PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

PANZOLYM OTC 20 mg Modified release tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PANZOLYM OTC tablet contains:

Pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole

Contains mannitol 20,85 mg.(sugar)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Modified release tablets.

Identification of tablet:

A dark yellow, film-coated, oval, approximately 4,3 mm X 8,4 mm, biconvex tablet that is blank on both sides

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PANZOLYM OTC is indicated for the treatment of gastric acid reflux symptoms such as

heartburn and acid regurgitation.

4.2 Posology and method of administration

Posology:

The recommended once daily dose of PANZOLYM OTC should be taken in the morning.

The dose is one 20 mg PANZOLYM OTC tablet per day. If no symptom relief is obtained within 2 weeks of continuous treatment the patient must be referred to the doctor.

The treatment must not exceed 4 weeks without consulting a doctor.

Special populations

No dosage adjustment is necessary in the elderly or in those with impaired renal or liver function.

Method of administration

For oral use. PANZOLYM OTC should be swallowed whole with a little water either before or during breakfast.

4.3 Contraindications

- Known hypersensitivity to pantoprazole or any of the excipients (see section 6.1).
- Safety and efficacy in children has not been established.
- Severely impaired liver function (see section 4.4).
- Co-administration with atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

Hepatic impairment

In patients with mild and moderate liver impairment the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise of the liver enzymes the treatment should be discontinued. PANZOLYM OTC is contraindicated in patients with severe liver impairment (see section 4.2).

PANZOLYM OTC may increase the risk of subclinical acute or chronic interstitial nephritis associated with proton pump inhibitors (PPI) leading to chronic renal inflammation and reduced renal function (tubular injury being “tubulointerstitial nephritis”)

Co-administration with NSAIDs

The use of PANZOLYM OTC as a preventive of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Gastric malignancy

Symptomatic response to PANZOLYM 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 should be excluded.

Further investigation is to be considered if symptoms persist despite adequate treatment.

Co-administration with HIV protease inhibitors

Co-administration of PANZOLYM OTC is contraindicated with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, due to significant reduction in their bioavailability (see section 4.5).

Influence on vitamin B12 absorption

PANZOLYM OTC, 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.

Long term treatment

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Gastrointestinal infections caused by bacteria

Treatment with PANZOLYM OTC may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* or C. *difficile*.

PANZOLYM OTC, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with PPIs like PANZOLYM OTC for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular dysrhythmia can occur, but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or medicinal products that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Bone fractures

Proton pump inhibitors as in PANZOLYM 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.

Observational studies suggest that proton pump inhibitors 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 as in PANZOLYM 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 PANZOLYM 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, PANZOLYM OTC treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). 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.

Mannitol:

PANZOLYM OTC contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

Medicinal products with pH-dependent absorption pharmacokinetics

Because of profound and long lasting inhibition of gastric acid secretion, PANZOLYM OTC may interfere with the absorption of other medicinal products where gastric pH is an important determinant of oral availability, e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other medicinal products such as erlotinib.

HIV protease inhibitors

Co-administration of PANZOLYM OTC is contraindicated with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir due to significant reduction in their bioavailability (see section 4.4).

If the combination of HIV protease inhibitors with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g virus load) is recommended. A pantoprazole dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitor may need to be adjusted.

Warfarin

Co-administration of pantoprazole with warfarin did not affect the pharmacokinetics of warfarin or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Patients treated with pantoprazole 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 has 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 pantoprazole may need to be considered.

Other interactions studies

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.

Interaction studies with medicinal products also metabolised with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions.

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

Results from a range of interaction studies demonstrate that pantoprazole 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) or does not interfere with p-glycoprotein related absorption of digoxin.

There were no interactions with concomitantly administered antacids.

Interaction studies have also been performed by concomitantly administering pantoprazole with the respective antibiotics (clarithromycin, metronidazole, amoxicillin) No clinically relevant interactions were found.

Medicinal products that inhibit or induce CYP2C19

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 PANZOLYM OTC, 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 metabolised through these enzyme systems.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

A moderate amount of data on pregnant women indicate no malformative or foeto/ neonatal toxicity of pantoprazole.

Animal studies have shown reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of PANZOLYM OTC during pregnancy.

Breast-Feeding

Safety in lactation has not been established. 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.

Fertility

There was no evidence of impaired fertility following the administration of pantoprazole in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

PANZOLYM OTC has adverse drug reactions such as dizziness and visual disturbances which may occur (see section 4.8). If affected, patients should not drive or operate machines.

