Approved Professional Information for Medicines for Human Use:

PAZIPEP OTC

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

PAZIPEP OTC gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PAZIPEP OTC gastro-resistant tablet

Each gastro-resistant tablet contains 20 mg pantoprazole (as sodium sesquihydrate).

Contains sugar, mannitol.

Each 20 mg gastro-resistant tablet contains 37,5 mg mannitol.

Contains less than 1 mmol sodium per dose.

Each 20 mg gastro-resistant tablet contains 7,998 mg (0,348 mmol) sodium, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablets (tablets).

PAZIPEP OTC gastro-resistant tablet

Yellow to pale yellow coloured, oval, biconvex enteric-coated tablets plain on both the sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

PAZIPEP 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.

Special populations

Elderly population

No dosage adjustment is necessary in the elderly.

Renal impairment

No dosage adjustment is required in the presence of impaired renal function (see section 5.2).

Hepatic impairment

A daily dose of PAZIPEP OTC should not be exceeded in patients with mild to moderately severe liver impairment (see sections 4.4 and 5.2).

Paediatric population

PAZIPEP OTC is not recommended for use in children due to limited data on safety and efficacy.

Method of administration

PAZIPEP OTC tablets should be taken in the morning, swallowed whole with little water either before or

during breakfast.

The gastro-resistant tablet should not be crushed, chewed or broken before swallowing because coating prevents pH sensitive degradation in the gut.

4.3 Contraindications

- Hypersensitivity to the pantoprazole or to any of the excipients listed in section 6.1.
- Safety and efficacy in children have not been established.
- Severely impaired liver function (see section 4.4)).
- Pregnancy and lactation (see section 4.6).
- PAZIPEP OTC should not be co-administered with atazanavir or nelfinavir and other HIV medicines with pH dependent absorption (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Combination therapy for the eradication of *H. pylori*

In the case of combination therapy for the eradication of *H. pylori,* the professional information for the antibiotics used in the combination should be observed.

Gastric malignancy

Symptomatic response to pantoprazole 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.

Hepatic impairment

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

PAZIPEP OTC should be discontinued (see section 4.2).

***Clostridium difficile* associated diarrhoea (CDAD)**

Treatment with proton pump inhibitors (PPIs) such as PAZIPEP 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 PAZIPEP OTC treatment appropriate to the condition being treated.

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

Influence on vitamin B12 absorption

Daily treatment with any acid-blocking medicines such PAZIPEP OTC over a long period of time may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Cases of cyanocobalamin deficiency under acid-blocking therapy have been reported. 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.

Co-administration with non-steroidal anti-inflammatory drugs (NSAIDs)

The use of pantoprazole for prevention of gastroduodenal ulcers and dyspeptic symptoms associated with 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.

Co-administration with 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 4.5).

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 healthcare professional should consider stopping Pantoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Bone fractures

PPI such as PAZIPEP OTC 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 doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute interstitial nephritis (AIN)

Acute interstitial nephritis has been observed in patients taking PPIs including pantoprazole (see section 4.8). Acute interstitial nephritis may occur at any point during PPI therapy and is generally associated to an idiopathic hypersensitivity reaction which may progress to kidney injury and/or chronic renal failure. Discontinue PAZIPEP OTC if acute interstitial nephritis develops. Symptoms of AIN may persist even when treatment is discontinued.

Patients on treatment with PPIs must be frequently monitored for renal function and the urine checked for haematuria and/or proteinuria. Patients should be advised to report any decrease in urine volumes or if they suspect that there is blood in their urine.

Hypomagnesaemia

Severe hypomagnesaemia has been rarely reported in patients treated with PPIs like pantoprazole for

at least three months (in most cases for a year of therapy). Serious consequences of hypomagnesaemia include tetany, dysrhythmia, seizure, delirium, fatigue and dizziness, but they may begin insidiously and be overlooked. 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).

Long-term treatment

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

Interference with laboratory tests

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

Patients should consult their doctor before taking PAZIPEP OTC if they are due to have an endoscopy or urea breath test.

Excipient sodium

Contains less than 1 mmol sodium per dose.

Each 20 mg gastro-resistant tablet contains 7,998 mg (0,348 mmol) sodium, that is to say essentially

'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P450 enzyme

Pantoprazole is extensively metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4 (see section 5.2).

In addition, CYP1A2, CYP2D6, CYP2C9 – 10 and CYP2E1 were implicated in other studies. An interaction of pantoprazole with other medicines which are metabolised using the same enzyme system cannot be excluded.

However, no clinically significant interactions were observed in specific tests with a number of such medicines, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive (levonorgestrel and ethinyl estradiol).

