PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NEXIAM® 40 mg IV: 40 mg powder for solution for injection and infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains esomeprazole 40 mg (as sodium salt) and disodium edetate (EDTA) as chelating agent.

Excipient with known effect:

NEXIAM 40 mg IV contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection and infusion.

A white to off-white porous cake or powder in a vial of 5 mL.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NEXIAM 40 mg IV is indicated for Gastro-oesophageal reflux disease as an alternative where oral therapy is not appropriate and for the shortest possible time.

Gastro-oesophageal reflux disease:

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- treatment of severe symptoms of reflux disease

NEXIAM 40 mg IV is indicated for the short-term maintenance of haemostasis and prevention of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

4.2 Posology and method of administration

Posology

Adults:

Gastro-oesophageal reflux disease (GORD):

Treatment with NEXIAM 40 mg IV can be given for up to 7 days as part of a full treatment period for the specified indications. When oral therapy is possible or appropriate, intravenous therapy with NEXIAM 40 mg IV should be discontinued and the therapy should be continued orally.

Treatment of erosive reflux oesophagitis:

40 mg once daily.

The duration of treatment should be 4 weeks. An additional 4 weeks treatment is recommended for patients in whom the oesophagitis has not healed or who have persistent symptoms. *Long-term management of patients with healed oesophagitis to prevent relapse and treatment of severe symptoms of reflux disease:*

20 mg once daily.

Maintenance of haemostasis and prevention of rebleeding of gastric or duodenal ulcers:

80 mg administered as bolus infusion over 30 minutes followed by a continuous intravenous infusion of 8 mg/hr given over 3 days.

The parenteral treatment period should be followed by acid-suppression therapy with NEXIAM 40 mg once daily for 4 weeks.

Method of administration

NEXIAM 40 mg IV should be reconstituted with sodium chloride 0,9 % solution for injection/infusion before use. No other solvent should be used.

To reduce contamination the product should be used immediately after reconstitution. If the entire reconstituted content of the vial is not required for a single dose, any unused reconstituted solution should be discarded. NEXIAM 40 mg IV is for single use in one patient only.

Injection (40 mg vial):

A solution for injection is prepared by adding 5 mL of 0,9 % sodium chloride for intravenous use to the vial.

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.

Infusion (40 mg vial):

A solution for infusion is prepared by dissolving the contents of 1 vial in up to 100 mL 0,9 % sodium chloride for intravenous use.

40 mg dose:

The reconstituted solution should be given as an intravenous infusion over a period of 10 – 30 minutes.

20 mg dose:

Half of the reconstituted solution should be given as an intravenous infusion over a period of 10 – 30 minutes.

Continuous infusion (40 mg vial):

A solution for infusion is prepared by dissolving the content of 2 vials of esomeprazole 40 mg in up to 100 mL of 0,9 % sodium chloride for intravenous use.

80 mg bolus dose:

The reconstituted solution containing 80 mg esomeprazole should be given as an intravenous infusion over a period of 30 minutes.

8 mg/hour dose:

The reconstituted solution should be given as a continuous intravenous infusion over a period of 71,5 hours (calculated rate of infusion of 8 mg/hr).

Special Populations

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.

Impaired hepatic function:

Gastro-oesophageal reflux disease (GORD):

Dose adjustment is not required in patients with mild to moderate liver impairment (Child-Pugh class A, B). For patients with severe liver impairment (Child-Pugh class C), a maximum daily dose of 20 mg NEXIAM IV should not be exceeded.

Bleeding ulcers:

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, following an initial bolus dose of 80 mg NEXIAM IV, a continuous intravenous infusion dose of 4 mg/hour may be sufficient to maintain adequate acid control.

Elderly:

Dose adjustment is not required in the elderly.

Children:

NEXIAM 40 mg IV should not be used in children since no data are available.

4.3 Contraindications

- Known hypersensitivity to esomeprazole, to substituted benzimidazoles or to any of the excipients of NEXIAM 40 mg IV listed in section 6.1.
- Concomitant administration of esomeprazole with atazanavir or nelfinavir (see section 4.5).

4.4 Special warnings and 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 NEXIAM 40 mg IV may alleviate symptoms and delay diagnosis.

Co-administration of clopidogrel and esomeprazole results in decreased exposure to the active metabolite of clopidogrel by an average of 40 %. The maximum inhibition of (ADP induced) platelet aggregation decreased by an average of 14 %. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole for at least three months, and in most cases for a year.

Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular dysrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or other medicines that may cause hypomagnesaemia (e.g. diuretics), the medical practitioner should consider measuring magnesium serum levels before starting PPI treatment and periodically during treatment.

Clostridium difficile is a bacteria that can cause severe debilitating diarrhoea, that does not improve. Symptoms may include watery stools, abdominal pain, fever, and patients may develop more serious intestinal conditions.

Concomitant administration with NEXIAM 40 mg IV and medicines such as atazanavir and nelfinavir is not recommended (see section 4.5).

Therapeutic medicine monitoring is recommended during concomitant treatment with warfarin.

Other effects related to acid inhibition:

During treatment with NEXIAM 40 mg IV serum gastrin increases, in response to decreased acid secretion.

During long-term oral treatment with NEXIAM 40 mg IV gastric glandular cysts occur. 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 such as NEXIAM 40 mg IV, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and also *Clostridium difficile* in hospitalised patients.

Proton pump inhibitor (PPI) therapy has a potential association with an increased risk of osteoporosis-related fractures, particularly with long-term use, potentially impacting the hip, spine, and wrist bones. The risk is more apparent in patients with secondary risk factors of osteoporosis, such as renal dysfunction.

In AstraZeneca's randomised, double-blind and controlled clinical studies on omeprazole and esomeprazole (including two open long-term studies of up to more than 12 years) there are no indications that PPIs are associated with osteoporotic fractures.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Serious cutaneous adverse reactions (SCARs):

Serious cutaneous adverse reactions (SCARs) such as erythema multiforme (EM), StevensJohnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening, have been reported very rarely in association with esomeprazole treatment.

Patients should be advised of the signs and symptoms of the severe skin reaction EM/SJS/TEN/DRESS and should seek medical advice from their medical practitioner immediately when observing any indicative signs or symptoms.

NEXIAM 40 mg IV should be discontinued immediately upon signs and symptoms of severe skin reactions and additional medical care/close monitoring should be provided as needed.

Re-challenge should not be undertaken in patients with EM/SJS/TEN/DRES.

Children:

NEXIAM 40 mg IV should not be used in children since no data are available.

4.5 Interactions with other medicines and other forms of interaction

Effects of NEXIAM 40 mg IV on the pharmacokinetics of other medicines:

The gastric acid suppression during treatment with NEXIAM 40 mg IV may 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 esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin

in healthy subjects increased the bioavailability of digoxin by 10 % (up to 30 % in 2 out of 10 subjects). Digoxin toxicity has been reported. Caution should be exercised when NEXIAM 40 mg IV is given at high doses in elderly patients. Therapeutic monitoring of digoxin levels should be done.

The absorption of ketoconazole and itraconazole can decrease during treatment with NEXIAM 40 mg IV.

NEXIAM 40 mg IV inhibits CYP2C19, the major esomeprazole metabolising enzyme.

Concomitant oral administration of 30 mg esomeprazole resulted in a 45 % decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance. Concomitant oral administration of 40 mg esomeprazole resulted in a 13 % increase in trough plasma levels of phenytoin in epileptic patients; dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with NEXIAM 40 mg IV is introduced or withdrawn.

Concomitant oral administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketed use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring of the INR is recommended when warfarin is coadministered with NEXIAM at initiation of treatment, during the treatment and at ending treatment.

Omeprazole as well as esomeprazole act as inhibitors of CYP 2C19. 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 metabolites by 29 % and 69 % respectively.

In healthy volunteers, concomitant oral administration of 40 mg esomeprazole 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.

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

When given together with PPIs, methotrexate levels have been reported to increase in some patients by up to three-fold. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Omeprazole has been reported to interact with some antiretroviral medicines. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral medicine. Other possible interaction mechanisms are via inhibition of CYP2C19. For some antiretroviral medicines, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral medicines, such as saquinavir, increased serum levels of 80 – 100 % have been reported. There are also some antiretroviral medicines for which unchanged serum levels have been reported when given with omeprazole. Close monitoring or dose alteration is recommended. Concomitant administration with NEXIAM 40 mg IV and antiretroviral medicines such as atazanavir and nelfinavir is not recommended. NEXIAM 40 mg IV substantially decreases the concentration of atazanavir and nelfinavir (see section 4.3).