4.8 Undesirable effects

a. Summary of the safety profile

Approximately 5 % of patients can be expected to experience adverse drug reactions (ADRs). The most frequent reported ADRs are diarrhoea and headache, both occurring in approximately 1 % of patients.

b. Tabulated summary of adverse reactions

The table below lists adverse reactions reported with pantoprazole according to system organ class, ranked under the following frequency classification:

Frequent, Less frequent and Frequency unknown (for post-marketing experience).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions with pantoprazole in clinical trials and post-marketing experience:

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Agranulocytosis Thrombocytopenia; Leukopenia Pancytopenia

Immune system disorders	Less frequent	Hypersensitivity (including anaphylactic reactions and anaphylactic shock) Angioedema
Metabolism and nutrition disorders	Less frequent	Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes
	Frequency unknown	Hyponatraemia Hypomagnesaemia (see section 4.4). Hypocalcaemia in association with hypomagnesaemia; Hypokalaemia.
Psychiatric disorders	Less frequent	Sleep disorders Depression (and all aggravations) Disorientation (and all aggravations)
	Frequency unknown	Hallucination; Confusion (especially in predisposed patients, as well as the aggravation of these symptoms in case of pre-existence)
Nervous system disorders	Less frequent	Headache; Dizziness Taste disorders
	Frequency unknown	Paraesthesia

Eye disorders	Less frequent	Disturbances in vision / blurred vision
Gastrointestinal disorders	Frequent	Fundic gland polyps (benign)
	Less frequent	Diarrhoea; Nausea / vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort
	Frequency unknown	Microscopic colitis
Hepato-biliary disorders	Less frequent	Liver enzymes increased (transaminases, γ-GT) Bilirubin increased
	Frequency unknown	Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and subcutaneous tissue disorders	Less frequent	Rash / exanthema / eruption; Pruritus; Urticaria
	Frequency unknown	Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity; Subacute cutaneous lupus Erythematosus (see section 4.4)

Musculoskeletal and connective tissue disorders	Less frequent	Fracture of the hip, wrist or spine (see section 4.4) Arthralgia; Myalgia
	Frequency unknown	Muscle spasm as a consequence of electrolyte disturbances
Renal and urinary disorders	Frequency unknown	Interstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders	Less frequent	Gynaecomastia
General disorders and administration site conditions	Less frequent	Body temperature increased; Oedema peripheral

Post-marketing exposure:

The renal effect of proton pump inhibitors (PPIs) may progress to renal failure as it is not necessarily reversed when treatment is discontinued.

There is an increased risk of subclinical acute or chronic interstitial nephritis associated with proton pump inhibitors (PPIs) leading to chronic renal inflammation and reduced renal function (tubular injury being “tubulointerstitial nephritis”).

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

Interstitial nephritis may lead to renal failure.

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 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:

There are no known symptoms of overdose in man. Systemic exposure with up to 240 mg administered intravenously over 2 minutes were well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable.

Management of overdose:

In the case of overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid related disorders, 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. In the parietal cell it is protonated and chemically re-arranged to the active inhibitor, a cyclic sulphonamide, 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.
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Effect on gastric acid secretion

Following oral administration, pantoprazole inhibits the pentagastrin-stimulated gastric acid secretion. After stopping the administration of pantoprazole, there is no evidence of rebound hypersecretion and 7 days after administering the last dose the acid output is normal.

Pantoprazole maintains the physiological pH-rhythm. The values, however, are 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 antisecretory 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 absorbed and the maximal plasma concentration is achieved after one single 20 mg oral dose. Maximum serum concentrations of about 1,0- 1,5 µg/ml are achieved about 2,0- 2,5 hours after administration and these values remain constant after multiple administration.

Distribution and metabolism

The volume of distribution is about 0,15 l/kg and the clearance is about 0,10 l/h/kg. The terminal half-life is about 1 hour. There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole to the proton pumps of the parietal cell, the elimination half-life does not correlate with the much longer duration of action [inhibition of acid secretion].

The serum protein binding of pantoprazole is about 98 %. Pantoprazole is almost exclusively metabolised in the liver.

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 main metabolite in both serum and urine is desmethylpantoprazole, which is conjugated with sulphate. The half-life of the main metabolite is approximately 1 ½ hours which is not much longer than that of pantoprazole.

Special population

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 3 and 6 hours. The AUC values increase by a factor of 3 to 5, while the maximum serum concentration only increases by a factor of 1,3 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

Tablet core:

Sodium carbonate anhydrous

Mannitol

Crospovidone

Povidone

Calcium stearate

Methacrylic acid- ethyl acrylate copolymer (1:1) dispersion 30 %

Triethyl citrate

Tablet coating:

Opadry Yellow IH (OY-52945), containing:

Hypromellose

Titanium dioxide

Macrogol

Iron oxide yellow

Imprinting:

Opacode black IH (S-1-17823), containing:

Shellac

Isopropyl alcohol

Ferrosoferric oxide

N-Butyl alcohol

Propylene glycol

Ammonium hydroxide 28 %

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ºC. Protect from light.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

Blister pack of form laminate with desiccant layer on one side with a back of hard-tempered aluminium foil (dull side lacquered and bright side PE extrusion side).

Blister of aluminium foil laminated to polyamide on one side & laminated PVC on the other side and hard tempered aluminium foil coated with heat seal lacquer.

7 or 14 tablets are be packed in a cardboard carton.

6.6 Special precautions for disposal and other handling

No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Mylan (Pty) Ltd

4 Brewery Street

Isando

Johannesburg, 1609

Republic of South Africa

8 REGISTRATION NUMBER

54/11.4.1/0740.739

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 January 2023

10 DATE OF REVISION OF THE TEXT