SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

PENTOZ 20, 20 mg, delayed release film-coated tablet

PENTOZ 40, 40 mg, delayed release film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PENTOZ 20: Each film-coated tablet (enteric coated) contains pantoprazole sodium sesquihydrate equivalent to pantoprazole 20 mg.

PENTOZ 40: Each film-coated tablet (enteric coated) contains pantoprazole sodium sesquihydrate equivalent to pantoprazole 40 mg.

Contains sugar (mannitol).

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

PENTOZ 20: Yellow, round, biconvex, film-coated tablets printed with "P20" on one side with black ink and plain on the other side.

PENTOZ 40: Yellow, round, biconvex, film-coated tablets printed with "P40" on one side with black ink and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PENTOZ 20 is indicated for:

- Symptomatic improvement (e.g. heartburn, acid regurgitation, pain on swallowing) and healing of mild gastro-oesophageal reflux disease (GORD).
- Long term management and prevention of relapse in gastro-oesophageal reflux disease (GORD).

PENTOZ 40 is indicated for:

- Short term treatment of duodenal ulcer, gastric ulcer and reflux oesophagitis. If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori* infection, PENTOZ 40 used in combination with appropriate antibiotics, may be useful.
- Treatment of Zollinger-Ellison syndrome.

4.2 Posology and method of administration

Posology

Mild gastro-oesophageal reflux disease (GORD)

PENTOZ 20: One tablet once daily. A 4-week period is usually required for healing of mild GORD. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Long term management and prevention of relapse in GORD

PENTOZ 20: One tablet once daily is recommended, increased to one PENTOZ 40 once daily if relapse occurs. After healing of the relapse the dose can be reduced to one PENTOZ 20 once daily. Experience with long-term administration is limited.

Gastric ulcer

PENTOZ 40: One tablet once daily for 4 to 8 weeks.

In the case of a suspected gastric ulcer, malignancy of the gastric ulcer should be excluded, as treatment

could conceal the symptoms and may delay diagnosis.

Duodenal ulcer

PENTOZ 40: One tablet once daily. The total duration of treatment should be 2 to 4 weeks. If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori* infection, PENTOZ 40 used in combination with appropriate antibiotics may be useful.

Reflux oesophagitis

PENTOZ 40: One tablet once daily in the morning for 4 to 8 weeks.

Zollinger-Ellison Syndrome

For the management of Zollinger-Ellison syndrome, patients should be started with a daily dose of 80 mg PENTOZ. Thereafter, the dosage can be titrated up or down as needed, using measurements of gastric acid secretion as a guide. With doses above 80 mg daily, the dose should be divided and given twice daily.

Elderly patients

No dosage adjustment is necessary in the elderly.

Impaired renal and liver function

No dosage adjustment is required in the presence of impaired renal function.

A daily dose of one PENTOZ 20 should not be exceeded in patients with mild to moderately severe liver impairment (See Sections 4.4 and 5.2).

Method of administration

PENTOZ should be taken in the morning, swallowed whole with a little water either before or during breakfast.

4.3 Contraindications

Hypersensitivity to pantoprazole, or to any of the ingredients of PENTOZ tablets**.**

Safety in pregnancy and lactation have not been established.

Safety and efficacy in children have not been established.

Severely impaired liver function (See Section 4.4).

Co-administration of atazanavir, nelfinavir and other HIV medicines with pH dependent absorption (See Section 4.5).

4.4 Special warnings and precautions for use

Hypomagnesaemia

Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia have been reported after treatment with PPI's such as PENTOZ for at least 3 months and in most cases for one year. The symptoms may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

Measuring magnesium levels before starting treatment and periodically during treatment is recommended in patients who are expected to require treatment long term (3 months or longer), and particularly in patients who are taking digoxin or other medicines that may cause hypomagnesaemia (e.g. diuretics). The risk of digoxin toxicity may increase.

