**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

14 Lautre Road

Stormill Ext.1

Roodepoort, 1724

South Africa

## 8 REGISTRATION NUMBER(S)

**NEXIPRAZ 20**: 45/11.4.3/0125

**NEXIPRAZ 40**: 45/11.4.3/0126

## 9 DATE OF FIRST AUTHORISATION

02 October 2014

## 10 DATE OF REVISON OF THE TEXT

14 August 2022

**Namibia:**

NS2

**Nexipraz 20: Registration No. 15/11.4.3/0002**

**Nexipraz 40: Registration No. 15/11.4.3/0001**

**Professionele Inligting**

**SKEDULERINGSTATUS**

S4

## 1. NAAM VAN DIE MEDISYNE

**NEXIPRAZ 20** filmbedekte tablette

**NEXIPRAZ 40** filmbedekte tablette

## 2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

**NEXIPRAZ 20**

Elke gastries-weerstandbiedende tablet bevat esomeprasoolmagnesium 20,7 mg gelykstaande aan esomeprasool 20 mg.

Bevat 30 mg suiker (sukrose) per tablet

**NEXIPRAZ 40**

Elke gastries-weerstandbiedende tablet bevat esomeprasoolmagnesium 41,4 mg gelykstaande aan esomeprasool 40 mg.

Bevat 60 mg suiker (sukrose) per tablet

Vir volledige lys van hulpstowwe, sien afdeling 6.1

## 3. FARMASEUTIESE VORM

Gastries-weerstandbiedende tablette

**NEXIPRAZ 20**

Ligte baksteenrooi tot bruinkleurige, ovaal, bikonvekse, filmbedekte tablette met 'E5' gepers aan die een kant en skoon aan die ander kant.

**NEXIPRAZ 40**

Ligte baksteenrooi tot bruinkleurige, ovaal, bikonvekse, filmbedekte tablette met 'E6' gepers aan die een kant en skoon aan die ander kant.

## 4. KLINIESE BESONDERHEDE

### 4.1 Terapeutiese indikasies

*Gastro-esofageale refluksiekte (GERS):*

- behandeling van eroderende refluksesofagitis
- langtermynbehandeling van pasiënte met geneesde esofagitis om 'n terugval te voorkom
- simptomatiese behandeling van gastro-esofageale reflukssiekte (GERS),

*Pasiënte wat voortdurende NSAIM-behandeling benodig:*

- voorkoming van gastriese en duodenale ulkusse geassosieer met nie-stereodale anti-inflammatoriese middel (NSAIM)-behandeling by risiko-pasiënte.

*In kombinasie met toepaslike antibakteriële regimens vir die uitwissing van Helicobacter pylori:*

- genesing van duodenale ulkus vanweë *Helicobacter pylori*
- voorkoming van terugkeer van 'n peptiese ulkus vanweë *Helicobacter pylori* by pasiënte met sodanige siekte.

**NEXIPRAZ** is gebruik in patologiese hipersekretoriese toestande insluitend Zollinger-Ellison-sindroom en idiopatiese hiperafskeiding.

**4.2 Posologie en toedieningsmetode**

**Posologie**

***Gastro-esofageale reflukssiekte (GERS)***

*Erosiewe refluks-esofagitis:* 40 mg eenmaal daagliks vir 4 weke. Indien simptoombeheer nie bereik is na vier weke se behandeling met die voorgeskrewe daaglikse dosis nie, word verdere ondersoek aanbeveel.

*Langtermyn hantering van pasiënte met geneesde esofagitis om terugval te voorkom:* 20 mg eenmaal per dag

*Simptomatiese behandeling van gastriese-esofageale refluksiekte (GERS)*: 20 mg eenmaal per dag by pasiënte sonder slukdermontsteking.

Indien simptoombeheer nie na 4 weke bereik is nie, moet die pasiënt verder ondersoek word. Sodra simptome opgelos het, kan daaropvolgende simptoombeheer verkry word deur 'n op aanvraag regimen te gebruik, waar 20 mg eenmaal per dag geneem word, wanneer nodig.

***Pasiënte wat voortgesette NSAIM-behandeling benodig***

Voorkoming van maag- en duodenale ulkusse geassosieer met NSAIM-behandeling by pasiënte op risiko: 20 mg of 40 mg eenmaal per dag.

