PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NEXIAM® 20 mg: 20 mg gastric resistant tablet

NEXIAM® 40 mg: 40 mg gastric resistant tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NEXIAM 20 mg:

Each gastric-resistant tablet contains esomeprazole magnesium trihydrate 22,3 mg (equivalent to esomeprazole 20 mg) in the form of a multiple unit pellet system (MUPS).

NEXIAM 40 mg:

Each gastric-resistant tablet contains esomeprazole magnesium trihydrate 44,5 mg (equivalent to esomeprazole 40 mg) in the form of a multiple unit pellet system (MUPS).

Excipients with known effects:

Contains sugar**:** sucrose.

NEXIAM 20 mg: 28 mg sugar spheres per tablet.

NEXIAM 40 mg: 30 mg sugar spheres per tablet.

NEXIAM 20 mg and NEXIAM 40 mg contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Gastric resistant tablet.

NEXIAM 20 mg:

A light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side.

NEXIAM 40 mg:

A pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NEXIAM 20 mg and 40 mg tablets are indicated for:

Gastro-oesophageal reflux disease (GORD):

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring continued NSAID therapy:

prevention of gastric and duodenal ulcers associated with nonsteroidal anti-inflammatory drug (NSAID) therapy in patients at risk

In combination with appropriate antibacterial therapeutic regimen for the eradication of Helicobacter pylori:

- healing of *Helicobacter pylori* associated duodenal ulcer and
- prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcer disease

NEXIAM has been used in pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion.

4.2 Posology and method of administration

Posology

Adults:

Gastro-oesophageal reflux disease (GORD):

- treatment of erosive reflux oesophagitis

  40 mg once daily for 4 weeks.

  An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

- long-term management of patients with healed oesophagitis to prevent relapse

  20 mg once daily.

- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

  20 mg once daily in patients without oesophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using an on demand regimen, taking 20 mg once daily, when needed.

Patients requiring continued NSAID therapy:

- prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk 20 mg or 40 mg once daily.

In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori and:

- healing of *Helicobacter pylori* associated duodenal ulcer and prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcer disease

  20 mg NEXIAM with 1 g amoxicillin and 500 mg clarithromycin, all twice daily for 7 days.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic

hypersecretion:

The recommended initial dosage is NEXIAM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

Adolescents 12 – 18 years:

Gastro-oesophageal reflux disease (GORD):

- treatment of erosive reflux oesophagitis

  40 mg once daily for 4 weeks.

  An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

- long-term management of patients with healed oesophagitis to prevent relapse

  20 mg once daily.

- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

  20 mg once daily in patients without oesophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

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:

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.

Method of administration

The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed.

The tablets can also be dispersed in half a glass of non-carbonated water. No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed. For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered through a gastric tube.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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.

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

Concomitant 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 NEXIAM and clopidogrel should be avoided.

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.
During treatment with antisecretory medicines, serum gastrin increases in response to the decreased acid secretion. Also chromogranin A (CgA) increase due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

Decreased gastric acidity increases gastric contents 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, in hospitalised patients, possibly also *Clostridium difficile*.

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.

Serious cutaneous adverse reactions (SCARs)

Serious cutaneous adverse reactions (SCARs) such as erythema multiforme (EM), Stevens-Johnson 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 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/DRESS.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with 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 medicines that may cause hypomagnesaemia (e.g. diuretics, digoxin), the medical practitioner should consider measuring magnesium serum levels before starting PPI treatment and periodically during treatment.

NEXIAM contains sucrose and is not suitable for patients with glucose-galactose malabsorption syndrome, fructose intolerance, or sucrose isomaltase deficiency.

4.5 Interactions with other medicines and other forms of interaction

Effects of NEXIAM on the pharmacokinetics of other medicines:

The gastric acid suppression during treatment with NEXIAM, might decrease or increase the absorption of medicines with a gastric pH dependent absorption. 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). Digoxin toxicity has been reported. Caution should be exercised when NEXIAM is given at high doses in elderly patients. Therapeutic monitoring of digoxin levels should be done.

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 elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range.

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 co-administered with NEXIAM at initiation of treatment, during the treatment and at ending treatment.

Results from studies in healthy subjects have shown a pharmacokinetic/ pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of

clopidogrel by an average of 40 % and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14 %.

