

NEW ZEALAND DATA SHEET**NAME OF MEDICINE**

LOSEC

Omeprazole 40 mg/10 mL for intravenous injection

Omeprazole 40 mg for intravenous infusion

PRESENTATION

LOSEC IV injection combination pack consisting of a vial and a separate ampoule of reconstituting solution. Each 10 mL clear glass vial contains a white to off-white lyophilised powder consisting of omeprazole sodium 42.6 mg equivalent to 40 mg of omeprazole. The reconstituted solution is clear. The cap is a colourless aluminium frame with a white coloured plastic lid.

LOSEC IV infusion 40 mg. Each vial contains a white to off-white lyophilised powder consisting of omeprazole sodium 42.6 mg, equivalent to omeprazole 40 mg, which is intended to be reconstituted with 100 mL normal saline or 5% glucose (neither solution supplied with the dosage form). No other infusion solution should be used. The cap is a golden coloured aluminium frame with a blue coloured plastic lid.

USES**ACTIONS**

LOSEC (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

Intravenous omeprazole produces a dose dependent inhibition of gastric acid secretion in humans. In order to immediately achieve a similar reduction of intragastric acidity as after repeated dosing with 20 mg orally, a first dose of 40 mg intravenously is recommended. This results in an immediate decrease in intragastric acidity and a mean decrease over 24 hours of approximately 90%.

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*

See LOSEC Capsules/Tablets datasheet for information.

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

PHARMACOKINETICS

Distribution

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. 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 intravenously 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 LOSEC.

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: There is limited experience with LOSEC for intravenous use in children.

INDICATIONS

LOSEC IV is indicated primarily for the treatment of Zollinger-Ellison syndrome, and may also be used for the treatment of gastric ulcer, duodenal ulcer and reflux oesophagitis.

DOSAGE AND ADMINISTRATION

In patients with duodenal ulcer, gastric ulcer or reflux oesophagitis where oral medication is inappropriate, LOSEC IV 40 mg once daily is recommended. In patients with Zollinger-Ellison syndrome the recommended initial dose of LOSEC given intravenously is 60 mg daily. Higher daily doses may be required and the dose should be adjusted individually. When doses exceed 60 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 plasma half-life of omeprazole is 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 limited experience with LOSEC IV in children.

METHOD OF ADMINISTRATION**Injection**

LOSEC IV injection 40 mg should be given as a slow intravenous injection. The solution for IV injection is obtained by adding to the vial 10 mL of the solvent provided. (No other solvent should be used). Discoloration may occur if incorrect reconstitution technique is used. For practical information about the reconstitution see the package insert. After reconstitution the injection should be given slowly over a period of at least 2.5 minutes at a maximum rate of 4 mL per minute. The solution should be used within 4 hours of reconstitution.

Infusion

LOSEC IV infusion 40 mg should be given as an intravenous infusion (over a period of 20-30 minutes or more). The contents of one vial must be dissolved in 100 mL saline for infusion or 100 mL 5% dextrose for infusion. The solution should be used within 12 hours when omeprazole is dissolved in saline and within 6 hours when dissolved in 5% dextrose. After reconstitution, start the infusion immediately. The constituted solution should not be mixed or co-administered in the same infusion set with any other drug.

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 foetus/newborn child. LOSEC 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 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, 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)

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

Irreversible visual impairment has been reported in isolated cases of critically ill patients who have received omeprazole intravenous injection, especially at high doses, but no casual relationship has been established.

INTERACTIONS**EFFECTS OF OMEPRAZOLE ON THE PHARMACOKINETICS OF OTHER MEDICINES**

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

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 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. 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.

Omeprazole is partly metabolised also by CYP3A4, but omeprazole does not inhibit this enzyme. Thus, omeprazole does not affect the metabolism of drugs 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.

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.

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

LOSEC IV doses of up to 270 mg on a single day and up to 650 mg over a three-day period have been given in clinical trials without any dose-related adverse reactions.

PHARMACEUTICAL PRECAUTIONS

SHELF-LIFE AND STORAGE CONDITIONS

Intravenous Injection

Unopened carton: 2 years at a temperature not exceeding 25°C.

Vials (outside the carton): Should be protected from light and stored at normal indoor light for not more than 24 hours.

Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C after reconstitution.

The solution can be handled at normal indoor light without special precaution.

Substance for Infusion

Unopened carton: 2 years at a temperature not exceeding 25°C.

Vials (outside the carton): Should be protected from light and stored at normal in-door light for not more than 24 hours.

Substance for infusion must be dissolved in 100 mL saline for infusion or 100 mL 5% dextrose for infusion.

Chemical and physical in-use stability has been demonstrated for 12 hours after reconstitution with saline or for 6 hours after reconstitution with 5% dextrose.

From a microbiological point of view, the product should be used immediately, unless reconstitution has taken place in controlled and validated aseptic conditions. The solution can be handled at normal indoor light without special precaution.

INCOMPATIBILITIES

None known when instructions in DOSAGE AND ADMINISTRATION are followed.

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

LOSEC IV for Injection: Individual injection packs.

LOSEC IV for Infusion: 5 x vials of lyophilised powder.

FURTHER INFORMATION

EXCIPIENTS

LOSEC IV Injection

LOSEC IV injection 40 mg combination pack consisting of a vial and an ampoule. Each vial contains sodium hydroxide q.s. for pH adjustment. Each reconstituting solution ampoule contains citric acid monohydrate 5 mg (for pH adjustment), macrogol 400 (polyethylene glycol 400) 4 g, and water for injection up to 10 mL.

LOSEC IV Infusion

LOSEC IV infusion 40 mg. Each vial contains disodium edetate 1.5 mg and sodium hydroxide q.s. for pH adjustment.

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

DATE OF PREPARATION

1 June 2011

CDS April 2011

© This data sheet is copyrighted to AstraZeneca Limited and may be reproduced but not altered in any way.