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.

PENTOZ 20: contains sugar (mannitol 38,95 mg per tablet).

PENTOZ 40: contains sugar (mannitol 77,90 mg per tablet).

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Delayed release 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 in the following:

- For the symptomatic improvement (e.g., heartburn, acid regurgitation, pain on swallowing) and healing of mild gastro-oesophageal reflux disease (GORD).

- In patients with healed reflux disease, recurring symptoms can be controlled using an on-demand regimen of 20 mg once daily when required.
- For long term management and prevention of relapse in gastro-oesophageal reflux disease (GORD).
- For the prevention of gastroduodenal lesions and dyspeptic symptoms induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk, and with a need for continuous NSAID treatment.

PENTOZ 40 is indicated in the following:

- For the short-term treatment of duodenal ulcer.
- Gastric ulcer.
- 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.
- For the treatment of Zollinger-Ellison Syndrome.

4.2 Posology and method of administration

Posology

Mild gastro-oesophageal reflux disease (GORD)

The recommended dose is:

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. In patients with healed reflux disease, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily when required.

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.

For prevention of gastro-duodenal lesions and dyspeptic symptoms induced by non-selective non-steroidal anti-inflammatory drugs (NSAID's) in patients at risk and with a need for continuous NSAID treatment, the recommended oral dose is one PENTOZ 20 once daily.

If symptom control has not been achieved after four weeks of treatment with the prescribed daily dose, further investigation is recommended.

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.

Special populations

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).

Paediatric population

Safety and efficacy in children have not been established (see Section 4.3).

Method of administration

PENTOZ should be taken in the morning.

PENTOZ may be taken with food or without food.

PENTOZ should be swallowed whole with a little water either before or during breakfast.

Do not crush, break, or chew the tablet.

4.3 Contraindications

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

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 and Mineral Metabolism

Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia have been reported after treatment with proton pump inhibitor (PPI's) such as PENTOZ for at least 3 months and in most cases for one year.

Hypomagnesemia may lead to hypocalcaemia and/or hypokalaemia and may exacerbate underlying hypocalcaemia in at-risk patients. 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.

Consider monitoring magnesium and calcium levels prior to initiation of PENTOZ and periodically while on

treatment in patients with a pre-existing risk of hypocalcaemia (e.g., hypoparathyroidism). Supplement with magnesium and/or calcium as necessary. If hypocalcaemia is refractory to treatment, consider discontinuing the PPI.

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.

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 Gastric Malignancy

(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.

Diagnosis of reflux oesophagitis

Diagnosis should be confirmed by endoscopy.

Bone fractures

Observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.

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 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 PPI's 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.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, including erythema multiforme, Stevens-Johnson syndrome (SJS),

toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in association with the use of PPI's. Discontinue PENTOZ at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPI's, including pantoprazole sodium. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematous cases were CLE.

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 healthcare provider should consider stopping PENTOZ.

Fundic Gland Polyps

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

Interference with Investigations for Neuroendocrine Tumours

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumours. To avoid this interference, PENTOZ treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Interference with Urine Screen for Tetrahydrocannabinol (THC)

There have been reports of false-positive urine screening tests for THC in patients receiving PPIs, including PENTOZ.

Sodium content

PENTOZ 20 contains 1.350 mg sodium per tablet and PENTOZ 40 contains 3.342 mg sodium per tablet. Thus, this medicine contains less than 1 mmol sodium (23 mg) per dose of one tablet per day.

4.5 Interaction with other medicines and other forms of interaction

Concomitant intake of food has no influence on bioavailability of PENTOZ.

The active ingredient of PENTOZ is metabolised in the liver via the cytochrome P450 enzyme system. An interaction of PENTOZ with other medicines or compounds which are metabolised using the same enzyme system cannot be excluded.

No clinically significant interactions were observed when used concomitantly with caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, warfarin and oral contraceptives.

However, the response to anticoagulants such as warfarin, phenprocoumon and acenocoumarol may be affected by any concomitant medicine. It is therefore good practice to monitor the patient with additional PT (prothrombin time)/INR (international normalised ratio) determinations when PENTOZ is initiated, discontinued or taken irregularly.

PENTOZ may reduce or increase the absorption of medicines whose bioavailability is pH-dependent, e.g., ketoconazole, itraconazole, osaconazole and other medicines like erlotinib.

