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Approved Package Insert for NEXIPRAZ IV

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NEXIPRAZ IV powder for solution for injection and infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains esomeprazole sodium equivalent to 40 mg esomeprazole.

NEXIPRAZ IV is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection and infusion.

NEXIPRAZ IV is a white to off-white lyophilised cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NEXIPRAZ IV is indicated for gastro-oesophageal reflux disease (GORD) as an alternative to oral therapy in patients where oral therapy is not appropriate and for the shortest possible time.

Gastro-oesophageal reflux disease (GORD):

- Treatment of erosive reflux oesophagitis
- Long-term management of patients with healed oesophagitis to prevent relapse
- Treatment of severe symptoms of reflux disease.

NEXIPRAZ IV is indicated for short-term maintenance of haemostasis and prevention of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal

ulcers.

4.2 Posology and method of administration

Posology

Adults:

Gastro-oesophageal reflux disease (GORD):

Treatment with NEXIPRAZ IV can be given for up to 7 days as part of a full treatment period for the specified indications. When oral therapy is possible or appropriate, intravenous therapy with NEXIPRAZ IV should be discontinued and the therapy should be continued orally.

Treatment of Erosive reflux oesophagitis:

40 mg once daily.

The duration of treatment should be 4 weeks. An additional 4 weeks treatment is recommended for patients in whom the oesophagitis has not healed or who have persistent symptoms.

Long-term management of patients with healed oesophagitis to prevent relapse and treatment of severe symptoms of reflux disease:

20 mg once daily.

Maintenance of haemostasis and prevention of rebleeding of gastric or duodenal ulcers:

80 mg administered as bolus infusion over 30 minutes followed by a continuous IV infusion of 8 mg/hour given over 3 days.

The parenteral treatment period should be followed by acid-suppression therapy with 40 mg esomeprazole orally once daily for 4 weeks.

Special populations

Elderly:

Dose adjustment is not required in the elderly.

Impaired renal function:

Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution.

Impaired hepatic function:

Gastro-oesophageal reflux disease (GORD):

Dose adjustment is not required in patients with mild to moderate liver impairment (Child-Pugh class A, B). For patients with severe liver impairment (Child-Pugh class C), a maximum daily dose of 20 mg of NEXIPRAZ IV should not be exceeded.

Bleeding ulcers:

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, following an initial bolus dose of 80 mg of NEXIPRAZ IV, a continuous IV dose of 4 mg/hour may be sufficient to maintain adequate acid control.

Paediatric population

NEXIPRAZ IV should not be used in children since no data are available.

Method of administration

For information on instructions for preparation or reconstitution, see section 6.6

Injection:

40 mg dose:

The reconstituted solution should be given as an IV injection over a period of at least 3 minutes.

20 mg dose:

Half the reconstituted solution should be given as an IV injection over a period of approximately 3 minutes.

Infusion:

40 mg dose:

The reconstituted solution should be given as an IV infusion over a period of 10 – 30 minutes.

20 mg dose:

Half of the reconstituted solution should be given as an IV infusion over a period of 10 – 30 minutes.

Continuous infusion (40 mg vial):

A solution for infusion is prepared by dissolving the content of 2 vials of 40 mg esomeprazole in up to 100 ml of 0,9 % sodium chloride for IV use.

80 mg bolus dose:

The reconstituted solution containing 80 mg esomeprazole should be given as a continuous IV infusion over 30 minutes.

8 mg/hour dose:

The reconstituted solution should be given as a continuous IV infusion over a period of 71,5 hours (calculated rate of infusion of 8 mg/hour.

4.3 Contraindications

- Hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of NEXIPRAZ IV (see section 6.1).
- Concomitant use with nelfinavir and atazanavir (see section 4.5)

4.4. Special warnings and precautions for use

In the presence of any alarming symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with NEXIPRAZ IV may alleviate symptoms and thereby delay diagnosis.

Concomitant administration of NEXIPRAZ IV with medicines such as atazanavir and nelfinavir is contraindicated (see section 4.5 and 4.3).

Therapeutic medicine monitoring is recommended during concomitant treatment with warfarin.

