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).

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 used for the short term temporary relief of heartburn and hyperacidity.

4.2 Posology and method of administration

Posology

PENTOZ OTC is indicated for short term relief of heartburn and hyperacidity.

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 (mild to moderate).

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

4.3 Contraindications

Hypersensitivity to pantoprazole or any of the ingredients of PENTOZ OTC.

Safety in pregnancy and lactation (see Section 4.6).

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

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.

Treatment with PENTOZ OTC may lead to slightly increased risk of gastrointestinal infections caused by bacteria (*Salmonella* and *Campylobacter)*.

Bone fractures

PENTOZ OTC, 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. PENTOZ OTC 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.

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.

Mild gastrointestinal complaints

PENTOZ OTC is not indicated for mild gastrointestinal 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 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.

Proton pump inhibitors, such as PENTOZ OTC, 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.

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.

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.*

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very 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 PENTOZ OTC. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

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.

4.5 Interaction with other medicines and other forms of interaction

Concomitant intake of food has no influence on bioavailability.

PENTOZ OTC may increase the availability of digoxin if administered for prolonged periods.

Decreased absorption of medicines that are gastric pH dependent

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

- some azole antifungals such as ketoconazole, itraconazole and posaconazole;
- other medicines such as erlotinib, atazanavir, nelfinavir and other HIV medicines with pH-dependent absorption (See "~~CONTRAINDICATIONS~~" Section 4.3).

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 OTC.

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

Other interactions studies

Pantoprazole, as in PENTOZ OTC, is extensively metabolised in the liver via the cytochrome P450 enzyme system (by CYP2C19 and other metabolic pathways including oxidation by CYP3A4) and may affect or be affected by other medicines metabolised by the same enzymes.

Voriconazole

Voriconazole inhibits the metabolism of proton-pump inhibitors: The exposure of both medicines is increased when PENTOZ OTC is co-administered with voriconazole.

Methotrexate

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

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

The elimination of diazepam and phenytoin may be prolonged.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and during lactation has not been established (see Section 4.3).

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

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 disorders

Less frequent: Agranulocytosis, leukopenia, thrombocytopenia, pancytopenia.

Immune system disorders

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

Metabolism and nutrition disorders

Less frequent: Hyperlipidaemias and lipid increases (triglycerides, cholesterol); weight changes.

Frequency unknown: Hypomagnesaemia, hyponatraemia, hypocalcaemia.

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.

Vascular disorders

Less frequent: Peripheral oedema.

Gastrointestinal disorders

Frequent: Gastrointestinal complaints such as upper abdominal pain and discomfort, diarrhoea, constipation, abdominal distention and bloating.

Less frequent: Nausea, vomiting, dry mouth.

Hepato-biliary disorders

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

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, subacute cutaneous lupus erythematosus.

Musculoskeletal, connective tissue and bone disorders

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

Renal and urinary system disorders

Less frequent: Interstitial nephritis.

Reproductive system and breast disorders

Frequency unknown: Gynaecomastia.

General disorders and administration site conditions

Less frequent: Asthenia, fatigue, malaise, increased body temperature.

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

See Section 4.8.

Treatment is symptomatic and supportive.

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 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 %.

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 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.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8 REGISTRATION NUMBER(S)

45/11.4.3/0592

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 May 2013

10 DATE OF REVISION OF TEXT

Date of revision of the text: 27 January 2021