***In kombinasie met toepaslike antibakteriese terapeutiese regimens vir die uitwissing van Helicobacter pylori***

- genesing van *Helicobacter pylori*-geassosieerde duodenale ulkus
- voorkoming van terugval van peptiese ulkusse by pasiënte met *Helicobacter pylori*-geassosieerde ulkussiekte:

**NEXIPRAZ 20** met 1 g amoksisillien en 500 mg klaritromisien, alles tweemaal per dag vir 7 dae.

***Patologiese hipersekretoriese toestande insluitend Zollinger-Ellison-sindroom en idiopatiese hiperafskeiding***

Die aanbevole aanvanklike dosis is **NEXIPRAZ 40** mg tweemaal per dag. Die dosis moet dan individueel aangepas word en behandeling moet voortgesit word solank as wat klinies aangedui word. Dosisse tot 120 mg tweemaal per dag is toegedien.

***Adolessente 12-18 jaar***

***Gastro-esofageale refluksiekte (GERS)***

*Behandeling van erosiewe refluks-esofagitis*

40 mg eenmaal daagliks vir 4 weke. 'n Bykomende 4 weke behandeling word aanbeveel vir pasiënte by wie slukdermontsteking nie genees het nie of wat aanhoudende simptome het.

*Langtermyn hantering van pasiënte met geneesde esofagitis om terugval te voorkom*

20 mg eenmaal per dag.

*Simptomatiese behandeling van gastro-esofageale refluksiekte (GERS)*

20 mg eenmaal per dag by pasiënte sonder slukdermontsteking. Indien simptoombeheer nie na 4 weke bereik is nie, moet die pasiënt verder ondersoek word. Sodra simptome opgelos het, kan daaropvolgende simptoombeheer bereik word deur 20 mg eenmaal per dag onder mediese toesig te gebruik.

**Kinders**

Aangesien 'n **NEXIPRAZ** 10 mg doseervorm nie beskikbaar is nie, kan gebruik by kinders jonger as 12 jaar nie aanbeveel word nie.

**Spesiale bevolkings**

*Verswakte nierfunksie*

Dosisaanpassing is nie nodig by pasiënte met verswakte nierfunksie nie. As gevolg van beperkte ondervinding by pasiënte met ernstige nierversaking, moet sulke pasiënte met omsigtigheid behandel word.

*Verswakte lewerfunksie*

Dosisaanpassing is nie nodig by pasiënte met ligte tot matige lewerversaking nie. Vir pasiënte met ernstige lewerversaking moet 'n maksimum daaglikse dosis van 20 mg **NEXIPRAZ** gebruik word.

**Toedieningsmetode**

Die tablette moet heel met vloeistof ingesluk word. Die tablette moet nie gekou of fyngedruk word nie.

Die tablette kan ook in 'n halwe glas nie-koolsuurhoudende water versprei word. Geen ander vloeistowwe moet gebruik word nie. Roer totdat die tablette disintegreer en drink die vloeistof saam met die pille onmiddellik of binne 30 minute. Spoel die glas uit met 'n halwe glas water en drink. Die korrels moet nie gekou of fyngemaak word nie.

Vir pasiënte wat nie kan sluk nie, kan die tablette in nie-koolsuurhoudende water versprei word en deur 'n maagbuis toegedien word.

**4.3 Kontraindikasies**

- Bekende hipersensitiwiteit vir esomeprasool, gesubstitueerde bensimidasole of enige ander bestanddele van **NEXIPRAZ** (sien afdeling 6.1).
- Gesamentlike toediening met atazanavir en nelfinavir (sien afdeling 4.5)

**4.4 Spesiale waarskuwings en voorsorgmaatreë**

**NEXIPRAZ** is nie aangedui vir ligte maagderm-klagtes soos senuweedispepsie nie.

Voor behandeling of in die teenwoordigheid van enige waarskuwingssimptoom (bv. beduidende onbedoelde gewigsverlies, herhalende braking, disfagie, hematemese of

melaena) en wanneer maagseer vermoed of teenwoordig is, die moontlikheid van maligniteit van maagseer of 'n kwaadaardige siekte van die slukderm moet uitgesluit word aangesien die behandeling met **NEXIPRAZ** die simptome van kwaadaardige ulkusse kan verlig en dus die diagnose kan vertraag.