Clostridium difficile associated diarrhoea (CDAD)

Treatment with proton pump inhibitors such as PENTOZ have been associated with an increased risk of CDAD, especially in hospitalised patients. If a patient develops persistent diarrhoea this diagnosis should be excluded. Patients should be advised not to exceed the recommended dose and duration of treatment.

Diagnosis of reflux oesophagitis

Diagnosis should be confirmed by endoscopy.

Liver impairment

In patients with severe liver impairment, the liver enzymes should be monitored regularly during treatment with PENTOZ, particularly during long term use. In the case of a rise of the liver enzymes, PENTOZ should be discontinued.

Mild gastrointestinal complaints

PENTOZ is not indicated for mild gastro-intestinal complaints such as nervous dyspepsia.

Presence of alarm symptoms e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena)

Prior to treatment, the possibility of malignancy of gastric or duodenal ulcers or malignant disease of the oesophagus should be excluded as treatment with PENTOZ may alleviate the symptoms of malignancy and thus delay diagnosis.

Bone fractures

Observational studies suggest that proton pump inhibitors, such as PENTOZ, especially if used in high doses and over long periods of time (> 1 year), may increase the risk of hip, wrist and spine fracture by 10 to 40 %, mainly in the elderly or in presence of other recognised 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.

Effect on cyanocobalamin (vitamin B12) absorption

Daily treatment with any acid-blocking medicines such as PENTOZ, over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption or if deficiency symptoms are observed.

Gastrointestinal infections caused by bacteria

PENTOZ, as a proton pump inhibitor (PPI), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract and may therefore lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter.*

Co-administration with NSAIDs

The use of PENTOZ to prevent gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory medicines (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications (for example high age - > 65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding)**.**

Acute Tubulointerstitial Nephritis

Acute Tubulointerstitial Nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy.

TIN is characterised by an inflammatory reaction within the tubulointerstitial space of the kidney. Acute interstitial inflammatory reactions are associated with damage to the tubulointerstitium, leading to acute kidney injury.

TIN may be drug-related, infectious, systemic, autoimmune, genetic, and idiopathic with the most common cause being related to a medication or drug exposure.

Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decrease renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extrarenal manifestations (e.g., fever rash or arthralgia).

Discontinue PENTOZ and evaluate patients with suspected acute TIN.

4.5 Interaction with other medicines and other forms of interaction

Concomitant intake of food has no influence on bioavailability.

Digoxin

PENTOZ may increase the availability of digoxin if administered for prolonged periods. Dosage reduction of digoxin may be required.

Decreased absorption of medicines that are gastric pH dependent

The bioavailability of the following medicines may be reduced when co-administered with PENTOZ, thereby impacting on their efficacy e.g.

- some azole antifungals such as ketoconazole, itraconazole and posaconazole;
- other medicines such as erlotinib, ampicillin esters, iron salts;
- atazanavir, nelfinavir and other HIV medicines. If concomitant use is judged unavoidable, close clinical monitoring (e.g. viral load in the case of HIV medicines), is recommended (See ~~"CONTRAINDICATIONS"~~ Section 4.3).

The bio-availability of digoxin may be increased with prolonged concomitant administration of PENTOZ.

Coumarin anticoagulants (e.g. warfarin)

There have been reports of increased PT (Prothrombin Time)/INR (International Normalised Ratio) in patients receiving proton pump inhibitors, including PENTOZ.

Therefore, patients must be advised that additional PT/INR determinations may be required when taking PENTOZ.

Other interactions studies

Pantoprazole, as in PENTOZ, is extensively metabolised in the liver via the cytochrome P450 enzyme system (by CYP2C19 and other metabolic pathways including oxidation by CYP3A4).

Voriconazole

Voriconazole inhibits the metabolism of proton-pump inhibitors: The exposure of both medicines is

increased when PENTOZ is co-administered with voriconazole.

No clinically significant interactions were, however, observed in specific tests with a number of such medicines or compounds, namely antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, warfarin and oral contraceptives.

Methotrexate

Concomitant use of PENTOZ and high doses of methotrexate (e.g. 300 mg daily) is not recommended as proton-pump inhibitors have been reported to increase methotrexate levels in some patients.

Antacids

There were no interactions with concomitantly administered antacids, and with antibiotics (clarithromycin, metronidazole, amoxicillin).

The elimination of diazepam and phenytoin may be prolonged when co-administered with PENTOZ.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and during lactation has not been established.

4.7 Effects on ability to drive and use machines

PENTOZ can cause dizziness and blurred vision.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, while taking PENTOZ.

4.8 Undesirable effects

Infections and Infestations

Frequency not known: Clostridium difficile associated diarrhoea and increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter.*

Blood and lymphatic system

Less frequent: Agranulocytosis, leukopenia, thrombocytopenia, pancytopenia.

Gastro-intestinal disorders

Frequent: Gastrointestinal complaints such as upper abdominal pain, diarrhoea, constipation, flatulence.

Less frequent: Nausea, vomiting, dry mouth.

General disorders and administration site conditions

Less frequent: Asthenia, fatigue, malaise, peripheral oedema.

Immune system disorders

Less frequent: Hypersensitivity including anaphylactic reactions and anaphylactic shock, allergic reactions such as pruritus, skin rash, urticaria and angioedema.

Hepatobiliary disorders

Frequency unknown: Severe hepatocellular damage leading to jaundice with or without hepatic failure.

Investigations

Less frequent: Increased liver enzymes (transaminases, γ-GT), hyperlipidaemias and lipid increases (elevated triglycerides), weight changes, increased bilirubin.

Frequency unknown: Hypomagnesaemia, hyponatraemia.

Metabolic disorders

Less frequent: Increased body temperature.

Musculoskeletal, connective tissue and bone disorders

Less frequent: Arthralgia, myalgia, increased risk of hip, wrist and spine fractures.

Nervous System disorders

Frequent: Headache.

Less frequent: Dizziness, taste disorders.

Eye disorders

Less frequent: Vision disturbances (blurred vision).

Psychiatric disorders

Less frequent: Mental depression, sleep disorders, disorientation/confusion.

Frequency unknown: Hallucinations.

Renal and urinary system disorders

Less frequent: Interstitial nephritis.

Skin and subcutaneous tissue disorders

Less frequent: Severe skin reactions such as Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis (TEN) (Lyell syndrome) and photosensitivity.

Reproductive system and breast disorders

Frequency unknown: Gynaecomastia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. 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

There are no known symptoms of overdosage in man. No specific therapeutic recommendation can be made in cases of overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

11.4.3 Medicines acting on the gastrointestinal tract – Other

Pantoprazole is a proton pump inhibitor i.e. it inhibits specifically and dose-proportionally H^+, K^+-ATPase, the enzyme responsible for gastric acid secretion in the parietal cells of the stomach.

Pantoprazole is a substituted benzimidazole which accumulates in the acidic compartment of the parietal cells after absorption.

In the parietal cell it is protonated and chemically re-arranged to the active inhibitor, a cyclic sulphenamide, which binds to the H^+, K^+-ATPase, thus inhibiting the proton pump and causing

suppression of stimulated and basal gastric acid secretion after single and multiple intravenous and oral pantoprazole dosing.

Because pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus.

Pantoprazole exerts its full effect in a strongly acidic environment (pH < 3) and remains mostly inactive at higher pH values, which explains its selectivity for the acid secreting parietal cells of the stomach.

Therefore, the complete pharmacological and therapeutic effect for pantoprazole can only be achieved in the acid-secreting parietal cells.

By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

Effect on gastric acid secretion

Following oral administration, pantoprazole inhibits the pentagastrin-stimulated gastric acid secretion. The mean acid inhibition is 85 %, 2½ to 3½ hours after dosing with pantoprazole 40 mg per day for 7 days.