Other effects related to acid inhibition:

During treatment with NEXIPRAZ IV serum gastrin increases, in response to the decreased acid secretion.

Gastrointestinal infections:

Decreased gastric acidity due to any means including proton pump inhibitors such as NEXIPRAZ IV increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with NEXIPRAZ IV may lead to increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Absorption of vitamin B_{12}:

NEXIPRAZ IV may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} absorption on long-term therapy.

Hypomagnesaemia:

There have been reports of severe hypomagnesaemia in patients treated with proton pump inhibitors (PPIs) like NEXIPRAZ IV 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 NEXIPRAZ IV.

If patients are expected to be on prolonged NEXIPRAZ IV treatment, or given NEXIPRAZ IV with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting NEXIPRAZ IV treatment and periodically during treatment.

Subacute cutaneous lupus erythematosus (SCLE):

Proton pump inhibitors, such as NEXIPRAZ IV, are associated with rare cases of subacute cutaneous lupus erythematosus (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 discontinuation of NEXIPRAZ IV treatment should be considered.

SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Risk of fracture:

NEXIPRAZ IV, especially if used in high doses and over long durations (> 1 year), increases the risk of hip, wrist and spine fracture, predominantly in the elderly or in the presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors increase the overall risk of fracture by 10 – 40 %. Patients at risk of developing osteoporosis should be appropriately managed and they should have an adequate intake of vitamin D and calcium.

Clopidogrel:

NEXIPRAZ IV is a CYP2C19 inhibitor. When starting or ending treatment with NEXIPRAZ IV, the potential for interactions with medicines metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and NEXIPRAZ IV.
Concomitant use of NEXIPRAZ IV and clopidogrel should be discouraged, since the clinical relevance of this interaction is uncertain (see section 4.5).

Chromogranin A (CgA) measurements:

NEXIPRAZ IV treatment may lead to an increased CgA level and interfere with investigations for neuroendocrine tumours. NEXIPRAZ IV treatment should be discontinued for at least 5 days before CgA measurements, in order to avoid this interaction.
If CgA and gastrin levels have not returned to reference range after the initial measurement, measurements should be repeated 14 days after NEXIPRAZ IV treatment has been discontinued.

Renal Failure:

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

Paediatric population

NEXIPRAZ IV should not be used in children, since no data are available.

4.5 Interactions with other medicines and other forms of interaction

Effects of NEXIPRAZ IV on the pharmacokinetics of other medicines:

Protease inhibitors:

Omeprazole has been reported to interact with some antiretroviral medicines. The clinical

importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral medicine. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral medicines, e.g. atazanavir and nelfinavir, decreased serum levels have been reported when given together with esomeprazole and concomitant administration is not recommended. For other antiretroviral medicines, e.g. saquinavir, increased serum levels have been reported. There are also some antiretroviral medicines for which unchanged serum levels have been reported when given with omeprazole. Due to similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with NEXIPRAZ IV and antiretroviral medicines, e.g. atazanavir and nelfinavir is contraindicated (see section 4.3).

Methotrexate:

There have been reports of increased methotrexate levels in some patients when NEXIPRAZ IV was co-administered with methotrexate. In high-dose methotrexate administration, a temporary withdrawal of NEXIPRAZ IV may need to be considered.

Tacrolimus:

Concomitant administration of NEXIPRAZ IV with tacrolimus 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 it may be necessary to adjust the dosage of tacrolimus.

Medicines with pH dependent absorption:

The absorption of ketoconazole, erlotinib and itraconazole can decrease, and the absorption of digoxin can increase during treatment with NEXIPRAZ IV.

Medicines metabolised by CYP2CY19:

NEXIPRAZ IV inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when NEXIPRAZ IV 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.

Diazepam:

Concomitant administration of 30 mg esomeprazole resulted in a 45 % decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

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 in this study. It is recommended to monitor plasma concentrations of phenytoin when treatment with NEXIPRAZ IV is introduced or withdrawn.

Cilostazol:

NEXIPRAZ IV acts as a CYP2C19 inhibitor and may increase AUC for cilostazol and one of its active metabolites.