Pasiënte op langtermynbehandeling (veral dié wat vir meer as 'n jaar behandel word) moet gereeld onder toesig gehou word.

***Clostridium difficile-geassosieerde diarree:*** Protonpompinhibeerders (PPI)-behandeling met esomeprasool soos in **NEXIPRAZ** kan geassosieer word met 'n verhoogde risiko van *Clostridium difficile*-geassosieerde diarree, veral in gehospitaliseerde pasiënte. Simptome sluit in waterige diarree, maagpyn en koors. Hierdie diagnose moet oorweeg word vir diarree wat nie verbeter nie. Pasiënte moet die laagste dosis en kortste duur van **NEXIPRAZ**-behandeling gebruik wat geskik is vir die toestand wat behandel word.

***Hipomagnesemia***

Ernstige hipomagnesemie is aangemeld by pasiënte wat behandel is met protonpompinhibeerders (PPI's) soos esomeprasool in **NEXIPRAZ** vir ten minste drie maande, en in die meeste gevalle vir 'n jaar. Ernstige manifestasies van hipmagnesemie soos moegheid, tetanie, delirium, stuiptrekkings, duiseligheid en ventrikulêre disaritmie kan voorkom, maar hulle kan verraderlik begin en oor die hoof gesien word. In die meeste pasiënte wat aangetas is, het hipogmagnesemie verbeter na magnesiumvervanging en staking van die PPI. Ernstige hipomagnesemie kan met hipokalsemie korreleer en kan ook met hipokalemie geassosieer word.

Vir pasiënte wat verwag word om op langdurige behandeling te wees of wat PPI's saam met digoksien of medisyne gebruik wat hipmagnesemie (bv. diuretika) kan veroorsaak, moet gesondheidswerkers dit oorweeg om magnesiumvlakke te meet voordat PPI-behandeling begin word en periodiek tydens behandeling.

***Risko van fraktuur***

Protonpomp-inhibeerders, veral as dit in hoë dosisse en oor lang duur (> 1 jaar) gebruik word, kan die risiko van heup-, pols- en ruggraatfraktuur matig verhoog, hoofsaaklik by bejaardes of in die teenwoordigheid van ander erkende risikofaktore.

Waarnemingstudies dui daarop dat protonpompinhibeerders die algehele risiko van fraktuur met 10 – 40 % kan verhoog. Sommige van hierdie toename kan as gevolg van ander risikofaktore wees.

Pasiënte met 'n risiko van osteoporose moet sorg ontvang volgens huidige kliniese riglyne en hulle moet 'n voldoende inname van vitamien D en kalsium hê.

***Subakute kutane lupus erythematosus (SCLE)***

Protonpomp-inhibeerders word geassosieer met seldsame gevalle van SCLE.

Indien letsels voorkom, veral in son-blootgestelde areas van die vel, en as dit gepaard gaan met artralgie, moet die pasiënt onmiddellik mediese hulp soek en die gesondheidsorgwerker moet dit oorweeg om **NEXIPRAZ** te stop. SLCE na vorige behandeling met 'n protonpompinhibeerder kan die risiko van SCLE met ander protonpomp-inhibeerders verhoog.

***Helicobacter pylori uitwissing***

Wanneer **NEXIPRAZ** voorgeskryf word vir die uitwissing van *Helicobacter pylori*, moet moontlike interaksies vir alle komponente in die drievoudige behandeling oorweeg word..

Klaritromisien is 'n kragtige inhibeerder van CYP3A4 en daarom moet kontra-indikasies en interaksies vir klaritromisien oorweeg word wanneer die drievoudige behandeling gebruik word by pasiënte wat gelyktydig ander medisyne gebruik wat deur CYP3A4 gemetaboliseer word, soos sisapried.

***Gastrointestinale infeksies***

Behandeling met protonpomp-inhibeerders kan lei tot effens verhoogde risiko van maag-derminfeksies soos *Salmonella* en *Campylobacter*.

***Nierversaking***

Interstisiële nefritis kan vorder tot chroniese nierontsteking en nierversaking aangesien dit nie noodwendig omgekeer word wanneer behandeling gestaak word nie.