After stopping the administration of pantoprazole, there is no evidence of rebound hyper-secretion and 7 days after administering the last dose the acid output is normal.

Although pantoprazole has a half-life of approximately 1 hour, the anti-secretory effect increases during repeated once daily administration, demonstrating that the duration of action markedly exceeds the serum elimination half-life.

5.2 Pharmacokinetic properties

Absorption

Pantoprazole is unstable in acid and is administered orally in the form of an enteric-coated delayed release tablet. Absorption takes place in the small intestine.

In a crossover fed bioequivalence study conducted in 52 healthy adult human volunteers, the mean

values (± SD) of the pharmacokinetic parameters (T_{max}, C_{max}, AUC_{0-t} and $T_{1/2}$) of pantoprazole were 5,538 (± 1,2201) hr, 2772,887 (± 990,2138) ng/ml, 10985,420 (± 10274,0358) ng.hr/ml), 3,643 (± 5,6228) hr., respectively.

In a crossover fasting bioequivalence study conducted in 42 healthy adult human volunteers, the mean values (± SD) of the pharmacokinetic parameters (T_{max}, C_{max}, AUC_{0-t} and $T_{1/2}$) of pantoprazole were 3,166 (± 0,9477) hr, 3031,755 (± 936,9575) ng/ml, 10660,574 (± 8351,7563) ng.hr/ml), 2,746 (± 2,5280) hr., respectively.

The plasma kinetics of pantoprazole, after oral administration, is linear over the dose range 10 to 80 mg.

Metabolism

Pantoprazole is extensively metabolised in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.

Elimination

Renal elimination represents the most important route of excretion (approximately 80 %) for the metabolites of pantoprazole.

The balance is excreted with the faeces.

The half-life of the main metabolite is approximately 1,5 hours which is slightly longer than that of pantoprazole.

Pharmacokinetic profile in patients with impaired liver or renal function

For patients with mild to moderately severe hepatic cirrhosis, the elimination half-life values increase from 1 hour to between 7 to 9 hours. The AUC values increase by a factor of 5 to 8, while the maximum serum concentration only increases by a factor of 1,5 in comparison with healthy subjects.

In patients with renal impairment, the half-life of the main metabolite is moderately increased but there is no accumulation at therapeutic doses. The half-life of pantoprazole in patients with renal impairment is

comparable to the half-life of pantoprazole in healthy subjects. Pantoprazole is poorly dialysed.

A slight increase in AUC and C_{max} occurs in elderly volunteers compared with younger people.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium stearate

Crospovidone

Hydroxypropyl cellulose

Methacrylic acid/ethyl acrylate copolymer

Sodium carbonate anhydrous

Talc

Titanium dioxide

Triethyl citrate

Zein.

<u>The film-coating contains:</u>

Hydroxypropyl methylcellulose

Polyethylene glycol (macrogol)

Synthetic yellow iron oxide

Titanium dioxide.

<u>The black printing ink contains:</u>

Ammonium hydroxide (trace amounts)

Iron oxide black

Propylene glycol

Shellac.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep tablets in the original container and keep containers tightly closed.

Keep the tablets in the blister and the blisters in the carton until required for use.

6.5 Nature and contents of container

The film-coated tablets (30, 90, 100, 500, or 1000) are packed in white HDPE containers. The containers with 30 and 90 tablets have child-resistant, white plastic caps with opening instructions on the top and are packed in cardboard cartons. The containers with 100, 500, or 1000 have white, ribbed, plastic caps with smooth tops.

The film-coated tablets (7, 14 and 10) are packed in silver coloured aluminium/aluminium laminate (polyamide /aluminium/PVC) blister strips then packed in cardboard cartons.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8 REGISTRATION NUMBER(S)

PENTOZ 20: 41/11.4.3/0641

PENTOZ 40: 41/11.4.3/0642

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9 March 2010

10 DATE OF REVISION OF TEXT

Date of revision of the text: 27 January 2021