PROFESSIONAL INFORMATION FOR PRAZOLOC OTC

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

PRAZOLOC OTC (20 mg enteric-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric-coated tablet contains pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

Contains: Mannitol 49,145 mg

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

Enteric coated tablets

Yellow coloured, capsule shaped, biconvex tablet plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PRAZOLOC 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

PRAZOLOC OTC should be taken preferably in the morning. PRAZOLOC OTC may be taken with food or on an empty stomach.

PRAZOLOC OTC should be swallowed whole with a little water either before or during breakfast. Do not crush, break, or chew the tablet.

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

Special populations

Elderly patients

No dosage adjustment is necessary in the elderly.

Impaired renal function

No dosage adjustment is required in the presence of impaired renal function.

Impaired liver function

A daily dose of PRAZOLOC OTC should not be exceeded in patients with mild to moderate liver impairment (see **section 4.4** and **5.2**).

Paediatric population

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

Method of administration

For oral use only.

4.3 Contraindications

PRAZOLOC OTC is contraindicated in the following:

- Hypersensitivity to pantoprazole or to any of the other ingredients of PRAZOLOC OTC (see **section 6.1**).
- Severe impairment of liver function.
- Safety and efficacy in children have not been established.
- Co-administration with atazanavir and nelfinavir (see **section 4.5**).

4.4 Special warnings and precautions for use

PRAZOLOC OTC is not indicated for mild gastro-intestinal complaints such as nervous dyspepsia.

Prior to treatment the possibility of malignancy of gastric ulcer or a malignant disease of the oesophagus should be excluded, as the treatment with PRAZOLOC OTC may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Daily treatment with any acid-blocking medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin caused by hypo- or achlorhydria. Rare cases of cyanocobalamin deficiency under acid-blocking therapy have been reported in the literature. This should be considered when respective clinical symptoms are observed.

In the case of a rise of the liver enzymes, PRAZOLOC OTC should be discontinued.

Diagnosis of reflux oesophagitis should be confirmed by endoscopy.

The risk of tubulointerstitial nephritis leading to chronic renal inflammation and reduced renal function is associated with the use of PPI's. Tubulointerstitial nephritis may progress to renal failure as is it not necessarily reversed when treatment is discontinued.

Use of PRAZOLOC OTC as preventative 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 gastro-intestinal complications.

Co-administration with anticoagulants

The response to anticoagulants such as warfarin may be affected by any concomitant medication. It is therefore good practice to monitor the patient with additional PT (prothrombin time)/INR (international normalised ratio) determinations when PRAZOLOC OTC is initiated, discontinued or taken irregularly. Changes in absorption should be observed when medicines whose absorption is pH-dependent, e.g. ketoconazole, are taken concomitantly.

Clostridium difficile associated diarrhoea (CDAD)

PRAZOLOC OTC may be associated with an increased risk of Clostridium difficile associated diarrhoea (CDAD). A diagnosis of CDAD should be considered for patients taking PRAZOLOC OTC who develop diarrhoea that does not improve. Patients should use the lowest dose and shortest duration of PRAZOLOC OTC therapy appropriate to the condition being treated.

Gastrointestinal infections caused by bacteria

Treatment with Pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as Salmonella and Campylobacter or C. difficile especially in hospitalised patients. Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. This diagnosis should be considered for diarrhoea that does not improve (see **section 4.8**).

Hypomagnesaemia

Severe hypomagnesaemia has been rarely reported in patients treated with proton pump inhibitors (PPIs) like PRAZOLOC 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 arrhythmia can occur but they may begin insidiously and be overlooked. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8). In most affected patients, hypomagnesaemia (and hypomagnesaemia associated hypocalcaemia and/or hypokalaemia) improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or medicines 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

The use of PRAZOLOC OTC may be associated with an increased risk of bone fractures in the hip, wrist or spine. This effect has been reported mostly in people taking high

doses, on long-term treatment, and in those who were 50 years and older 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.

Hepatic impairment

In patients with severe liver impairment the liver enzymes should be monitored regularly during treatment with PRAZOLOC OTC. In the case of a rise of the liver enzymes, PRAZOLOC OTC should be discontinued.