***Absorpsie van vitamien B12***

**NEXIPRAZ** kan die absorpsie van vitamien B12 (sianokobalamien) verminder as gevolg van hipo- of achloorhidrie. Dit moet oorweeg word by pasiënte met verminderde liggaamsstore of risikofaktore vir verminderde vitamien B12-absorpsie tydens langtermyn-behandeling.

***Sukrose***

**NEXIPRAZ** bevat sukrose. Pasiënte met seldsame oorerflike toestande soos fruktose-intoleransie, glukose-galaktose wanabsorpsie of sukrase-isomaltase ontoereikendheid moet nie **NEXIPRAZ** neem nie.

Sukrose kan 'n effek hê op die glukemiese beheer van pasiënte met diabetes melitis.

**4.5 Interaksie met ander medisyne en ander vorme van interaksie**

***Effekte van NEXIPRAZ op die farmakokinetika van ander medisyne***

*Klopidogrel*

Studies by gesonde proefpersone het getoon dat die gelyktydige gebruik van esomeprasool en klopidogrel tot verlaagde plasmakonsentrasies van die aktiewe metaboliet van klopidogrel en 'n vermindering in bloedplaatjie-inhibisie gelei het. 'n Toename in kardiovaskulêre gebeure is ook aangemeld. Gelyktydige gebruik van **NEXIPRAZ** en klopidogrel moet vermy word.

*Atazanavir en nelfinavir*

Esomeprazol verlaag die konsentrasie van atazanavir en nelfinavir. Gesamentlike toediening van **NEXIPRAZ** en atazanavir of nelfinavir is teenaangedui (sien afdeling 4.3).

*Metotreksaat*

Wanneer dit saam met PPI's soos in **NEXIPRAZ** gegee word, is gerapporteer dat metotreksaatvlakke in sommige pasiënte toeneem. In hoë-dosis metotreksaat toediening moet 'n tydelike onttrekking van **NEXIPRAZ** dalk oorweeg word.

*Takrolimus*

Daar is gerapporteer dat gelyktydige toediening van esomeprasool soos in **NEXIPRAZ** die serumvlakke van takrolimus verhoog. Verhoogde monitering van takrolimuskonsentrasies

sowel as nierfunksie (kreatinienopruiming) moet uitgevoer word, en die dosis takrolimus moet aangepas word indien nodig.

*Medisyne met pH-afhanklike absorpsie*

Die verlaagde intragastriese suurheid tydens behandeling met **NEXIPRZ** kan die absorpsie van medisyne verhoog of verlaag indien die meganisme van absorpsie deur maagsuur beïnvloed word. Die absorpsie van ketokonasool, itrakonasool en erlotinib kan afneem en die absorpsie van digoksien kan toeneem tydens behandeling met **NEXIPRAZ**. Omsigtigheid moet aan die dag gelê word wanneer **NEXIPRAZ** teen hoë dosisse aan bejaarde pasiënte gegee word. Terapeutiese monitering van digoksien moet versterk word.

*Medisyne wat deur CYP2C19 gemetaboliseer word*

Esomeprazol inhibeer CYP2C19, die belangrikste esomeprazol-metaboliserende ensiem. Dus, wanneer esomeprasool gekombineer word met medisyne wat deur CYP2C19 gemetaboliseer word, soos diasepam, citalopram, imipramien, klomipramien, fenitoïen ens., kan die plasmakonsentrasies van hierdie medisyne verhoog word en 'n dosisvermindering kan nodig wees. Dit moet veral in ag geneem word wanneer **NEXIPRAZ** vir op aanvraag behandeling voorgeskryf word.

*Diasepam*

Gelyktydige toediening van 30 mg esomeprasool het gelei tot 'n 45 % afname in opruiming van die CYP2C19 substraat diasepam.

*Fenitoïen*

Gelyktydige toediening van 40 mg esomeprasool het gelei tot 'n 13 % toename in die laagste plasmavlakke van fenitoïen by epileptiese pasiënte; dosisaanpassing was nie nodig nie.

*Vorikonasool*

Omeprasool (40 mg eenmaal daagliks) het vorikonasool ('n CYP2C19-substraat) $C_{max}$ en AUC met onderskeidelik 15 % en 41 % verhoog.

