1.3.1.1 PROFESSIONAL INFORMATION (CURRENT APPROVED)

SCHEDULING STATUS: **S4**

PROPRIETARY NAME AND DOSAGE FORM:

Nexiam® 5 mg Sachets; Nexiam® 2,5 mg Sachets (Granules)

COMPOSITION:

NEXIAM 5 mg Sachets:

Each sachet contains esomeprazole 5 mg (as magnesium trihydrate) in the form of gastro-resistant granules for oral suspension.

NEXIAM 2,5 mg Sachets:

Each sachet contains esomeprazole 2,5 mg (as magnesium trihydrate) in the form of gastro-resistant granules for oral suspension.

Contains sugar (sucrose).

List of excipients: glycerol monostearate 40-55, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, triethyl citrate, dextrose, xanthan gum, crospovidone, citric acid, iron oxide, hyprolose.

PHARMACOLOGICAL CLASSIFICATION:

A 11.4.3 Medicines acting on gastro-intestinal tract. Other.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Esomeprazole, the S-isomer of omeprazole, reduces gastric acid secretion through specific inhibition of 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 and inhibits the enzyme H^+K^+-ATPase – the acid pump. This effect on the final step of the gastric acid secretion is dose-dependent and provides for effective inhibition of both basal and stimulated acid secretion.

Effect on gastric acid secretion:

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within 1 hour. After repeated administration with 20 mg esomeprazole once daily for 5 days, mean peak acid output after pentagastrin stimulation is decreased by 90 % when measured 6-7 hours after dosing on day 5.

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 Gastro-Oesophageal Reflux Disease (GORD) patients.

The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours were 76 %, 54 % and 24 % respectively for esomeprazole 20 mg. Corresponding proportions for esomeprazole 40 mg were 97 %, 92 % and 56 % respectively.

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

Following repeated dose administration of 0,5 mg/kg and 0,1 mg/kg esomeprazole in < 1 month old and 1-11 month old infants, respectively, the effect on intragastric pH, expressed as change in percentage of time with intragastric pH > 4 from baseline, is similar to that observed after esomeprazole 20 mg in adults. In addition, 0,5 mg/kg and 1,0 mg/kg esomeprazole in < 1 month old and 1-11 month old infants, respectively, results in a significant reduction in oesophageal acid exposure.

Food intake had no significant influence on the effect of esomeprazole on intragastric acidity.

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 esomeprazole treatment should be temporarily stopped 5 days before CgA measurements.

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 esomeprazole.

During long-term treatment with antisecretory medicines 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, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

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:

Absorption and distribution:

Esomeprazole is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose.

The absolute bioavailability is 89 % after repeated once-daily administration. The apparent volume of distribution at steady state in healthy subjects is approximately 0,22 litres/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 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 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 an 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.
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 populations:
Approximately 3 % of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100 % higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60 %.

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

Following a single 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. These findings have no implications for the dosage 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 area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum 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.

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma concentration (t_{max}) for the 10 mg dose was similar across the 1-11 year-olds and similar to the total exposure seen with the 20 mg dose in 12-18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6-11 year-olds compared to 12-18 year-olds and adults.

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1-5 year-olds.

Following repeated dose administration of 1,0 mg/kg esomeprazole in 1-11 month old infants, the exposure (AUC) was slightly higher than that observed after 0,5 mg/kg esomeprazole in < 1 month old infants, but similar to that observed after 10 mg in

1-11 year-olds, and 20 mg in 12-18 year-olds as well as adults.

INDICATIONS:

NEXIAM granules for oral suspension are indicated for:

- the reduction in intra-oesophageal pH, by reducing the acidity of the gastric reflux in neonates and infants
- the treatment of Gastro Oesophageal Reflux Disease (GORD) confirmed by pH probe or endoscopy

CONTRAINDICATIONS:

Known hypersensitivity to NEXIAM, substituted benzimidazoles or any other constituents of NEXIAM.

WARNINGS AND SPECIAL PRECAUTIONS:

NEXIAM is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

Prior to treatment or 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 of gastric ulcer or a malignant disease of the oesophagus should be excluded as the treatment with NEXIAM may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

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

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter.*

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

INTERACTIONS:

Interaction with other medicinal products and other forms of interaction:

Effects of NEXIAM on the pharmacokinetics of other medicines:

The gastric acid suppression during treatment with NEXIAM 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 NEXIAM. 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).

NEXIAM inhibits CYP2C19, the major NEXIAM metabolising enzyme. Concomitant administration of 30 mg NEXIAM resulted in a 45 % decrease in clearance of the CYP2C19

substrate diazepam. This interaction is unlikely to be of clinical relevance. Concomitant administration of 40 mg NEXIAM resulted in a 13 % increase in trough plasma levels of phenytoin in epileptic patients; dose adjustment was not required in this study.

Concomitant administration of 40 mg NEXIAM 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 coumarine derivatives.

In healthy volunteers, concomitant administration of 40 mg NEXIAM resulted in a 32 % increase in area under the plasma concentration-time curve (AUC) and a 31 % prolongation of elimination half-life ($t_{½}$) but no significant increase in peak plasma levels of cisapride. This interaction did not alter the influence of cisapride on cardiac electrophysiology.

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 esomeprazole may need to be considered.

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 active metabolites by 29 % and 69 % respectively.

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 esomeprazole 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.

