Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NEXIPRAZ 20 film-coated tablets

NEXIPRAZ 40 film-coated tablets

2. QUALITATIVE AND QUANTITAIVE COMPOSITION

NEXIPRAZ 20

Each gastric-resistant tablets contains esomeprazole magnesium 20,7 mg equivalent to esomeprazole 20 mg.

Contains 30 mg sugar (sucrose) per tablet

NEXIPRAZ 40

Each gastric-resistant tablets contains esomeprazole magnesium 41,4 mg equivalent to esomeprazole 40 mg.

Contains 60 mg sugar (sucrose) per tablet

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Gastric-resistant tablets

NEXIPRAZ 20

Light brick red to brown coloured, oval, biconvex, film coated tablets with ‘E5’ debossed on one side and plain on the other side.

NEXIPRAZ 40

Light brick red to brown coloured, oval, biconvex, film coated tablets with ‘E6’ debossed on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gastric-oesophageal Reflux Disease (GORD):

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

Patients requiring continued NSAID therapy:

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

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

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

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

4.2 Posology and method of administration

Posology

Gastric-oesophageal Reflux Disease (GORD)

Erosive reflux oesophagitis: 40 mg once daily for 4 weeks. If symptom control has not been achieved after four weeks of treatment with the prescribed daily dose, further investigation is recommended.

Long-term management of patients with healed oesophagitis to prevent relapse: 20 mg once daily

Symptomatic treatment of gastric-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

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

NEXIPRAZ 20 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 **NEXIPRAZ** 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.

Children

As a **NEXIPRAZ** 10 mg dosage form is not available, use in children younger than 12 years of age cannot be recommended.

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 **NEXIPRAZ** 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, substituted benzimidazoles or any other constituents of **NEXIPRAZ** (see section 6.1).

- Co-administration with atazanavir and nelfinavir (see section 4.5)

4.4 Special warnings and precautions for use

NEXIPRAZ is not indicated for mild gastric-intestinal 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 **NEXIPRAZ** 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.

Clostridium difficile associated diarrhoea: Proton pump inhibitors (PPI) therapy like esomeprazole as in **NEXIPRAZ** may be associated with an increased risk of *Clostridium difficile* associated diarrhoea, especially in hospitalised patients. Symptoms include watery diarrhoea, stomach pain and fever. This diagnosis should be considered for diarrhoea that does not improve. Patients should use the lowest dose and shortest duration of **NEXIPRAZ** therapy appropriate to the condition being treated.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole as in **NEXIPRAZ** 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 dysarrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. Severe hypomagnesaemia can correlate with hypocalcaemia and may also be associated with hypokalaemia.

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

Risk of fracture

Proton pump inhibitors, especially if used in high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10 – 40 %. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Subacute cutaneous lupus erythematosus (SCLE):

Proton pump inhibitors are associated with infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping **NEXIPRAZ.** SLCE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Helicobacter pylori eradication

When prescribing **NEXIPRAZ** for eradication of Helicobacter pylori possible interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contra-indications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other medicines metabolised via CYP3A4 such as cisapride.

Gastrointestinal infections

Treatment with proton pump inhibitors may lead to slightly increased risk of gastric intestinal infections such as Salmonella and Campylobacter.

Renal failure

Interstitial nephritis may progress to chronic renal inflammation and renal failure as it is not necessarily reversed when treatment is discontinued.

Absorption of vitamin B12

NEXIPRAZ 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.

Sucrose

NEXIPRAZ contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take **NEXIPRAZ.**

Sucrose may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Effects of NEXIPRAZ on the pharmacokinetics of other medicines

Clopidogrel

Studies in healthy subjects have shown that concomitant use of esomeprazole and clopidogrel resulted in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. An increase in cardiovascular events has also been reported. Concomitant use of **NEXIPRAZ** and clopidogrel should be avoided

Atazanavir & nelfinavir

Esomeprazole decreases the concentration of atazanavir and nelfinavir. Co-administration of **NEXIPRAZ** and atazanavir or nelfinavir is contra-indicated (see section 4.3).

Methotrexate

When given together with PPIs in **NEXIPRAZ** methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of **NEXIPRAZ** may need to be considered.

Tacrolimus

Concomitant administration of esomeprazole as in **NEXIPRAZ** has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

Medicines with pH dependent absorption

The decreased intragastric acidity during treatment with **NEXIPRZ**, might increase or decrease the absorption of medicines if the mechanism of absorption is influenced by gastric acidity. The absorption of ketoconazole, itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with **NEXIPRAZ**. Caution should be exercised when **NEXIPRAZ** is given at high doses in elderly patients. Therapeutic monitoring of digoxin should be reinforced.

Medicines metabolised by CYP2C19

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with medicines metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these medicines may be increased and a dose reduction could be needed. This should be considered especially when prescribing **NEXIPRAZ** for on demand therapy.

Diazepam

Concomitant administration of 30 mg esomeprazole resulted in a 45 % decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13 % increase in trough plasma levels of phenytoin in epileptic patients; dose adjustment was not required.

Voriconazole

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

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. 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.