*Cilostazol*

Omeprasool sowel as esomeprasool dien as inhibeerders van CYP2C19. Omeprasool, gegee in dosisse van 40 mg aan gesonde proefpersone in 'n oorkruisstudie, het $C_{max}$ en

AUC vir cilostazol met onderskeidelik 18 % en 26 % verhoog, en een van sy aktiewe metaboliete met onderskeidelik 29 % en 69 %.

*Warfarien*

Gelyktydige toediening van 40 mg esomeprasool aan warfarien-behandelde pasiënte het getoon dat, ten spyte van 'n effense verhoging in die laagste plasmakonsentrasie van die minder kragtige R-isomeer van warfarien, die stollingstye binne die aanvaarde reeks was. Soos met alle pasiënte wat warfarien ontvang, word monitering egter aanbeveel tydens gelyktydige behandeling met **NEXIPRAZ**.

*Sisapried*

By gesonde vrywilligers het gelyktydige toediening van 40 mg esomeprasool gelei tot 'n 32 % toename in area onder die plasma konsentrasie-tyd kurwe (AUC) en 'n 31 % verlenging van eliminasie halfleeftyd ($t_{1/2}$), maar geen beduidende toename in piek plasmavlakke van sisapried nie. Hierdie interaksie het nie die invloed van sisapried op kardiale elektrofisiologie verander nie.

***Effek van ander medisyne op die farmakokinetika van esomeprasool***:

*Medisyne wat CYP2C19 en/of CYP3A4 inhibeer*

Esomeprasool word gemetaboliseer deur CYP2C19 en CYP3A4. Gelyktydige toediening van esomeprasool en 'n CYP3A4-remmer, klaritromisien (500 mg twee keer per dag), het gelei tot 'n verdubbeling van die blootstelling (AUC) aan esomeprasool. Dosisaanpassing van **NEXIPRAZ** is nie nodig nie.

*Medisyne wat CYP2C19 en/of CYP3A4 induseer*

Medisyne wat bekend is om CYP2C19 of CYP3A4 of albei te induseer (soos rifampisien en St John's wort) kan lei tot verlaagde esomeprasool serumvlakke deur die esomeprasoolmetabolisme te verhoog.

**4.6 Vrugbaarheid, swangerskap en borsvoeding**

**Swangerskap**

Veiligheid tydens swangerskap is nie vasgestel nie.

**Borsvoeding**

Veiligheid tydens borsvoeding is nie vasgestel nie.

**Vrugbaarheid**

Geen beskikbare data nie.

**4.7 Effekte op die vermoë om te bestuur en masjiene te gebruik**

**NEXIPRAZ** kan slaperigheid, duiseligheid en versteurde visie veroorsaak. Aangesien konsentrasie verswak kan word, moet pasiënte aangeraai word om versigtig te wees wanneer hulle bestuur of masjinerie gebruik (sien afdeling 4.8).

**4.8 Ongewenste effekte**

**Opsomming van die veiligheidsprofiel**

Hoofpyn, abdominale pyn, diarree en naarheid is van die nadelige reaksies wat die meeste in kliniese proewe (en ook van post-bemarking gebruik) aangemeld is. Daarbenewens is die veiligheidsprofiel soortgelyk vir verskillende formulerings, behandelingsindikasies, ouderdomsgroepe en pasiëntpopulasies. Geen dosisverwante nadelige reaksies is geïdentifiseer nie.

**Getabelleerde lys van nadelige reaksies**

**Tabel 1**

| Stelsel Orgaanklas | Dikwels | Minder Dikwels | Frekwensie Onbekend |
|---|---|---|---|
| **Infeksies en besmettings** | | *Clostridium difficile*-geassosieerde diarree. | |
| **Bloed en die limfatiese stelsel versteurings** | | Agranulositose, leukopenie, trombositopenie, pansitopenie. | |
| **Immuunstelsel-afwykings** | | Hipersensitiwiteits-reaksies bv. angioedeem, anafilaktiese reaksie. | |
| **Metabolisme en voedingsafwy-kings** | | Hiponatraemia. | Hipomagne-semie (sien afdeling 4.4) ernstige hipomagne-semie kan met hipokalsemie korreleer. Hipomagne-semie kan ook met hipokalemie geassosieer word. |

