NEXIUM 40 mg
esomeprazole

Powder for solution for injection/infusion

Composition
Each vial contains esomeprazole 40 mg (as sodium salt).

Pharmaceutical form
Powder for solution for injection/infusion.
White to off-white porous cake or powder.

Therapeutic indications
Nexium for injection and infusion is indicated for gastric antisecretory treatment when the oral route is not possible, such as:

- gastroesophageal reflux disease in patients with esophagitis and/or severe symptoms of reflux.
- healing of gastric ulcers associated with NSAID therapy.
- prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.

Posology and method of administration
Patients who cannot take oral medication may be treated parenterally with 20-40 mg once daily. Patients with reflux oesophagitis should be treated with 40 mg once daily. Patients treated symptomatically for reflux disease should be treated with 20 mg once daily. For healing of gastric ulcers associated with NSAID therapy the usual dose is 20 mg once daily. For prevention of gastric and duodenal ulcers associated with NSAID therapy, patients at risk should be treated with 20 mg once daily. Usually the IV treatment duration is short and transfer to oral treatment should be made as soon as possible.

Method of administration
Injection
40 mg dose
The reconstituted solution should be given as an intravenous injection over a period of at least 3 minutes.

20 mg dose
Half of the reconstituted solution should be given as an intravenous injection over a period of approximately 3 minutes. Any unused solution should be discarded.

Infusion
40 mg dose
The reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes.

20 mg dose

Half of the reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes. Any unused solution should be discarded.

Children and adolescents
Nexium should not be used in children since no data is available.

Impaired renal function
Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution. (See section Pharmacokinetic properties).

Impaired hepatic function
Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum daily dose of 20 mg Nexium should not be exceeded. (See section Pharmacokinetic properties).

Elderly
Dose adjustment is not required in the elderly.

Contraindications
Hypersensitivity to the active substance esomeprazole or to other substituted benzimidazoles or to any of the excipients of this medicinal product.
Esomeprazole like other PPIs should not be administered with atazanavir. (See section 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 melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with Nexium may alleviate symptoms and delay diagnosis.

Interactions
Effects of esomeprazole on the pharmacokinetics of other drugs

Medicinal products with pH dependent absorption
The decreased intragastric acidity during treatment with esomeprazole might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole.

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

Drugs metabolised by CYP2C19
Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these drugs may be increased and a dose reduction could be needed. Concomitant oral administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam. Concomitant oral administration of 40 mg esomeprazole and phenytoin resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn. Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC_{τ} by 15% and 41%, respectively.

Concomitant oral administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing of oral esomeprazole, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

In healthy volunteers, concomitant oral administration of 40 mg esomeprazole and cisapride resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole.

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effects of other drugs on the pharmacokinetics of esomeprazole
Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant oral administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP 3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC_{τ} by 280%. A dose adjustment of esomeprazole 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 and lactation
For esomeprazole limited data on exposed pregnancies are available. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/fetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing Nexium to pregnant women.

It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore Nexium should not be used during breast-feeding.

Effects on ability to drive and use machines
Nexium is not likely to affect the ability to drive or use machines.

Undesirable effects
The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole administered orally or intravenously and post-marketing when administered orally. 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
Very rare: Agranulocytosis, pancytopenia

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

Metabolism and nutrition disorders
Uncommon: Peripheral oedema
Rare: Hyponatraemia

Psychiatric disorders
Uncommon: Insomnia
Rare: Agitation, confusion, depression
Very rare: Aggression, hallucinations

Nervous system disorders
Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders
Uncommon: 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
Uncommon: Dry mouth
Rare: Stomatitis, gastrointestinal candidiasis

Hepatobiliary disorders
Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: Hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders
Uncommon: Dermatitis, pruritus, rash, urticaria
Rare: Alopecia, photosensitivity
Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders
Rare: Arthralgia, myalgia
Very rare: Muscular weakness

Renal and urinary disorders
Very rare: Interstitial nephritis

Reproductive system and breast disorders
Very rare: Gynaecomastia

General disorders and administration site conditions
Rare: malaise, increased sweating

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

Overdose
There is very limited experience to date with deliberate overdose. The symptoms described in connection with an oral dose of 280 mg were gastrointestinal symptoms and weakness. Single oral doses of 80 mg esomeprazole and intravenous doses of 100 mg were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Pharmacodynamic properties
Pharmacotherapeutic group: Proton pump inhibitor
ATC Code: A02B C05

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.