Vitamin B12 absorption

PRAZOLOC OTC, over a long period of time (e.g. longer than 3 years), may lead to malabsorption of vitamin B12 caused by 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.

Combination therapy

In the case of combination therapy, the summaries of product characteristics of the respective medicines should be observed.

Co-administration with HIV protease inhibitors

Co-administration of PRAZOLOC OTC is not recommended 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**).

Long-term treatment

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

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of Subacute cutaneous lupus erythematosus (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 healthcare provider should consider stopping PRAZOLOC 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, PRAZOLOC 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 proton pump inhibitor treatment.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including PRAZOLOC OTC. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction and is associated with damage to the tubulointerstitium, leading to acute kidney injury. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia). Interstitial nephritis may lead to renal failure. Discontinue PRAZOLOC OTC if acute interstitial nephritis develops (see **section 4.8**).

Sodium

PRAZOLOC OTC contains sodium.

To be taken into consideration in patients on a sodium-controlled diet.

4.5 Interaction with other medicinal products and other forms of interaction

Coumarin anticoagulants (phenprocoumon or warfarin)

The response to anticoagulants such as warfarin, phenprocoumon and acenocoumarol may be affected by any concomitant medicine. There have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. It is therefore good practice to monitor the patient with additional PT (prothrombin time)/INR (international normalised ratio) determinations when PRAZOLOC OTC is initiated, discontinued or taken irregularly.

Pantoprazole decreases the concentrations of atazanavir and nelfinavir. Co-administration of PRAZOLOC OTC and atazanavir or nelfinavir is contraindicated (see **section 4.3**).

HIV protease inhibitors

It has been shown that co-administration of atazanivir 300 mg/ritonavir 100 mg with proton pump inhibitors (PPIs) such as PRAZOLOC OTC resulted in a substantial reduction in the bioavailability of atazanivir. The absorption of atazanavir is pH-dependent. Therefore, PPIs, including PRAZOLOC OTC, should not be co-administered with atazanavir (see **section 4.3**).

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 PRAZOLOC OTC dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitor may need to be adjusted.

Inhibitors of 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 PRAZOLOC OTC, or those with hepatic impairment.

Methotrexate

Concomitant use of PPIs, including PRAZOLOC 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.

Therefore, in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of PRAZOLOC OTC may need to be considered.

Enzyme inducers affecting CYP2C19 and CYP3A4

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.

Other interactions studies

The active ingredient of PRAZOLOC OTC is metabolised in the liver via the cytochrome P450 enzyme system. An interaction of PRAZOLOC OTC with other medicines or compounds which are metabolised using the same enzyme system cannot be excluded. However no clinically significant interactions were, however, observed in specific tests with a number of such medicines or compounds, namely antipyrine, 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, may be affected by PRAZOLOC OTC. It is therefore good practice to monitor the patient with additional PT (prothrombin time) / INR (international normalised ratio) determinations when PRAZOLOC OTC is initiated, discontinued or taken irregularly.

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

Medicines with pH-dependent absorption pharmacokinetics

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

There are no interactions with concomitantly administered antacids.

Concomitant intake of food has no influence on the bioavailability of PRAZOLOC OTC.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and during lactation has not been established.

Pregnancy

Animal studies have shown reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of PRAZOLOC OTC during pregnancy.

Breastfeeding

There is insufficient information on the excretion of pantoprazole in human milk but excretion into human milk has been reported. A risk to the new-borns/infants cannot be excluded. Therefore, breastfeeding while on PRAZOLOC OTC is not recommended.

Fertility

There was no evidence of impaired fertility following the administration of pantoprazole in animal studies. There is no data on fertility in humans with PRAZOLOC OTC.

4.7 Effects on ability to drive and use machines

PRAZOLOC OTC may cause dizziness, disturbances in vision, somnolence or vertigo. Patients should be advised to refrain from operating machinery or driving, until they know how PRAZOLOC OTC affects them.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly reported side effects are diarrhoea and headache.