Studies evaluating concomitant administration of NEXIAM and either naproxen (non-selective NSAID) or rofecoxib (COX-2-selective NSAID) did not identify any clinically relevant interaction.

Effects of other medicines on the pharmacokinetics of NEXIAM:

NEXIAM is metabolised by CYP2C19 and CYP3A4. Concomitant administration of NEXIAM and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to NEXIAM.

Concomitant administration of NEXIAM and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the NEXIAM exposure. Dose adjustment of NEXIAM is not required.

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

PREGNANCY AND LACTATION:

Safety during pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Granules for oral suspension:

The contents of the 2,5 mg and 5 mg strengths sachet should be emptied into a container containing a teaspoon (5 ml) of non-carbonated water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir, and drink immediately. In cases where there is a need to use 2 sachets, they may be mixed in a similar way adding twice the required amount of water. Do not use carbonated water.

For patients who have a nasogastric or gastric tube in place, the contents of the 2,5 mg and 5 mg strength sachets can be added to a syringe containing 5 ml of non-carbonated water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with an

equal amount of water (5 ml) and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Alternatively, the suspension can be prepared first and then drawn up into a syringe. Empty the contents of the 2,5 mg and 5 mg strengths sachets into 5 ml of water. Stir and leave for a few minutes to thicken. Stir again and then draw the suspension into a syringe. Inject through the enteric tube, into the stomach within 30 minutes after reconstitution. Refill the syringe with an equal amount of water (5 ml). Shake and flush any remaining contents from the enteric tube into the stomach.

Children 0-1 years:

Gastro-Oesophageal Reflux Disease (GORD):

- Treatment of Gastro-Oesophageal Reflux Disease (GORD) diagnostically confirmed through pH probe or endoscopy.

1-11 months:

Weight 3-5 kg: 2,5 mg once daily for up to 6 weeks.

Weight > 5-7,5 kg: 5 mg once daily for up to 6 weeks.

Weight > 7,5-12 kg: 10 mg once daily for up to 6 weeks.

Doses over 1,33 mg/kg/day have not been studied.

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:

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 NEXIAM should be used.

Elderly:

Dose adjustment is not required in the elderly.

SIDE EFFECTS:

The following adverse reactions have been identified or suspected in the clinical trials programme for NEXIAM. None, however, were found to be dose-related.

The following definitions of frequency 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

Nervous system disorders:

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Gastrointestinal disorders:

Common:	Abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon:	Dry mouth
Rare:	Stomatitis, gastrointestinal candidiasis

Skin and subcutaneous tissue disorders:

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

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

Psychiatric disorders:

Uncommon: Insomnia

Rare: Agitation, confusion, depression

Very rare: Aggression, hallucination

Eye disorders:

Rare: Blurred vision

Ear and labyrinth disorders:

Uncommon: Vertigo

Respiratory, thoracic and mediastinal disorders:

Rare: Bronchospasm

Hepatobiliary disorders:

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: Hepatic failure, hepatic encephalopathy

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, hyperhidrosis

Post marketing experience:

The following adverse events have been reported during the post marketing use of NEXIAM. Because these are spontaneous reports from a population of uncertain size, it is not possible to reliably estimate their frequency.

Nervous system disorders:

Headache, dizziness, paraesthesia, somnolence, taste disturbance

Gastrointestinal disorders:

Abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation, dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis

Skin and subcutaneous tissue disorders:

Dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Blood and lymphatic system disorders:

Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders:

Hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders:

Peripheral oedema, hyponatraemia, hypomagnesaemia

Psychiatric disorders:

Insomnia, agitation, confusion, depression, aggression, hallucination

Eye disorders:

Blurred vision

Ear and labyrinth disorders:

Vertigo

Respiratory, thoracic and mediastinal disorders:

Bronchospasm

Hepatobiliary disorders:

Increased liver enzymes, hepatitis with or without jaundice, hepatic failure, hepatic encephalopathy

Reproductive system and breast disorders:

Gynaecomastia

General disorders and administration site conditions:

Malaise, hyperhidrosis

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The symptoms described in connection with deliberate NEXIAM overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg NEXIAM were uneventful. No specific antidote is known. NEXIAM 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:

NEXIAM 2,5 mg Sachets:

Pale yellow fine granules in a unit dose sachet. Brownish granules may be visible.

Reconstituted suspension: The oral suspension is a thick yellow liquid containing suspended pellets.

NEXIAM 5 mg Sachets:

Pale yellow fine granules in a unit dose sachet. Brownish granules may be visible.

Reconstituted suspension: The oral suspension is a thick yellow liquid containing suspended pellets.

PRESENTATION:

NEXIAM 2,5 and 5 mg Sachets:

The esomeprazole pellets and excipient granules are packed into a sachet made out of 3 layers of an aluminium laminate, where the aluminium layer provides a moisture barrier.

Cartons containing 28 sachets.

STORAGE INSTRUCTIONS:

NEXIAM 2,5 and 5 mg Sachets:

Store at or below 25 °C.

Store in a dry place. Do not open sachets until prior to use.

Reconstituted suspension must be taken within 30 minutes after reconstitution.

Keep out of reach of children.

REGISTRATION NUMBERS:

NEXIAM 2,5 mg Sachets: 44/11.4.3/0208

NEXIAM 5 mg Sachets: 44/11.4.3/0209

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

AstraZeneca Pharmaceuticals (Pty) Limited

Building 2, Northdowns Office Park

17 Georgian Crescent West,

Bryanston, Johannesburg

2191, South Africa

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