Professional Information

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

PANTOCID OTC 20 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

Excipients with known effect:

Contains sugar: Each tablet contais 5,0 mg lactose and 21,35 mg mannitol.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablets.

Yellow, circular, biconvex, coated tablet, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PANTOCID OTC is used for the short-term temporary relief of heartburn and hyperacidity.

4.2 Posology and method of administration

Posology

PANTOCID 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 medical practitioner.

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 (mild to moderate).

A daily dose of one PANTOCID 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

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

4.3 Contraindications

- Hypersensitivity to pantoprazole or to any of the excipients (see section 6.1).
- 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 human immunodeficiency virus (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 PANTOCID 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.

Hepatic Impairment

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

Mild gastrointestinal complaints

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

Gastric malignancy

Symptomatic response to PANTOCID OTC may mask the symptoms of gastric malignancy and may delay diagnosis. In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy of gastric ulcer or of the oesophagus should be excluded. Further investigation is to be considered if symptoms persist despite adequate treatment.

Co-administration with HIV protease inhibitors

Co-administration of PANTOCID OTC is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir and nelfinavir, due to significant reduction in their bioavailability (see sections 4.3 and 4.5).

Influence on vitamin B12 absorption

Daily treatment with any acid-blocking medicine, such as PANTOCID OTC, over a long period of time (e.g. longer than 3 years), may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo-or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

Gastrointestinal infections caused by bacteria

Treatment with PANTOCID OTC may be associated with a slightly increased risk of gastrointestinal infections caused by bacteria, such as *Salmonella, Campylobacter and C. difficile*.

Clostridium difficile-associated diarrhoea (CDAD), especially in hospitalised patients, may occur. If a patient develops persistent diarrhoea, this diagnosis should be excluded. Patients should use the lowest dose and shortest duration of PANTOCID OTC treatment appropriate to the condition being treated.

Bone fractures

PANTOCID 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.

PANTOCID 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.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors, such as PANTOCID OTC, 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 PANTOCID OTC. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests

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

Acute tubulointerstitial nephritis (TIN)

Acute tubulointerstitial nephritis 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 PANTOCID OTC and evaluate patients with suspected acute TIN.

Lactose

PANTOCID OTC contains lactose anhydrous. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take PANTOCID OTC.

4.5 Interaction with other medicines and other forms of interaction

Medicines with pH-dependent absorption pharmacokinetics

Because of profound and long-lasting inhibition of gastric acid secretion, PANTOCID OTC may interfere with the absorption
of other medicines where gastric is an important determinant of oral availability, e.g. ketoconazole, itraconazole, posaconazole and other medicine, such as erlotinib.

HIV protease inhibitors

Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir and nelfinavir, due to significant reduction in their bioavailability (see sections 4.3 and 4.4).

Coumarin anticoagulants (e.g. warfarin)

Co-administration of PANTOCID OTC with warfarin did not affect the pharmacokinetics of warfarin or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs, including PANTOCID OTC, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death.
Patients treated with PANTOCID OTC and warfarin may need to be monitored for increase in INR and prothrombin time.

Methotrexate

Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors, such as

PANTOCID OTC, have been reported to increase methotrexate levels in some patients. Therefore, in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of PANTOCID OTC may need to be considered.

Voriconazole

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

Other interactions studies

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

Interaction studies with medicines also metabolised with these pathways, such as carbamazepine, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl estradiol did not reveal clinically significant interactions.

The elimination of diazepam and phenytoin may be prolonged.

An interaction of pantoprazole with other medicines or compounds, which are metabolised using the same enzyme system, cannot be excluded.

Results from a range of interaction studies demonstrate that pantoprazole, as in PANTOCID OTC, does not affect the metabolism of active substances metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol).

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

Medicines that inhibit or induce CYP2C19

Inhibitors of CYP2C19, such as fluvoxamine, could increase the systemic exposure of pantoprazole, as in PANTOCID OTC. 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 metabolised through these enzyme systems.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

Animal studies have shown excretion of pantoprazole in breast milk. There is insufficient information on the excretion of pantoprazole in human milk but excretion into human milk has been reported. A risk to the newborns/infants cannot be excluded. PANTOCID OTC should be avoided during breastfeeding (see section 4.3)

Fertility

There was no evidence of impaired fertility following the administration of pantoprazole in animal studies.

