, reddish-brown body, **marked 40** and an opaque reddish-brown cap marked A/OL. Each capsule contains omeprazole 40 mg as enteric coated pellets.

USES

ACTIONS

LOSIVA (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 rapid 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 the stimulus.

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

Effect on gastric acid secretion

Oral dosing with LOSIVA 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 LOSIVA 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 LOSIVA 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/normalises 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 acid peptic 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* has been found to play a causal role in the development of gastric carcinoma.

Omeprazole has a bactericidal effect on *H.pylori in vitro*.

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 anti-secretory treatment.

Other effects related to acid inhibition

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. To avoid this interference the omeprazole treatment should be temporarily stopped five days before CgA measurements.

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 possibly also *Clostridium difficile* in hospitalised patients.

PHARMACOKINETICS

Absorption and distribution

Omeprazole is acid labile and is therefore administered orally as enteric-coated pellets in capsules.

Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSIVA is approximately 40%. 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 insufficiency. In elderly patients, and in patients with hepatic insufficiency, 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

Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed, specific isoform 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 orally given dose is excreted as metabolites in the urine, and the remainder is found 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 LOSIVA.

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 DOSAGE AND ADMINISTRATION), is similar to those reported in adults.

INDICATIONS

LOSIVA capsules are indicated for the treatment of:

- reflux oesophagitis
- duodenal ulcer
- gastric ulcer
- NSAID-associated gastric and duodenal ulcers or erosions
- Symptoms of acid related dyspepsia
- Zollinger-Ellison syndrome.

In the treatment of peptic ulceration, the eradication of *H.pylori*, as the causative organism, must be a high priority.

Accordingly, LOSIVA should be used as part of combination therapy for the eradication of *H.pylori*.

Maintenance

LOSIVA capsules are indicated for maintenance treatment of:

- reflux oesophagitis
- duodenal ulcer
- gastric ulcer
- Zollinger-Ellison syndrome.

DOSAGE AND ADMINISTRATION

LOSIVA capsules are recommended to be given in the morning and swallowed whole with half a glass of water. The contents of the capsule should not be chewed or crushed.

For patients with swallowing difficulties and for children who can drink or swallow semi-solid food

For patients with swallowing difficulties the capsule can be opened and the contents swallowed directly with half a glass of liquid or after mixing the contents in a slightly acidic fluid e.g. fruit juice, yoghurt or in non carbonated water. The dispersion should be taken immediately or within 30 minutes. Alternatively patients can suck the capsule and swallow the pellets with liquid. The pellets must not be chewed or crushed.

For patients who cannot drink or swallow semi-solid food and for intubated patients

It is recommended to use an oral solution prepared from LOSEC IV for infusion or injection 40 mg. (Please refer to the New Zealand Datasheet for LOSEC IV.)

REFLUX OESOPHAGITIS

The recommended dosage is LOSIVA 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 LOSIVA 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 LOSIVA 10 mg once daily. If needed the dose can be increased to LOSIVA 20-40 mg once daily.

SEVERE REFLUX OESOPHAGITIS IN CHILDREN FROM ONE YEAR AND OLDER

The management of severe reflux oesophagitis should be diagnosed or recommended by a specialist paediatrician or gastroenterologist.

The recommended dosage regime for healing is:

<u>Weight</u>	<u>Dosage</u>
10-20 kg	LOSIVA 10 mg daily
>20 kg	LOSIVA 20 mg daily

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

HELICOBACTER PYLORI (HP) ERADICATION REGIMENS IN PEPTIC ULCER DISEASE

Triple therapy regimens

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

or

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

or

LOSIVA 40 mg once daily with amoxicillin 500 mg and metronidazole 400 mg both three times a day for one week.

Dual therapy regimens

LOSIVA 40-80 mg daily with amoxicillin 1.5 g daily in divided doses for two weeks. In clinical studies daily doses of 1.5-3 g of amoxicillin have been used

or

LOSIVA 40 mg once daily and clarithromycin 500 mg three times a day for two weeks.

To ensure healing in patients with active peptic ulcer disease, see further dosage recommendations for *duodenal* and *gastric ulcer*.

In each regimen if the patient is still *Hp* positive, therapy may be repeated.

DUODENAL ULCER

The recommended dosage in patients with an active duodenal ulcer is LOSIVA 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 LOSIVA 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 LOSIVA 10 mg once daily. If needed the dose can be increased to LOSIVA 20-40 mg once daily.

For NSAID-associated duodenal ulcers see “NSAID-Associated Gastroduodenal Lesions”.

GASTRIC ULCER

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

For NSAID-associated gastric ulcers see “NSAID-Associated Gastroduodenal Lesions”.

NSAID-ASSOCIATED GASTRODUODENAL LESIONS

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

SYMPTOMS OF ACID-RELATED DYSPEPSIA

For the 24-hour relief, and prevention of symptoms in patients with epigastric pain/discomfort with or without heartburn and indigestion, 20 mg LOSIVA once daily in the morning for 14 –28 days*. If symptom control has not been achieved after 4 weeks treatment with LOSIVA 20 mg daily, further investigation is recommended.

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

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 LOSIVA 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 LOSIVA 20-120 mg daily. When doses exceed LOSIVA 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.

WARNINGS AND PRECAUTIONS

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, the possibility of malignancy should be excluded as treatment may alleviate symptoms and delay diagnosis.

USE IN 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. LOSIVA 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

LOSIVA is not likely to affect the ability to drive or use machines.

ADVERSE EFFECTS

The following adverse 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, <1/10; uncommon >1/1000, <1/100; rare >1/10000, <1/1000; very rare <1/10000).

Blood and lymphatic system disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very Rare: Hypomagnesaemia

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, 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

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)

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

INTERACTIONS

EFFECTS OF OMEPRAZOLE ON THE PHARMACOKINETICS OF OTHER MEDICINES

Absorption: The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of medicines with a gastric pH dependent absorption. Like with other gastric acid suppressive medicines, the absorption of medicines, such as ketoconazole and itraconazole, can decrease and the absorption of 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).

Metabolism: 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 LOSIVA 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 LOSIVA 20 mg daily did, however, not change coagulation time in patients on continuous treatment with warfarin. 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.

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: Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus.

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 CYP 2C19. 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.

EFFECTS OF OTHER MEDICINES ON THE PHARMACOKINETICS OF OMEPRAZOLE

Metabolism: Since omeprazole is metabolised by CYP2C19 and CYP3A4, medicines known to inhibit CYP 2C19 or CYP 3A4 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 required during temporary concomitant use. Medicines known to induce CYP 2C19 or CYP 3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

OVERDOSAGE

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.

PHARMACEUTICAL PRECAUTIONS

SHELF-LIFE AND STORAGE CONDITIONS

3 years when stored tightly closed in the original container below 25°C.
Shelf-life of three months when stored in non-original container.

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

HDPE bottles of 30 capsules

FURTHER INFORMATION

COMPOSITION

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

EXCIPIENTS

Capsules: Disodium hydrogen phosphate dihydrate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose anhydrous, magnesium stearate, mannitol, methacrylic acid co-

polymer, microcrystalline cellulose, macrogol (polyethylene glycol), sodium lauryl sulphate, iron oxide (E 172), titanium dioxide (E 171) and gelatine.

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.

NAME AND ADDRESS

AstraZeneca Limited
Level 5, 15 Hopetoun Street, Freemans Bay.
P299 Private Bag 92175, Auckland 1142
Telephone: (09) 306 5650

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