Methotrexate:

Concomitant use of PPIs, including PENTOZ, with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities.

It has been shown that co-administration of atazanivir 300 mg/ritonavir 100 mg with PPI's such as PENTOZ resulted in substantial reduction in the bioavailability of atazanivir. The absorption of atazanavir is pH-dependent. Therefore PPI's, including PENTOZ, should not be co-administered with atazanavir (see Section 4.3).

Antacids:

There were no interactions with concomitantly administered antacids.

Inhibitors of CYP2C19, such as fluvoxamine, could increase the systemic exposure of pantoprazole. A dose reduction may be considered for patients treated long-term with high doses of PENTOZ, or those with hepatic impairment.

Enzyme inducers affecting CYP2C19 and CYP3A4, such as rifampicin and St. John´s wort (*Hypericum perforatum*), may reduce the plasma concentrations of PPIs that are metabolized through these enzyme systems.

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 advised to refrain from operating machinery or driving, until they know how PENTOZ affects them.

4.8 Undesirable effects

Tabulated list of adverse effects

System Organ Class	Frequency	Adverse effects
Infections and Infestations	Frequency unknown	*Clostridium difficile*-associated diarrhoea*
Blood and lymphatic system disorders	Less frequent	Agranulocytosis, leukopaenia, thrombocytopaenia, pancytopaenia.
Immune system disorders	Less frequent	Anaphylactic reactions including anaphylactic shock and angioedema
Metabolism and nutrition disorders	Less frequent	Increased bilirubin, elevated triglycerides and increased body temperature, lipid increases, hypocalcaemia*, hyperlipidaemia, weight changes

Psychiatric disorders	Less frequent	Mental depression, sleep disorders, depression, disorientation
	Frequency unknown	Hallucination, confusion
Nervous system disorders	Frequent	Headache
	Less frequent	Dizziness, taste disorders
	Frequency unknown	Paraesthesia
Eye disorders	Less frequent	Disturbances in vision (blurred vision)
Gastrointestinal disorders	Frequent	Gastrointestinal complaints such as upper abdominal pain, diarrhoea, constipation or flatulence
	Less frequent	Nausea, vomiting, dry mouth, abdominal distension and bloating, abdominal pain and discomfort
Hepato-biliary disorders	Less frequent	Increased bilirubin
	Frequency unknown	Severe hepatocellular damage leading to jaundice with or without hepatic failure and increased liver enzymes (transaminases, γ-GT)
Skin and subcutaneous tissue disorders	Less frequent	Allergic reactions such as pruritus, and skin rash, urticaria
	Frequency unknown	Severe skin reactions such as Stevens-Johnson Syndrome, erythema multiforme, toxic epidermal necrolysis and photosensitivity
Musculoskeletal, connective tissue and bone disorders	Less frequent	Arthralgia, myalgia, fracture of the hip, wrist or spine
	Frequency unknown	Hyponatraemia, hypomagnesaemia, hypocalcaemia and hypokalaemia in association with hypomagnesaemia
Renal and urinary disorders	Frequency unknown	Interstitial nephritis (in some patients renal failure has been reported concomitantly) (see Section 4.4)
Reproductive	Less frequent	Gynaecomastia

system and breast disorders		
General disorders and administrative site conditions	Less frequent	Asthenia, fatigue, malaise, and peripheral oedema

*Hypocalcaemia in association with hypomagnesaemia.

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

Signs and symptoms:

The described side effects may be exacerbated.

Management of overdose:

No specific therapeutic recommendation can be made in cases of overdosage.

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Proton pump inhibitors ATC code: A02BC02

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

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. On average, the maximum serum/plasma concentrations are approximately 2 to 3 µg/ml about 2,5 hours after administration of 40 mg pantoprazole daily, as a single or multiple doses in healthy volunteers. The absolute systemic bioavailability of pantoprazole from single and multiple oral doses of pantoprazole is approximately 77 %.

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.

Linearity/non-linearity

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

Pharmacokinetics in special patient groups

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

The film-coating contains:

Hydroxypropyl methylcellulose

Polyethylene glycol (macrogol)

Synthetic yellow iron oxide

Titanium dioxide.

The black printing ink contains:

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

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