Co-administration of NEXIAM (40 mg once daily) reduced mean nelfinavir exposure by approximately 40 % and the mean exposure of the pharmacologically active metabolite was reduced by approximately 75 – 90 %.

Tipranavir may decrease the concentration of NEXIAM 40 mg IV. Co-administration is not recommended. However, if used concurrently, the dose of NEXIAM 40 mg IV should be increased.

NEXIAM 40 mg IV has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effects of other medicines on the pharmacokinetics of NEXIAM 40 mg IV:

NEXIAM 40 mg IV is metabolised by CYP2C19 and CYP3A4. Concomitant oral administration of NEXIAM 40 mg IV and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily) resulted in a doubling of the exposure (AUC) to NEXIAM 40 mg IV. Concomitant administration of NEXIAM 40 mg IV and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the NEXIAM 40 mg IV exposure. However, dose adjustment of NEXIAM 40 mg IV is not required in either of these situations. However, dose adjustment should be considered in patients with severe (Child-Pugh Class C) hepatic impairment and if on long-term treatment.

Voriconazole:

Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC_t by 15 % and 41 %, respectively.

Medicines known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort (*Hypericum perforatum*)) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Absorption of vitamin B12:

Esomeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

Interference with laboratory tests:

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

For esomeprazole limited clinical data on exposed pregnancies are available.

Lactation

It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore, NEXIAM 40 mg IV should not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

NEXIAM 40 mg IV may cause dizziness and blurred vision, thereby affecting the ability to drive or use machinery.

4.8 Undesirable effects

Summary of the safety profile

Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported in clinical trials (and also from post-marketing use). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.

Tabulated summary of adverse reactions

The following adverse reactions have been reported.

The following definitions of frequency are used: Common: 1/100;

Uncommon: 1/1000 and 1/100; Rare: 1/10 000 and 1/1000; Very rare: 1/10 000

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia
	Very rare	Agranulocytosis, pancytopenia
Immune system disorders	Rare	Hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock.
Metabolism and nutrition disorders	Uncommon	Peripheral oedema
	Rare	Hyponatraemia
	Very rare	Hypomagnesaemia (see section 4.4), severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia.
Psychiatric disorders	Uncommon	Insomnia
	Rare	Agitation, confusion, depression

	Very rare	Aggression, hallucination
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, diarrhoea, flatulence, nausea/vomiting, constipation
	Uncommon	Dry mouth
	Rare	Stomatitis, gastrointestinal candidiasis,

		gastrointestinal infections
	Very rare	Microscopic colitis
Hepatobiliary disorders	Uncommon	Increased liver enzymes
	Rare	Hepatitis with or without jaundice
	Very rare	Hepatic failure, hepatic encephalopathy
Skin and subcutaneous tissue disorders	Common	Administration site reactions*
	Uncommon	Dermatitis, pruritus, urticaria, rash
	Rare	Alopecia, photosensitivity

	Very rare	Erythema multiforme, Stevens- Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Uncommon	Fracture of the hip, wrist or spine (see section 4.4)
	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, hyperhidrosis
*Administration site reactions have mainly been observed in a study with high-dose exposure over 3 days (72 hours). In the non-clinical programme for esomeprazole intravenous formulation there was no evidence of vaso-irritation but a slight tissue inflammatory reaction at the injection site after subcutaneous (paravenous) injection was noted. The non-clinical findings somewhat indicated that the clinical tissue irritation was concentration related.		

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of NEXIAM 40 mg IV is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 11.4.3 Medicines acting on gastro-intestinal tract. Other

Pharmacotherapeutic group: Drugs for acid-related disorders proton pump inhibitors ATC Code: A02B C05

Mechanism of action

Esomeprazole, the S-isomer of omeprazole, reduces gastric acid secretion through inhibition of the enzyme H^+K^+-ATPase, the acid pump in the parietal cell, where it is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi. This effect on the final step of the gastric acid secretion is dose-dependent and inhibitory for both basal and stimulated acid secretion.

Pharmacodynamic effects

Using Area Under the Curve (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.

During intravenous administration of 80 mg esomeprazole as a bolus infusion over 30 minutes followed by a continuous intravenous infusion of 8 mg/hr for 23,5 hours, intragastric pH above 4, and pH above 6 was maintained for a mean time of 21 hours, and 11 – 13 hours, respectively, over 24 hours in healthy subjects.

Therapeutic effects of acid inhibition:

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive esomeprazole IV for injection (n = 375) or placebo (n = 389). Following endoscopic haemostasis, patients received either 80 mg esomeprazole IV administered as bolus infusion over 30 minutes followed by a continuous infusion of 8 mg/hour or placebo for 72 hours. After the initial 72 hour period, all patients received oral esomeprazole 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5,9 % in the treatment group compared to 10,3 % for the placebo group. At 7 and 30 days post-treatment, the occurrence was 7,2 % vs 12,9 % and 7,7 % vs 13,6 %, respectively.

Comparative clinical trials:

In a 5-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 24 symptomatic GORD (gastro-oesophageal reflux disorder) patients. On day 5, intragastric pH was maintained above 4,0 for a mean of 15,3 hours with esomeprazole, 13,3 hours with rabeprazole, 12,9 hours with omeprazole, 12,7 hours with lansoprazole and 11,2 hours with pantoprazole (p □ 0,001 for differences between esomeprazole and all other comparators). Esomeprazole also provided a significantly higher percentage of patients with an intragastric pH greater than 4,0 for more than 12 hours relative to the other proton pump inhibitors (p < 0,05).

5.2 Pharmacokinetic properties

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0,22 litres/kg body weight.

Plasma protein binding

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, i.e. extensive metabolisers.

Total plasma clearance is about 17 litres/hour after a single dose and about 9 litres/hour after repeated administration. The plasma elimination half-life is about 1,3 hours after repeated oncedaily dosing. The area under the plasma concentration-time curve increases in a non-linear fashion with repeated administration of esomeprazole. Esomeprazole is completely eliminated from plasma between doses, with no tendency for accumulation during once-daily 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 compound is found in urine.

Linearity/non-linearity

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.

Following repeated doses of 40 mg administered as intravenous injections, the mean peak plasma concentration is approximately 13,6 micromol/l. The mean peak plasma concentration after corresponding oral doses is approximately 4,6 micromol/l. A smaller increase (of approximately 30 %) can be seen in total exposure after intravenous administration compared to oral administration. There is a dose-linear increase in total exposure following intravenous administration of esomeprazole as a 30-minute infusion (40 mg, 80 mg or 120 mg) followed by a continuous infusion (4 mg/h or 8 mg/h) over 23,5 hours.

Special patient populations

These findings have no implications for the dosing of esomeprazole.

Elderly

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

Gender

Following a single oral dose of 40 mg esomeprazole the mean area under the plasma concentration-time curve is approximately 30 % higher in females than in males. No gender difference is seen after repeated once-daily administration. Similar differences have been seen for intravenous administration of esomeprazole. These findings have no implications for the dosage of esomeprazole.

Renal impairment

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.

Hepatic impairment

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 GERD patients with severe dysfunction. For patients with bleeding ulcers and severe liver impairment, following an initial bolus dose of 80 mg, a maximum continuous intravenous infusion dose of 4 mg/h for 71,5 hours may be sufficient. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing.

In patients with severe liver impairment (Child-Pugh C) there is a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in GORD patients with severe impairment. For patients with bleeding ulcers and severe liver impairment, following an initial bolus dose of 80 mg, a maximum continuous intravenous infusion dose of 4 mg/hr may be sufficient in patients with bleeding ulcers. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate dihydrate

Sodium hydroxide

6.2 Incompatibilities

The degradation of the reconstituted solution is highly pH dependent and the product must therefore only be reconstituted with 0,9 % sodium chloride for intravenous use according to the instructions above. The reconstituted solution should not be mixed or co-administered in the same infusion set with any other medicine.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

NEXIAM 40 mg IV should be stored below 25 °C in the outer container, which it is provided in, since this protects the vial from light. Vials can be stored exposed to normal in-door light, for up to 24 hours outside the box.

Reconstituted solution for injection and infusion:

Chemical, physical and microbiological in-use stability of the reconstituted solution has been demonstrated for 12 hours in 0,9 % sodium chloride solution for intravenous use. The reconstituted solution can be kept in normal in-door light at up to 30 ºC.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ºC, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

NEXIAM 40 mg IV is filled in 5 mL vials made of colourless borosilicate glass. Grey stopper made of bromobutyl rubber, silver cap made of aluminium and a purple plastic flip-off seal.

Pack size: 1 or 10 vials.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER

A38/11.4.3/0384

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 March 2005

10. DATE OF REVISION OF THE TEXT

25 November 2025