| | | | |
|---|---|---|---|
| **Senuweestelsel versteurings** | Hoofpyn | Duiseligheid, slaperigheid parestese | |
| **Psigiatriese versteurings** | | Slapeloosheid, omkeerbare verwarringstoe-stand, agitasie, hallusinasies, depressie en aggressie | |
| **Oogafwykings** | | Versteurde visie | |
| **Respiratoriese torakale en mediastinale afwykings** | | Bronchospasma | |
| **Gastries-intestinale afwykings** | Buikpyn, diarree, winderigheid, naarheid / braking, hardlywigheid | Droë mond, stomatitis, smaakversteurings, maagderm candidiasis | |
| **Hepato-galafwykings** | | Verhoogde lewerensieme, hepatitis met of sonder geelsug. | Hepatiese enkefalopatie, lewerversaking |
| **Vel- en subkutane weefselafwy-kings** | Veluitslag | Dermatitis, pruritus, urtikaria, alopesie, bulleuse uitbarsting, erythema multiforme, Stevens-Johnson-sindroom, toksiese epidermale nekrolise, fotosensitiwiteit. | |
| **Muskuloskele-tale, bindweefsel - en beenafwykings** | | Artralgie, mialgie, fraktuur van heup, pols of ruggraat of spierswakheid. | |
| **Nier- en urinêre afwykings** | | Interstisiële nefritis, nierversaking. | |
| **Voortplanting-stelsel en borsversteu-rings** | | Impotensie, ginekomastie | |
| **Algemene versteurings en toedieningsplek toestand** | | Moegheid, verhoogde sweet, malaise | |

### Rapportering van vermoedelike nadelige reaksies:

Dit is belangrik om vermoedelike nadelige reaksies aan te meld na goedkeuring van die medisyne. Dit laat voortgesette monitering van die voordeel/risiko-balans van die medisyne toe. Gesondheidsorgverskaffers word gevra om enige vermeende nadelige reaksies by

SAHPRA aan te meld via die '6.04 Adverse Drug Reaction Reporting form', wat aanlyn gevind word onder SAHPRA se publikasies:

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

**4.9 Oordosis**

Geen spesifieke teenmiddel is bekend nie. Esomeprasool is omvattend plasmaproteïengebonde en is dus nie geredelik dialiseerbaar nie. Soos in enige geval van oordosis, moet behandeling simptomaties wees en algemene ondersteunende maatreëls moet gevolg word.

## 5 FARMAKOLOGIESE EIENSKAPPE

### 5.1 Farmakodinamiese eienskappe

Farmakoterapeutiese groep: Middels vir suurverwante afwykings protonpompinhibeerders.

ATC-kode: A02B C05

Farmakologiese klassifikasie: A 11.4.3 Medisyne wat op maag-dermkanaal inwerk. Ander.

Esomeprasool, die S-isomeer van omeprasool, 'n protonpompinhibeerder (PPI); verminder maagsuurafskeiding deur spesifieke inhibisie van die suurpomp in die pariëtale sel, waar dit gekonsentreer en omgeskakel word na die aktiewe vorm in die suur omgewing van die sekretoriese canaliculi en inhibeer die ensiem $H^+K^+$-ATPase – die suurpomp. Hierdie effek op die finale stap van die maagsuurafskeiding is dosisafhanklik en maak voorsiening vir effektiewe inhibisie van beide basale en gestimuleerde suurafskeiding.

***Effek op maagsuurafskeiding***

Na orale toediening met esomeprasool 20 mg en 40 mg vind die effek binne 1 uur plaas. Na herhaalde toediening met esomeprasool 20 mg eenmaal per dag vir 5 dae, word die gemiddelde piek suurproduksie na pentagastrienstimulasie met 90 % verminder, gemeet 6-7 uur na toediening op dag 5.

Na 5 dae van orale toediening met 20 mg en 40 mg esomeprasool, is intragastriese pH bo 4 gehandhaaf vir 'n gemiddelde tyd van 13 uur en 17 uur, onderskeidelik oor 24 uur in simptomatiese Maag-esofageale Reflukssiekte (GERS) pasiënte.

Deur AUC as 'n surrogaatparameter vir plasmakonsentrasie te gebruik, is 'n verband tussen inhibisie van suurafskeiding en blootstelling getoon.

Voedselinname het geen noemenswaardige invloed op die effek van esomeprasool op intragastriese suurheid nie.

***Ander effekte wat verband hou met suurinhibisie***

Tydens behandeling met antisekretoriese medisyne neem serumgastrien toe in reaksie op die verminderde suurafskeiding.