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, from post-marketed use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending concomitant NEXIPRAZ IV treatment with warfarin or other coumarin derivatives.

Clopidogrel:

Clopidogrel given concomitantly with NEXIPRAZ IV has shown a pharmacokinetic (PK)/ pharmacodynamic (PD) interaction between clopidogrel and NEXIPRAZ IV.

Concomitant use of NEXIPRAZ IV with clopidogrel should be discouraged, as inconsistent data is available with regards to the clinical implications of this PK/PD interaction on cardiovascular events (see section 4.4).

Effects of other medicines on the pharmacokinetics of NEXIPRAZ IV:

Medicines which inhibit CYP2C19 and/or CYP3A4:

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

Concomitant administration of NEXIPRAZ IV and a combined inhibitor of CYP2C19 and CYP3A4, e.g. voriconazole, may result in more than doubling of esomeprazole exposure. However, dose adjustment of NEXIPRAZ IV is not required in either of these situations.

In patients with severe hepatic impairment, and if long-term treatment is indicated, dose adjustment should be considered.

Medicines which induce CYP2C19 and/or CYP3A4:

Medicines known to induce CYP2C19 or CYP3A4 or both, such as St John's wort and rifampicin, may lead to decreased serum levels of NEXIPRAZ IV by increasing the metabolism of NEXIPRAZ IV.

Investigated medicines with no clinically relevant interaction:

Amoxicillin or quinidine:

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

Naproxen or rofecoxib:

Studies evaluating concomitant administration of NEXIPRAZ IV and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.

4.6 Fertility, pregnancy and lactation

Pregnancy

Limited clinical data on exposed pregnancies are available.

A moderate amount of data on pregnant women (between 300 – 1 000 pregnancy outcomes) indicated no malformative or foeto/neonatal toxicity of NEXIPRAZ IV. However, caution should be exercised when prescribing NEXIPRAZ IV to pregnant women.

Breastfeeding

It is not known whether NEXIPRAZ IV is excreted in human breast milk. No studies in lactating women have been performed. Therefore, NEXIPRAZ IV should not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

NEXIPRAZ IV may cause dizziness and blurred vision. Caution is advised before driving a vehicle or operating machinery until the effects of NEXIPRAZ IV are known.

4.8 Undesirable effects

b) Tabulated summary of adverse reactions

System organ class	**Frequency**	**Adverse reactions**
Blood and the	*Less frequent*	Leucopenia, thrombocytopenia,

lymphatic system disorders		agranulocytosis, pancytopenia
Immune system disorders	*Less frequent*	Hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders	*Less frequent* *Frequency unknown*	Peripheral oedema, hyponatraemia Hypomagnesaemia (Severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.)
Psychiatric disorders	*Less frequent*	Insomnia, agitation, confusion, depression, aggression, hallucinations
Nervous system disorders	*Frequent* *Less frequent*	Headache Dizziness, paraesthesia, somnolence, taste disturbance
Eye disorders	*Less frequent*	Blurred vision, eye disorders
Ear and labyrinth disorders	*Less frequent*	Vertigo, tinnitus
Cardiac disorders:	*Frequency unknown*	Angina, tachycardia, bradycardia
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Bronchospasm, coughing

Gastrointestinal disorders	*Frequent*	Abdominal pain, diarrhoea, flatulence, nausea, vomiting, constipation, fundic gland polyps (benign)
	Less frequent	Dry mouth, stomatitis, gastrointestinal candidiasis, pancreatitis
	Frequency unknown	Microscopic colitis
Hepato-biliary disorders	*Less frequent*	Increased liver enzymes, hepatitis with or without jaundice, hepatic failure, hepatic encephalopathy
Skin and subcutaneous tissue disorders:	*Less frequent*	Administration site reactions*, dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, bullous eruption
	Frequency unknown	Subacute cutaneous lupus erythematosus
Musculoskeletal, connective tissue and bone disorders:	*Less frequent*	Arthralgia, myalgia, muscular weakness, fractures of the hip, wrist or spine, back pain
Renal and urinary disorders	*Less frequent*	Interstitial nephritis, urinary disorders, renal failure
Reproductive system and breast disorders	*Less frequent*	Gynaecomastia, impotence

General disorders and administrative site conditions	*Less frequent* *Frequency unknown:*	Fatigue Malaise, hyperhidrosis

*Administration site reactions have mainly been observed in a reported study with high-dose exposure over 3 days (72 hours).