Site and mechanism of action
Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+K^+-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion
After 5 days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The effect is similar irrespective of whether esomeprazole is administered orally or intravenously.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown after oral administration of esomeprazole.

Therapeutic effects of acid inhibition
Healing of reflux esophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after 4 weeks, and in 93% after 8 weeks of oral treatment.

Other effects related to acid inhibition
During treatment with antisecretory drugs serum gastrin increases in response to the decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with orally administered esomeprazole.

During long-term oral treatment with antisecretory drugs gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Pharmacokinetic properties
Distribution
The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% plasma protein bound.

Metabolism and excretion
Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. Total exposure (AUC) increases with repeated administration of esomeprazole. 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 inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite.
Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.
Following repeated doses of 40 mg administered as intravenous injections, the mean peak plasma concentration is approx. 13.6 micromol/L. The mean peak plasma concentration after corresponding oral doses is approx. 4.6 micromol/L. A smaller increase (of approx. 30%) can be seen in the total exposure after intravenous administration compared to oral administration.

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

Special patient populations
Approximately 2.9±1.5% of the population lacks a functional CYP2C19 enzyme and is called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg oral esomeprazole, the mean total exposure was approximately 100% higher in poor metabolisers than in subjects with a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. Similar differences have been seen for intravenous administration of esomeprazole. These findings have no implications for the posology of esomeprazole.

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years of age).

Following a single oral dose of 40 mg esomeprazole the mean total exposure is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. Similar differences have been observed for intravenous administration of esomeprazole. These findings have no implications for the posology of esomeprazole.

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the total exposure of esomeprazole. Therefore, a maximum dose of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

List of excipients
Disodium edetate
Sodium hydroxide

Incompatibilities
This medicinal product should not be used with other medicinal products except those mentioned in Instruction for use and handling.

Shelf Life
Please refer to expiry date on the outer carton.

Shelf-life after reconstitution
Chemical and physical in-use stability has been demonstrated for 12 hours at 30°C. From a microbiological point of view, the product should be used immediately.

Special precautions for storage
Store in the original package, in order to protect from light. Vials can however be stored exposed to normal in door light outside the box for up to 24 hours. Do not store above 30°C.

Pack Size
Please refer to the outer carton for pack size.

Instructions for use and handling

Injection

A solution for injection is prepared by adding 5 mL of 0.9% sodium chloride for intravenous use to the vial with esomeprazole. The reconstituted solution for injection is clear and colourless to very slightly yellow.
The degradation of reconstituted solution is highly pH dependent and the product must therefore only be reconstituted in the specified volume of 0.9% sodium chloride for intravenous use. The reconstituted solution should not be mixed or co-administered in the same infusion set with any other drug.
The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. Only clear solution should be used.
The reconstituted solution should be used within 12 hours. From a microbiological point of view, the product should be used immediately. Do not store above 30^{o} C.

The reconstituted solution should be given as an intravenous injection over a period of at least 3 minutes.
Half of the volume should be given if 20 mg should be administrated. Any unused solution should be discarded.

Infusion

A solution for infusion is prepared by dissolving the content of one vial with esomeprazole in up to 100 mL 0.9% sodium chloride for intravenous use.
The reconstituted solution for infusion is clear and colourless to very slightly yellow.

The degradation of reconstituted solution is highly pH dependent and the product must therefore only be reconstituted in the specified volume of 0.9% sodium chloride for intravenous use.
The reconstituted solution should not be mixed or co-administered in the same infusion set with any other drug.
The reconstituted solution should be administrated separately from other drugs.
The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. Only clear solution should be used.
The reconstituted solution should be used within 12 hours. From a microbiological point of view, the product should be used immediately. Do not store above 30^{o} C.

The reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes.
Half of the volume should be given if 20 mg should be administrated. Any unused solution should be discarded.

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