Tydens langtermynbehandeling met antisekretoriese medisyne kom maagklier siste voor. Hierdie veranderinge is 'n fisiologiese gevolg van uitgesproke inhibisie van suurafskeiding, dit is nie-kwaadaardig en blyk omkeerbaar te wees.

## 5.2 Farmakokinetiese eienskappe

***Absorpsie***

Esomeprasool is suurlabiel en word oraal toegedien as enteries-bedekte tablette. *In vivo* omskakeling na die R-isomeer is weglaatbaar. Absorpsie van esomeprasol is vinnig, met piekplasmavlakke wat ongeveer 1-2 uur na dosis voorkom.

Die absolute biobeskikbaarheid is 89 % na herhaalde een-daagse toediening.

***Verspreiding***

Die skynbare verspreidingsvolume by bestendige toestand by gesonde proefpersone is ongeveer 0,22 liter/kg liggaamsgewig.

***Biotransformasie***

Esomeprasool word volledig deur die sitochroom P450-stelsel (CYP) gemetaboliseer. Die grootste deel van die metabolisme van esomeprasool is afhanklik van die polimorfiese CYP2C19, wat verantwoordelik is vir die vorming van die hidroksie- en desmetielmetaboliete van esomeprasool.

Die oorblywende deel is afhanklik van 'n ander spesifieke isovorm, CYP3A4, wat verantwoordelik is vir die vorming van esomeprasoolsulfon, die hoofmetaboliet in plasma.

***Eliminasie***

Die parameters hieronder weerspieël hoofsaaklik die farmakokinetika in individue met 'n funksionele CYP2C19-ensiem, uitgebreide metaboliseerders.

Totale plasmaopruiming is ongeveer 17 liter/uur na 'n enkele dosis en ongeveer 9 liter per uur na herhaalde toediening. Die plasma-eliminasiehalfleeftyd is ongeveer 1,3 uur na herhaalde een-daagse toediening. Esomeprasool word heeltemal uit plasma uitgeskei tussen dosisse met geen neiging tot akkumulasie tydens een-daagse toediening nie. Die belangrikste metaboliete van esomeprasool het geen effek op maagsuurafskeiding nie. Byna 80 % van 'n orale dosis esomeprasool word as metaboliete in die urine uitgeskei, die res in die stoelgang. Minder as 1 % van die moederverbinding word in urine aangetref.

***Lineariteit/Nie-lineariteit***

Die area onder die plasmakonsentrasie-tydkurwe neem toe met herhaalde toediening van esomeprasool. Hierdie toename is dosisafhanklik en lei tot 'n nie-lineêre dosis-AUC-verwantskap na herhaalde toediening.

Hierdie tyd- en dosisafhanklikheid is te wyte aan 'n afname in eerste deurgang metabolisme en sistemiese opruiming waarskynlik veroorsaak deur 'n inhibisie van die CYP2C19 ensiem deur esomeprasool en/of sy sulfoonmetaboliet.

**Spesiale bevolkings:**

***Gebrek aan 'n funksionele CYP2C10 ensiem***

Ongeveer 1-2 % van die bevolking het nie 'n funksionele CYP2C19-ensiem nie en word swak metaboliseerders genoem. By hierdie individue word die metabolisme van esomeprasool waarskynlik hoofsaaklik deur CYP3A4 gekataliseer. Na herhaalde een-daagse toediening van 40 mg esomeprasool, is die gemiddelde area onder die plasmakonsentrasie-tydkurwe ongeveer 100 % hoër by swak metaboliseerders as by proefpersone met 'n funksionele CYP2C19-ensiem (ekstensiewe metaboliseerders). Gemiddelde piek plasmakonsentrasies is met ongeveer 60 % verhoog.

***Bejaardes***

Die metabolisme van esomeprasool word nie beduidend verander by bejaarde proefpersone (71-80 jaar oud nie).

***Geslag***

Na 'n enkeldosis van 40 mg esomeprasool is die gemiddelde area onder die plasmakonsentrasie-tydkurwe ongeveer 30 % hoër by vroue as by mans. Geen geslagsverskil word gesien na herhaalde een-daagse toediening nie. Hierdie bevindings het geen implikasies vir die dosis van esomeprasool nie.