Warfarin

Concomitant 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, as with all patients receiving warfarin, monitoring is recommended during concomitant treatment with **NEXIPRAZ.**

Cisapride

In healthy volunteers, concomitant 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 (t1/2) but no significant increase in peak plasma levels of cisapride. This interaction did not alter the influence of cisapride on cardiac electrophysiology.

Effect of other medicines on the pharmacokinetics of esomeprazole:

Medicines which inhibit CYP2C19 and/or CYP3A4

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of **NEXIPRAZ** is not required.

Medicines which induce CYP2C19 and/or CYP3A4

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety during pregnancy has not been established.

Breastfeeding

Safety during breastfeeding has not been established.

Fertility

No available data

4.7 Effects on ability to drive and use machines

NEXIPRAZ may cause somnolence, dizziness and blurred vision. As concentration may be impaired, patients should be advised to exercise caution when driving or operating machinery (see section 4.8).

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 list of adverse reactions

Table 1

System Organ Class	Frequent	Less Frequent	Frequency Unknown
Infections and infestations		*Clostridium difficile* associated diarrhoea.	
Blood and the lymphatic system disorders		Agranulocytosis, leucopoenia, thrombocytopenia, pancytopenia.	

Immune system disorders		Hypersensitivity reactions e.g. angioedema, anaphylactic reaction.	
Metabolism and nutrition disorders		Hyponatraemia.	Hypomagnesaemia (see section 4.4) severe hypomagnesaemia can correlate with hypocalcaemia Hypomagnesaemia may also be associated with hypokalaemia.
Nervous system disorders	Headache	Dizziness, somnolence paraesthesia	
Psychiatric disorders		Insomnia, reversible confusional state, agitation, hallucinations, depression, and aggression	
Eye disorders		Blurred vision	
Respiratory, thoracic and mediastinal disorders		Bronchospasm	
Gastric-intestinal disorders	Abdominal pain, diarrhoea, flatulence, nausea / vomiting, constipation	Dry mouth, stomatitis, taste disturbances, gastric-intestinal candidiasis	
Hepato-biliary disorders		Increased liver enzymes, hepatitis with or without jaundice.	Hepatic encephalopathy, hepatic failure
Skin and subcutaneous tissue disorders	Skin rashes	Dermatitis, pruritus, urticaria, alopecia, bullous eruption, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity	
Musculoskeletal connective tissue and bone disorders		Arthralgia, myalgia, fracture of hip, wrist or spine or muscular weakness.	
Renal and urinary disorders		Interstitial nephritis, renal failure	

Reproductive system and breast disorders		Impotence, gynaecomastia	
General disorders and administration site condition		Fatigue, increased sweating, malaise	

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine 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 '6.04 Adverse Drug Reaction Reporting form', found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/index/8

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

Pharmacotherapeutic group: Drugs for acid-related disorders proton pump inhibitors.

ATC code: A02B C05

Pharmacological classification: A 11.4.3 Medicines acting on gastric-intestinal tract. Other.

Esomeprazole, the S-isomer of omeprazole, a proton pump inhibitor (PPI); 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 esomeprazole 20 mg 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 Gastric-oesophageal Reflux Disease (GORD) patients.

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

Food intake has 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.

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

Esomeprazole is acid labile and is administered orally as enteric-coated tablets*. 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.

Distribution

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

Biotransformation

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.

Elimination

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 per hour after repeated administration. The plasma elimination half-life is about 1,3 hours after repeated once-daily dosing. 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 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.

Special populations:

Lack of a functional CYP2C10 enzyme

Approximately 1-2 % 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 is 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.

Mild to moderate liver 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.

Impaired renal function

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The active substance is esomeprazole magnesium 20,7 mg and 41,4 mg equivalent to esomeprazole 20 mg and 40 mg respectively.

The other ingredients are sucrose, crospovidone, diethlyphthalate, hydroxypropyl cellulose, hypromellose phthalate, polyethylene glycol, purified talc, microcrystalline cellulose, povidone and sodium stearyl fumarate. Film coating material: Opadry brown, polyethylene glycol.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at or below 25 °C, protect from moisture.

Do not remove the blisters from the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Blister pack

The carton contains 14, 28 or 30 tablets packed in cold form blister strips or desiccant embedded cold form blister strips. Each blister strip contains 7 or 10 tablets.

Plastic HDPE bottle

The carton contains a white opaque HDPE bottle with screw cap closure containing 30 tablets.

Description of desiccant embedded cold form blister pack

Cold forming laminate composed of aluminium foil of one side bright, soft tempered, plain, dull side lacquer laminated to oriented polyamide film; other side extrusion coated with desiccant embedded polyethylene and further having an outer layer of HDPE with lidding foil.

Description of cold form blister pack

Cold form Blister pack comprise of cold form blister laminate composed of aluminium foil (one side bright, soft tempered, plain; dull side lacquer laminated to oriented polyamide film; bright side lacquer laminated to PVC film), PVC and polyamide with a backing of aluminium foil coated with heat seal lacquer.

Description of HDPE Bottle pack

The bottle is a white, opaque HDPE bottle with white opaque polypropylene screw cap closure having induction seal liner. Bottle also contains a desiccant sachet (1g).

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

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Stormill Ext.1

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South Africa

8 REGISTRATION NUMBER(S)

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Sign: PM