LOZICARE

OMEPRAZOLE FOR INJECTION 40MG

COMPOSITION
Each vial contains:
Omeprazole Sodium Sterile
Eq. to Omeprazole 40mg
(Lyophilized)

CLINICAL PHARMACOLOGY

Pharmacodynamics
Omeprazole reduces gastric acid secretion through a unique mechanism of action. It is a specific inhibitor of the gastric proton pump in the parietal cell. It is rapidly acting and produces reversible control of gastric acid secretion with once daily dosing.
Intravenous administration of omeprazole results in an immediate reduction of intragastric acidity and a mean decrease over 24 hours of approximately 90% in patients with duodenal ulcer disease. A single 40 mg i.v. dose has similar effect on intragastric acidity over a 24 hour period as repeated oral dosing with 20 mg once daily. A higher dose of 60 mg i.v. twice daily has been used in a clinical study in patients with Zollinger-Ellison syndrome.

Site and mechanism of action
Omeprazole is a weak base and is concentrated and converted to the active form in the acid environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme "H+/ K+ ATPase"the proton pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for effective inhibition of both basal acid secretion and stimulated acid secretion irrespective of the stimulus.
All pharmacodynamic effects observed are explained by the effect of omeprazole on acid secretion. No tachyphylaxis has been observed during treatment with omeprazole.

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 the elderly 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
The average half-life of the terminal phase of the plasma concentration-time curve following i.v. administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during treatment.
Omeprazole is completely metabolised by the cytochrome P450 system, 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.
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 biliary secretion.

Elimination of omeprazole is unchanged in patients with reduced renal function. The elimination half-life is increased in patients with impaired liver function, but omeprazole has not shown any accumulation with once daily oral dosing.

Preclinical safety data

Animal Toxicology
Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated with omeprazole or subjected to partial fundectomy. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition, and not from a direct effect of any individual drug.

INDICATIONS AND USAGE
LOZICARE Injection is indicated in patients who are unable to take oral therapy for the short term treatment (up to 5 days)

- Prophylaxis of acid aspiration
- Reflux oesophagitis
- Duodenal ulcer
- Benign gastric ulcer
- Zollinger-Ellison syndrome
- Complicating NSAID therapy e.g. perioperative use

CONTRAINDICATIONS

LOZICARE Injection is contraindicated in patients with Known hypersensitivity to any of the constituents of the formulation.

LOZICARE Injection like other should not be administered with atazanavir.

WARNINGS

When gastric ulcer is suspected, the possibility of malignancy should be excluded before treatment with LOZICARE Injection is instituted, as treatment may alleviate symptoms and delay diagnosis.

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 a slightly increased risk of gastrointestinal infections, such as Salmonella and Campylobacter.

INTERACTIONS

Due to the decreased intragastric acidity, the absorption of ketoconazole or itraconazole may be reduced during omeprazole therapy as it is during treatment with other acid secretion inhibitors.

As omeprazole is metabolised in the liver through cytochrome P450 it can prolong the elimination of diazepam, phenytoin, warfarin and other vitamin K antagonists, which are in part substrates for this enzyme.

Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary when LOZICARE Injection is added to treatment. However, concomitant treatment with LOZICARE Injection, did not change the blood concentration of phenytoin in patients on continuous treatment with phenytoin. 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 omeprazole 20 mg orally daily, did not change coagulation time in patients on continuous treatment with warfarin.

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

There is no evidence of an interaction with phenacetin, theophylline, caffeine, propranolol, metoprolol, ciclosporin, lidocaine, quinidine, estradiol, or antacids when omeprazole is given orally. The absorption of omeprazole given orally is not affected by alcohol or food.

There is no evidence of an interaction with piroxicam, diclofenac or naproxen, this is considered useful when patients are required to continue these treatments.

Simultaneous treatment with omeprazole and digoxin in healthy subjects led to a 10% increase in the bioavailability of digoxin as a consequence of the increased intragastric pH.

Interaction with other drugs also metabolised via the cytochrome P450 system cannot be excluded.

Co-administration of omeprazole (40mg once daily) with atazanavir 300 mg/ritonavir 100mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, Cmax, and Cmin). Increasing the atazanavir dose to 400mg did not compensate for the impact of omeprazole on atazanavir exposure. PPIs including omeprazole should not be co-administered with atazanavir.