***Ligte tot matige lewerversaking***

Die metabolisme van esomeprasool by pasiënte met ligte tot matige lewerversaking kan verswak word. Die metaboliese tempo word verlaag by pasiënte met ernstige lewerversaking, wat lei tot 'n verdubbeling van die area onder die plasmakonsentrasie-tydkurwe van esomeprasool. Daarom moet 'n maksimum van 20 mg nie oorskry word by pasiënte met ernstige versaking nie. Esomeprasool of sy hoofmetaboliete toon geen neiging om te akkumuleer met een keer daaglikse dosis nie.

***Verswakte nierfunksie***

Geen studies is uitgevoer in pasiënte met verminderde nierfunksie nie. Aangesien die nier verantwoordelik is vir die uitskeiding van die metaboliete van esomeprasool, maar nie vir die eliminasie van die moederverbinding nie, word verwag dat die metabolisme van esomeprasool nie verander sal word by pasiënte met verswakte nierfunksie nie.

## 6 FARMASEUTIESE BESONDERHEDE

### 6.1 Lys van hulpstowwe

Die aktiewe bestanddeel is esomeprasoolmagnesium 20,7 mg en 41,4 mg gelykstaande aan esomeprasool 20 mg en 40 mg onderskeidelik.

Die ander hulpstowwe is sukrose, krospovidoon, dietliftalaat, hidroksipropielsellulose, hipromelloseftalaat, polietileenglikool, gesuiwerde talk, mikrokristallyne sellulose, povidoon en natriumstearielfumaraat. Filmbedekkingsmateriaal: Opadry bruin, polietileenglikool.

### 6.2 Onverenigbaarheid

Nie van toepassing nie

### 6.3 Rakleeftyd

36 Maande

## 6.4 Spesiale voorsorgmaatreëls vir berging

Berg by of onder 25 °C, beskerm teen vog.

Moenie die stulpstroke uit die karton verwyder voordat dit benodig word vir gebruik nie.

HOU BUITE BEREIK VAN KINDERS.

## 6.5 Aard en inhoud van houer

***Stulpverpakking***

Die karton bevat 14, 28 of 30 tablette verpak in kouevorm stulpstroke of droogmiddel ingebedde kouevorm stulpstroke. Elke stulpstrook bevat 7 of 10 tablette.

***Plastiek HDPE-bottel***

Die karton bevat ‘n wit ondeursigtige HDPE-bottel met skroefdop sluiting wat 30 tablette bevat.

***Beskrywing van droogmiddelingelegde kouevorm stulpstrook verpakking.***

Kouevorm-laminaat bestaande uit aluminiumfoelie waarvan die een kant helder, saggetemper, effe, dowwe kant lakgelamineer aan georienteerde poliamiedfilm is; die ander kant uitgepers bedek met droogmiddelingelegde poli-etileen en verder het dit 'n buitenste laag van HDPE met 'n foeliebedekking.

***Beskrywing van kouevorm stulpstrook verpakking.***

Die kouevom, stulpverpakking bestaan uit kouevorm stulpstrooklaminaat bestaande uit aluminiumfoelie (eenkant helder, saggetemper, effe, dowweekant lakgelamineer aan georienteerde poliamiedfilm; helderkant lakgelamineer aan PVC-film), PVC en poliamied met 'n rugkant van aluminiumfoelie bedek met hitteseëllak.

***Beskrywing van HDPE-bottelpak***

Die bottel is 'n wit, ondeursigtige HDPE-bottel met 'n wit ondeursigtige polipropileen-skroefdop-sluiting met 'n induksie-seëlvoering. Bottel bevat ook ‘n droogmiddel sakkie (1g).

## 6.6 Spesiale voorsorgmaatreëls vir wegdoening en ander hantering

Geen spesiale vereistes nie.

## 7 HOUER VAN SERTIFIKAAT VAN REGISTRASIE

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Roodepoort, 1724

Suid-Afrika

## 8 REGISTRASIE NOMMER(S)

NEXIPRAZ 20: 45/11.4.3/0125

NEXIPRAZ 40: 45/11.4.3/0126

## 9 DATUM VAN EERSTE MAGTIGING

02 Oktober 2014

## 10 DATUM VAN HERSIENING VAN DIE TEKS

14 Augustus 2022