SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delayed release film-coated tablet contains pantoprazole sodium sesquihydrate equivalent to pantoprazole 20 mg.

Contains sugar (mannitol 38,95 mg per tablet).

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PENTOZ OTC is indicated when intended for the temporary short-term relief of heartburn and hyperacidity for a maximum of 14 days.

4.2 Posology and method of administration

Posology

The maximum dose is 20 mg per day and the treatment is for a maximum period of 14 days.

If no symptom relief is obtained within 2 weeks of continuous treatment, the patient must be advised to consult a doctor.

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 OTC tablet should not be exceeded in patients with mild to moderately severe liver impairment (See Sections 4.4 and 5.2).

Method of administration

PENTOZ OTC should be taken preferably in the morning.

PENTOZ OTC may be taken with food or on an empty stomach.

PENTOZ OTC 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 any of the ingredients of PENTOZ OTC.

Safety and efficacy in children have not been established.

Severely impaired liver function (See Section 4.4).

Co-administration with atazanavir and 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 OTC for at least 3 months and in most cases for one year. Hypomagnaesemia 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 OTC 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.

Patients should be advised to consult a medical practitioner if:

- They have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting with blood, previously had gastric ulcer or gastrointestinal surgery. In these cases, malignancy must be excluded as treatment with PENTOZ OTC may alleviate symptoms and delay diagnosis.
- They have been taking an indigestion or heartburn remedy continuously for 4 or more weeks in order to control their symptoms.
- They have jaundice or hepatic impairment.

Clostridium difficile associated diarrhoea (CDAD)

Treatment with proton pump inhibitors (PPIs), such as PENTOZ OTC, 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 use the lowest dose and shortest duration of PENTOZ OTC treatment appropriate to the condition being treated.

Gastrointestinal infections caused by bacteria

PENTOZ OTC, 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 an increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter*.

Mild gastrointestinal complaints

PENTOZ OTC is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

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.

Liver impairment

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

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 ulcer or a malignant disease of the oesophagus should be excluded, as the treatment with PENTOZ OTC may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Diagnosis of reflux oesophagitis

Diagnosis should be confirmed by endoscopy.

Effect on cyanocobalamin (vitamin B12) absorption

Daily treatment with any acid-blocking medicines such as PENTOZ OTC, 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.

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).

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 OTC 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 OTC.

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 of laboratory tests for neuro endocrine tumours

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, treatment with PENTOZ OTC 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.

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 OTC and evaluate patients with suspected acute TIN.

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 OTC.

4.5 Interaction with other medicines and other forms of interaction

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

The active ingredient of PENTOZ OTC is metabolised in the liver via the cytochrome P450 enzyme system. An interaction of PENTOZ OTC 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 OTC may reduce or increase the absorption of medicines whose bioavailability is pH-dependent, e.g., ketoconazole, itraconazole, posaconazole and other medicines like erlotinib.

Methotrexate

Concomitant use of PPIs, including PENTOZ OTC, 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 OTC resulted in substantial reduction in the bioavailability of atazanivir. The absorption of atazanavir is pH-dependent. Therefore PPI's, including PENTOZ OTC, 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 OTC can cause dizziness and blurred vision.

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

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 system and breast disorders	Less frequent	Gynaecomastia
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 which is 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 oral pantoprazole dosing. Because pantoprazole acts distally 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.

Pantoprazole maintains the physiological pH-rhythm. The values are, however, shifted to higher levels. During the night, periods with pH values approximating placebo have been found to occur.

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 dose 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 to between 7 and 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 the tablets in the blisters and the blisters in the outer carton until required for use.

Keep the tablets in the original HDPE container until required for use and keep the container tightly closed.

6.5 Nature and contents of container

7, 10 or 14 film-coated tablets are packed in white HDPE containers or in aluminium/aluminium blister strips packed in outer 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.

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2057

8 REGISTRATION NUMBER

45/11.4.3/0592

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 June 2013

10 DATE OF REVISION OF TEXT

18 January 2024