Approximately 5 % of patients can be expected to experience adverse drug reactions (ADRs).

b. Tabulated list of adverse effects

MedDRA system organ class	**Frequency**	**Side effects**
Infections and Infestations	Frequency unknown	Clostridium difficile associated diarrhoea*
Ear and labyrinth disorders	Less frequent	Vertigo, tinnitus.
Blood and lymphatic system disorders	Less frequent	Leukopenia, thrombocytopenia, pancytopenia, agranulocytosis
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

	Frequency unknown	Microscopic colitis*
Hepatobiliary 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* (Lyell syndrome) and photosensitivity*, Drug reaction with eosinophilia and systemic symptoms (DRESS)*, subacute cutaneous lupus erythematosus*
Musculoskeletal, connective tissue and bone disorders	Less frequent	Arthralgia, myalgia, fracture of the hip, wrist or spine

	Frequency unknown	Hyponatraemia, hypomagnesaemia, hypocalcaemia in association with hypomagnesaemia, muscle spasm as a consequence of electrolyte disturbance*
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, body temperature increased

*Post-marketing reports.

**Hypocalcaemia in association with hypomagnesaemia.

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 the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Signs and symptoms:

The described side effects may be exacerbated.

There are no known symptoms of overdose in man.

Systemic exposure with up to 240 mg administered intravenously over 2 minutes was well tolerated.

Management of overdose:

As pantoprazole is extensively protein bound, it is not readily dialysable.

No specific therapeutic recommendation can be made in cases of overdosage with clinical signs of intoxication.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A 11.4.3 Medicine acting on the gastro-intestinal tract - Other.

Pharmacotherapeutic group: A02BC02 Proton pump inhibitors

Pantoprazole is a proton pump inhibitor, which inhibits specifically and dose proportionally, gastric 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 rearranged 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 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 the 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 was 85 %, 2½ to 3½ hours after dosing with pantoprazole 40 mg/day for 7 days.

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 administered orally in the form of an enteric-coated tablet. Pantoprazole is unstable in acid.

Since an acidic pH in the parietal cell acid canaliculi is required for activation, and since food stimulates acid production, pantoprazole should be taken about 30 minutes before meals.

Absorption takes place in the small intestine. Concurrent administration of food may somewhat reduce the rate of absorption of proton pump inhibitors. Concomitant use of other medicines that inhibits acid secretion, such as H_2-receptor antagonists, might be predicted to lessen the effectiveness of the proton pump inhibitors, such as pantoprazole.

On average, the maximum serum/plasma concentrations are approximately 2 to 3 µg/mL about 2½ hours after administration of 40 mg pantoprazole daily, as a single or multiple dose. The absolute systemic bioavailability of pantoprazole from single and multiple oral doses of pantoprazole is approximately 77 %.

Distribution

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

Metabolism

Pantoprazole is almost exclusively metabolised in the liver. The main metabolite is desmethylpantoprazole, which is conjugated with sulphate other metabolic pathway includes 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 1½ hours which is slightly longer than that of pantoprazole.

Linearity/non-linearity:

The plasma kinetics for pantoprazole administration are linear over the dose range of 10 - 80 mg.

Pharmacokinetic profile in patients with impaired liver or renal function

For patients with mild to moderate hepatic cirrhosis the elimination half-life values increase to between 7 to 9 hours. The AUC values increase by a factor of 6 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.

Poor metabolisers

Approximately 3 % of the European population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60 %. These findings have no implications for the posology of pantoprazole.

Elderly

A slight increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is also not clinically relevant.

Paediatric population

Following administration of single oral doses of 20 or 40 mg pantoprazole to children aged 5 - 16 years AUC and C_{max} were in the range of corresponding values in adults.

Following administration of single i.v. doses of 0,8 or 1,6 mg/kg pantoprazole to children aged 2 - 16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium carbonate

Crospovidone (CLM)

Hydroxypropyl cellulose

Calcium stearate

Seal coating

Hypromellose

Titanium dioxide

Ferric oxide (Yellow)

Propylene glycol

Enteric coating

Methacrylic acid-Ethyl Acrylate copolymer (Eudragit L 30 D-55)

Triethyl citrate

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.

Keep the blisters in the outer carton until required for use.

6.5 Nature and contents of container

Plain aluminium foil blister strips of 7, 10 or 14 tablets packed in a carton.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

43/11.4.3/1145

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 September 2016

Date of renewal: Not applicable.

10 DATE OF REVISION OF THE TEXT

01 July 2026

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