4.7 Effects on ability to drive and use machines

PANTOCID OTC causes side effects, such as dizziness and visual disturbances (see section 4.8). Caution is advised before driving a vehicle or operating machinery until the effects of PANTOCID OTC are known.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported side effects are diarrhoea and headache.

Table 1. Adverse reactions in clinical trials and post-marketing experience

System organ class	Frequent	Less Frequent	Frequency unknown
Infections and infestations			*Clostridium difficile* associated diarrhoea and increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter*
Blood and lymphatic system disorders		agranulocytosis, thrombocytopenia, leukopenia, pancytopenia	
Immune system disorders		hypersensitivity (including anaphylactic reactions and anaphylactic shock)	
Metabolism and nutrition disorders		hyperlipidaemias and lipid increases (triglycerides,	hyponatraemia hypomagne-saemia, hypocalcaemia[1], hypokalaemia

		cholesterol), weight changes	
Psychiatric disorders		sleep disorders, depression (and all aggravations), disorientation, confusion (especially in predisposed patients, as well as the aggravation of these symptoms in case of pre-existence)	hallucination
Nervous system disorders	headache	dizziness, taste disorders	paraesthesia
Eye disorders		visual disturbances (blurred vision)	
Gastrointestinal disorders	fundic gland polyps (benign), upper abdominal pain and discomfort, diarrhoea, constipation, abdominal distention and bloating	nausea / vomiting, dry mouth,	microscopic colitis
Hepatobiliary disorders		liver enzymes increased (transaminases, γ-GT), bilirubin increased	hepatocellular injury, jaundice, hepatocellular failure

Skin and subcutaneous tissue disorders		rash / exanthema / eruption, pruritus, urticaria, angioedema, Stevens-Johnson syndrome, Lyell syndrome, erythema multiforme, photosensitivity, subacute cutaneous lupus erythematosus (see section 4.4)	
Musculoskeletal and connective tissue disorders		fracture of the hip, wrist or spine (see section 4.4), arthralgia, myalgia, muscle spasm[2]	
Renal and urinary disorders		interstitial nephritis	
Reproductive system and breast disorders			gynaecomastia

General disorders and administration site conditions		asthenia, fatigue and malaise, body temperature increased, oedema peripheral	

[1] Hypocalcaemia in association with hypomagnesemia

[2] Muscle spasm as a consequence of electrolyte disturbance.

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 11.4.3 Medicines acting on the gastro-intestinal tract – Other.

Pharmacotherapeutic group: Proton pump inhibitors

ATC code: A02BC02

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.

Pantoprazole is converted to its active form in the acidic environment

in the parietal cells where it inhibits the H^+, K^+-ATPase enzyme, i. e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. 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 %, 2,5 to 3,5 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.

Concomitant intake of food had no influence on area under the curve (AUC), maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

Distribution

Pantoprazole's serum protein binding is about 98 %. Volume of distribution is about 0,15 L/kg.

Biotransformation

Pantoprazole is almost exclusively metabolised in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathways include oxidation by CYP3A4.

Elimination

Renal elimination represents the major route of excretion (approximately 80 %) for the metabolites of pantoprazole, the rest is excreted with the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate.

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

Special populations

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

Core tablet:

Mannitol

Sodium carbonate anhydrous

Lactose anhydrous

Crospovidone

Povidone

Calcium stearate

Film-coating:

Hypromellose

Polyethylene glycol

Talc

Methacrylic acid copolymer type C

Triethyl citrate

Titanium dioxide (E171)

Iron oxide yellow (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep the blister strips 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

OPA/PVC/Aluminium foil blister strips placed in an outer carton.

White, round HDPE containers with a white, ribbed polypropylene child-resistant cap.

Pack size: 7, 10 or 14 tablets.

Not all pack sizes may be marketed simultaneously.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER

57/11.4.3/0190

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT