FINAL PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME (and Dosage Form):

Nexiam® 40 mg IV (Powder for Solution for Injection and Infusion)

COMPOSITION:

Each vial contains esomeprazole sodium 42,5 mg, equivalent to esomeprazole 40 mg and disodium edetate (EDTA) as chelating agent.

List of excipients:

Disodium edetate dihydrate and sodium hydroxide.

PHARMACOLOGICAL CLASSIFICATION:

A 11.4.3 Medicines acting on gastrointestinal tract. Other.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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 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.

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 ($p \leq 0,001$ 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 ($p < 0,05$).

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 once-daily 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.

Special patient population:

These findings have no implications for the dosing 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 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.

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.

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.

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.

CONTRAINDICATIONS:

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

WARNINGS:

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.

Concomitant administration with NEXIAM and medicines such as atazanavir and nelfinavir is not recommended (see "*Interactions*" section).

Therapeutic medicine monitoring is recommended during concomitant treatment with warfarin.

Other effects related to acid inhibition:

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

During long-term oral treatment with NEXIAM 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 NEXIAM may lead to increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Children:

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

INTERACTIONS:

Effects of NEXIAM on the pharmacokinetics of other medicines:

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

Esomeprazole 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 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 is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

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.

Omeprazole has been reported to interact with some antiretroviral medicines. The clinical importance and the mechanisms behind these reported 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 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 have been reported. There are also some antiretroviral medicines for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with NEXIAM and antiretroviral medicines such as atazanavir and nelfinavir is not recommended.

NEXIAM 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:

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant oral administration of NEXIAM and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily) resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of NEXIAM and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of NEXIAM is not required in either of these situations.

PREGNANCY AND LACTATION:

For esomeprazole limited clinical data on exposed pregnancies are available. It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore NEXIAM should not be used during breastfeeding.

DOSAGE AND DIRECTIONS FOR USE:

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:

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).

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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side Effects:

The following adverse reactions have been reported. The following definitions of frequencies are used:

Common ≥ 1/100; Uncommon ≥ 1/1 000 and < 1/100; Rare ≥ 1/10 000 and < 1/1 000;

Very rare < 1/10 000

Common:

Nervous system disorders:	Headache
Gastrointestinal disorders:	Abdominal pain, diarrhoea, flatulence, nausea/ vomiting, constipation
Skin and subcutaneous tissue disorders:	Administration site reactions*

Uncommon:

Metabolism and nutrition disorders:	Peripheral oedema
Psychiatric disorders:	Insomnia
Nervous system disorders:	Dizziness, paraesthesia, somnolence
Ear and labyrinth disorders:	Vertigo
Gastrointestinal disorders:	Dry mouth
Hepatobiliary disorders:	Increased liver enzymes
Skin and subcutaneous tissue disorders:	Dermatitis, pruritus, urticaria, rash

Rare:

Blood and lymphatic system disorders:	Leucopenia, thrombocytopenia
Immune system disorders:	Hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders:	Hyponatraemia
Psychiatric disorders:	Agitation, confusion, depression
Nervous system disorders:	Taste disturbance
Eye disorders:	Blurred vision
Respiratory, thoracic and mediastinal disorders:	Bronchospasm
Gastrointestinal disorders:	Stomatitis, gastrointestinal candidiasis
Hepatobiliary disorders:	Hepatitis with or without jaundice
Skin and subcutaneous tissue disorders:	Alopecia, photosensitivity
Musculoskeletal, connective tissue and bone disorders:	Arthralgia, myalgia
General disorders and administration site conditions:	Malaise, hyperhidrosis

Very rare:

Blood and lymphatic system disorders:	Agranulocytosis, pancytopenia
Psychiatric disorders:	Aggression, hallucination
Hepatobiliary disorders:	Hepatic failure, hepatic encephalopathy
Skin and subcutaneous tissue disorders:	Erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders:	Muscular weakness
Renal and urinary disorders:	Interstitial nephritis
Reproductive system and breast disorders:	Gynaecomastia

*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.

Special Precautions:

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.

Other effects related to acid inhibition:

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

During long-term oral treatment with NEXIAM 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 NEXIAM may lead to increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Effects on ability to drive and use machines:

NEXIAM 40 mg IV is not likely to affect the ability to drive or use machines.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The symptoms described in connection with deliberate NEXIAM overdose (limited experience of oral doses in excess of 240 mg/day) are transient. Single oral doses of 80 mg and intravenous doses of 308 mg NEXIAM over 24 hours were uneventful. 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.

IDENTIFICATION:

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

PRESENTATION:

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: 10 vials.

STORAGE INSTRUCTIONS:

NEXIAM 40 mg IV should be stored at or 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.

Keep out of reach of children.

REGISTRATION NUMBER:

A38/11.4.3/0384

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

AstraZeneca Pharmaceuticals (Pty) Ltd

Building 2, Northdowns Office Park

17 Georgian Crescent West,

Bryanston, Johannesburg

2191, South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

2 March 2012

AstraZeneca Logo

Ref: Nexiam 40 mg IV - EPI (08-07-2011)

CDS: June 2009

Inclusion of Namibia + Botswana registration details (15-10-2010)

NAMIBIA: NS2 Reg. No.: 06/11.4.3/0250

BOTSWANA: S2 Reg. No.: BOT 0801240