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 Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms of overdosage may be an exaggeration and/or exacerbation of side effects. 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:

A 11.4.3 Medicines acting on gastrointestinal tract. Other.

Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02B C05

Esomeprazole is the *S*-isomer of omeprazole and reduces gastric acid secretion through a specific inhibitor of the enzyme H^+K^+-ATPase, the acid pump in the parietal cell. Both the *R*- and *S*-isomer of omeprazole have similar pharmacodynamic activities.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+K^+-ATPase, the acid pump, and inhibits both basal and stimulated acid secretion. Using area under the curve (AUC) as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

During intravenous administration of 80 mg esomeprazole as a bolus infusion over 30 minutes followed by a continuous intravenous infusion of 8 mg/h for 23,5 hours, intragastric pH above 4, and pH above 6 was maintained for a mean time of 21 hours, and 11 – 13 hours, respectively, over 24 hours.

5.2 Pharmakokinetic Properties

Distribution:

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

Plasma protein binding:

Esomeprazole is 97 % plasma protein bound.

Metabolism and excretion:

Esomeprazole is extensively 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 following parameters reflect mainly the pharmacokinetics in individuals with a functional

CYP2C19 enzyme, i.e. extensive metabolisers.

Total plasma clearance is about 17 litres/hour after a single dose and about 9 litres/hour after repeated administration. The plasma elimination t½ 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 nonlinear 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 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.

Special patient populations:

Elderly:

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

Following a single oral dose of esomeprazole 40 mg, the mean area under the plasma concentration-time curve is approximately 30 % higher in females than in males. No gender difference is seen after repeated once-daily administration. Similar differences have been seen for IV administration of esomeprazole. These findings have no implications for the dosage of esomeprazole.

Renal impairment:

No studies have been performed in patients with decreased renal function. The kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound.

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 (Child-Pugh C) 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 hepatic dysfunction. For patients with bleeding ulcers and severe liver dysfunction, following an initial bolus dose of 80 mg, a maximum continuous IV infusion dose of 4 mg/hour may be sufficient in patients with bleeding ulcers. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Disodium edetate
- sodium hydroxide
- water for injection

6.2 Incompatibilities

The degradation of the reconstituted solution is highly pH dependent and NEXIPRAZ IV must therefore only be reconstituted with 0,9 % sodium chloride for intravenous use according to the instructions in section 4.2. The reconstituted solution should not be mixed or co-administered in the same infusion set with any other medicine.

6.3 Shelf life

24 months

Store at or below 25 °C. Protect from light.

Keep vial in outer carton until required for use.

Reconstituted solution for injection and infusion:

Although chemical and physical stability of reconstituted/diluted solutions have been demonstrated for 12 hours at 30 °C, from a microbiological point of view, the product should be

used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 – 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

For single use only.

Discard any unused portions.

6.4 Special precautions for storage

Store in the original package, in order to protect from light. Vials can however, be stored exposed to normal indoor light outside the box for up to 24 hours .For storage of reconstituted solution, refer to section 6.3 above.

6.5 Nature and contents of container

5 ml colourless type I glass vial with 20 mm grey bromobutyl rubber stopper and a grey flip-off aluminium seal.

Pack size: A carton containing either 1, 5 or 10 vials.

6.6 Special precautions for disposal and other handling

Information on instructions for preparation

Injection:

A solution for injection is prepared by adding 5 ml of 0,9 % sodium chloride for IV use to the vial.

Infusion:

A solution for infusion is prepared by dissolving the content of 1 vial in up to 100 ml of 0,9 % sodium chloride for IV use.

The degradation of the reconstituted solution is highly pH dependent and NEXIPRAZ IV must therefore only be reconstituted with 0,9 % sodium chloride for intravenous use according to the

instructions above. The reconstituted solution should not be mixed or co-administered in the same infusion set with any other medicine.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

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