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

Concomitant administration of omeprazole and a CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure. Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC by 15% and 41%, respectively. A dose adjustment of omeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

PREGNANCY & LACTATION

Pregnancy: There are no adequate and well-controlled studies on the use of Omeprazole in pregnant women. Therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk. Omeprazole should be used during pregnancy only if the

potential benefit to pregnant women justifies the potential risk to the fetus.

Lactation: Omeprazole is excreted in human milk. Thus, a decision should be taken to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PRECAUTIONS

Omeprazole may alleviate symptoms and delay diagnosis of gastric carcinoma.
Symptomatic response to therapy with Omeprazole does not preclude the presence of gastric malignancy. Immediate Release Omeprazole formulations contain sodium bicarbonate which should be taken into consideration for patients on a Sodium-restricted diet.

ADVERSE REACTIONS

LOZICARE Injection is well tolerated and adverse reactions have generally been mild and reversible. The following 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 - ≥ 1/1000 and < 1/100
Rare - < 1/1000

Common	Central and peripheral nervous system	Headache
	Gastrointestinal	Diarrhoea, constipation, abdominal pain, nausea/vomiting and flatulence
Uncommon	Central and peripheral nervous system	Dizziness, paraesthesia, somnolence, insomnia and vertigo
	Hepatic	Increased liver enzymes
	Skin	Rash, dermatitis and/or pruritus, urticaria
	Other	Malaise
Rare	Central and peripheral nervous system	Reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients
	Endocrine	Gynaecomastia
	Gastrointestinal	Dry mouth, stomatitis and gastrointestinal candidiasis
	Haematological	Leukopenia, thrombocytopenia, agranulocytosis and pancytopenia
	Hepatic	Encephalopathy in patients with pre - existing severe liver disease; hepatitis with or without jaundice, hepatic failure, increased liver enzymes
	Musculoskeletal	Arthritic and myalgic symptoms and muscular weakness
	Reproductive system and breast disorders	Impotence
	Skin	Photosensitivity, bullous eruption erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia
	Other	Hypersensitivity reactions e.g. angioedema, fever, broncho-spasm, interstitial nephritis and anaphylactic shock. Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia

Isolated cases of irreversible visual impairment have been reported in critically ill patients who have received LOZICARE Intravenous Injection, particularly at high doses, however no causal relationship has been established.

OVERDOSAGE

Symptoms were transient, and no serious clinical outcome has been reported with Omeprazole overdose. No specific antidote for Omeprazole overdose is known. Omeprazole is extensively bound with protein and is, therefore, not readily dialyzable. In the event of overdose, treatment should be symptomatic and supportive.

Intravenous 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 effects.

DOSAGE AND ADMINISTRATION

DOSAGE

Adults only

Prophylaxis of acid aspiration: LOZICARE Injection 40 mg to be given slowly (over a period of 5 minutes) as an intravenous injection, one hour before surgery.

Treatment in patients where oral therapy is inappropriate e.g. in severely ill patients with either reflux oesophagitis, duodenal ulcer or gastric ulcer: LOZICARE Injection 40 mg given as an intravenous injection once daily is recommended for up to 5 days.

Zollinger-Ellison syndrome: LOZICARE IV Injection 40mg once daily. Higher daily doses may be required and the dose should be adjusted individually. When dose exceed 60mg daily, the dose should be divided and given twice daily.

Children: There is limited experience with Omeprazole IV in children.

Elderly: Dose adjustment is not needed in the elderly.

Patients with impaired hepatic function:

As bioavailability and plasma half-life is increased in patients with impaired hepatic function, the dose requires adjustment and a daily dose of 10-20 mg may be sufficient.

Patients with renal impairment:

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

METHOD OF ADMINISTRATION

LOZICARE powder and solvent for solution for injection is for intravenous administration only and must not be given by any other route.

LOZICARE Injection should be given as a slow intravenous injection.

The duration of administration should be over 5 minutes.

Reconstitute the contents in vial with 10 ml Sterilised water for injections BP to the vial (No other solvent should be used). Discoloration may occur if incorrect reconstitution technique is used.

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.

Use only freshly prepared solution.

Reconstituted solution is stable for up to 4 hrs. at 25°C and any unused portion should be discarded.

RECONSTITUTION

To Reconstitute add 10 ml Sterilised water for Injections BP to make a solution containing 4mg/ml of Omeprazole (approximately).

Do not use if any particles are present in the reconstituted solution.

Storage:

Protect from heat and light. Store in a cool and dry place.

KEEP OUT OF THE REACH OF CHILDREN.

Presentation:

LOZICARE is available in a glass Vial.

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