Based on these data, concomitant use of NEXIAM and clopidogrel should be avoided.

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.
NEXIAM can be suspected to have a similar effect.

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 (t½) but no significant increase in peak plasma levels of cisapride. This interaction did not alter the influence of cisapride on cardiac electrophysiology.

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. In high-dose methotrexate administration a temporary withdrawal of NEXIAM may need to be considered.

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

Esomeprazole, as all gastric 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.

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.

Concomitant administration of NEXIAM may significantly reduce the plasma levels of atazanavir.

Omeprazole has been reported to interact with some antiretroviral medicines. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral medicines. 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 esomeprazole and antiretroviral medicines such as atazanavir and nelfinavir is not recommended. NEXIAM substantially decreases the concentration of atazanavir and nelfinavir (see section 4.3).

Co-administration of esomeprazole (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. Co-administration is not recommended. However, if used concurrently, the dose of NEXIAM should be increased.

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 b.i.d.), 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 tripling of the NEXIAM exposure. Dose adjustment of NEXIAM is not required.

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.

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

Safety during pregnancy and lactation has not been established.

4.7 Effects on ability to drive and use machines

NEXIAM 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 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

Clinical trials:

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

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia
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)
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 encephalopathy
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, pruritus, urticaria, rash
	Rare	Alopecia, photosensitivity
Musculoskeletal and connective tissue disorders	Uncommon	Fracture of the hip, wrist or spine (see section 4.4)
	Rare	Arthralgia, myalgia
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.

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, severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia.

Psychiatric disorders:

Insomnia, agitation, confusion, depression, aggression, hallucination

Nervous system disorders:

Headache, dizziness, paraesthesia, somnolence, taste disturbance

Eye disorders:

Blurred vision

Ear and labyrinth disorders:

Vertigo

Respiratory, thoracic and mediastinal disorders:

Bronchospasm

Gastrointestinal disorders:

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

Hepatobiliary disorders:

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

Skin and subcutaneous tissue disorders:

Dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity, 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:

Arthralgia, myalgia, muscular weakness

Renal and urinary disorders:

Interstitial nephritis

Reproductive system and breast disorders:

Gynaecomastia

General disorders and administration site conditions:

Malaise, hyperhydrosis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of NEXIAM is important. It allows continued monitoring of the benefit/risk balance of NEXIAM. 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. 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.

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 specific inhibition of 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 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.

Pharmacodynamic effects

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

Other effects related to acid inhibition

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.

5.2 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 per hour after a single dose and about 9 litres per 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.

Linearity/non-linearity

The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg b.i.d. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC 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.

Special patient populations

Poor metabolisers

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 %.

Elderly

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

Gender

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.

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 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.

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.

Paediatric population

Following repeated dose administration of 20 mg and 40 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma concentration (t_{max}) in 12 – 18 year-olds was similar to that in adults for both esomeprazole doses.

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol monostearate

Hypromellose

Iron oxide, reddish brown (20 mg and 40 mg Tablets)

Iron oxide, yellow (20 mg Tablet)

Magnesium stearate

Methacrylic acid-ethyl acrylate copolymer

Microcrystalline cellulose

Synthetic paraffin

Macrogol

Crospovidone

Hydroxypropylcellulose

Polysorbate 80

Sugar spheres (sucrose and maize starch)

Sodium stearyl fumarate

Talc

Triethyl citrate

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C. Store in a dry place. Keep the container tightly closed (bottle).

6.5 Nature and contents of container

White HDPE bottles (with desiccated caps) of 2, 5, 7, 14, 15, 28, 30, 56, 60, 100 tablets.

PVC/aluminium blister packages of 3, 7, 14, 15, 28, 30, 50, 56, 60, 98, 100 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Ltd

Building 2, Northdowns Office Park

17 Georgian Crescent West

Bryanston, Johannesburg, 2191

South Africa

Tel: 011 797 6000

8. REGISTRATION NUMBERS

NEXIAM 20 mg: 35/11.4.3/0263

NEXIAM 40 mg: 35/11.4.3/0264

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

NEXIAM 20 mg: 20 February 2002

NEXIAM 40 mg: 20 February 2002

10. DATE OF REVISION OF THE TEXT

24 November 2025