There were also no interactions with concomitantly administered antacids (aluminium hydroxide and magnesium hydroxide).

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

Clopidogrel

Clopidogrel is metabolised to its active metabolite in part by CYP2C19. Co-administration of clopidogrel and proton pump inhibitors like pantoprazole as in PAZIPEP OTC, which inhibits CYP2C19 metabolism

may result in a significant decreased exposure to the active metabolite of clopidogrel with a resultant decrease in inhibition of platelet aggregation and thus reduce the antiplatelet effect of clopidogrel.

As a precaution, concomitant use of pantoprazole and clopidogrel should be discouraged.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or International Normalised Ratio (INR). However, 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. Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

Medicines with pH-dependent absorption pharmacokinetics

The absorption of medicines whose bioavailability is pH dependent (e.g., ketoconazole, itraconazole, posaconazole, erlotinib), might be altered by co-administration with pantoprazole due to the profound and long-lasting inhibition of gastric acid secretion and resultant decrease in gastric acidity.

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, nelfinavir and other HIV medicines due to significant reduction in their bioavailability (see sections 4.3 and 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.

Mycophenolate mofetil

Co-administration of PPIs including pantoprazole receiving mycophenolate mofetil has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH.
The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving PPIs and mycophenolate mofetil. Use pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use of methotrexate (primarily at high-dose e.g., 300 mg) and proton-pump inhibitors may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. Therefore, in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

Medicines that inhibit or induce CYP2C19 or CYP3A4

Fluvoxamine

Inhibitors of CYP2C19 such as fluvoxamine would likely increase the systemic exposure of pantoprazole. A dose reduction may be considered for patients treated long-term with high doses of pantoprazole, or those with hepatic impairment.

Tacrolimus

Concomitant administration of pantoprazole, as in PAZIPEP OTC and tacrolimus may decrease the CYP3A4 metabolism and increase the whole blood levels of tacrolimus, especially in transplant patients who are intermediate to poor metabolisers of CYP2C19.

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.

Voriconazole

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

Digoxin

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

Diazepam and phenytoin

The elimination of diazepam and phenytoin may be prolonged.

4.6 Fertility, pregnancy and lactation

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

4.7 Effects on ability to drive and use machines

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions, such as dizziness and visual disturbances may occur (see section 4.8).

If affected, patients should not drive or operate machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported ADRs were diarrhoea and headache.

For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a “not known” frequency.

Tabulated summary of adverse reactions

The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification: frequent, less frequent and frequency not known.

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

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Frequency not known**
Infections and infestations			*Clostridium difficile* associated diarrhoea and increased risk of

			gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* (see section 4.4)
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, cholesterol), Weight changes		Hyponatraemia, Hypomagnesaemia (see section 4.4) Hypocalcaemia in association with hypomagnesaemia, Hypokalaemia

Psychiatric disorders	Sleep disorders	Depression (and all aggravations), Disorientation (and all aggravations)	Hallucination Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)
Nervous system disorders	Headache, Dizziness	Taste disorders	Paraesthesia
Eye disorders	Disturbances in vision / blurred vision		
Gastrointestinal disorders	Fundic gland polyps (benign), Diarrhoea, Nausea /vomiting, Abdominal distension and bloating, Constipation,		Microscopic colitis

	Dry mouth, Abdominal pain and discomfort		
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 as a consequence of electrolyte disturbances
Renal and urinary disorders			Interstitial nephritis (with possible progression to renal failure)

			(see section 4.4)
Reproductive system and breast disorders		Gynaecomastia	
General disorders and administration site conditions	Asthenia, fatigue and malaise	Increased body temperature, Peripheral oedema	

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There are no known symptoms of overdose in human.

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8). As pantoprazole is extensively protein bound, it is not readily dialysable. In case of over dosage, treatment should be symptomatic and supportive measures should be utilised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 11.4.3 Medicines acting on the gastro-intestinal tract.

Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02BC02

Mechanism of action

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.

Pharmacodynamic effects

Pantoprazole is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. In the parietal cell it is converted to the active form, a cyclic sulphenamide, which binds to the H+, K+-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity for the acid secreting parietal cells of the stomach is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at

higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, 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

Treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. The effect of pantoprazole sodium oral formulations (tablets and granules) and the intravenous formulation on gastric acidity is comparable.

5.2 Pharmacokinetic properties

Absorption

Pantoprazole is unstable in acid and is administered orally in the form of a gastro-resistant tablet.

Pantoprazole is well absorbed from the small intestine after oral administration and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2,5 h, with a C_{max} of approximately 2 to 3 µg/mL following a 40 mg pantoprazole daily in healthy volunteers.
Terminal half-life is approximately 1 h.

The absolute systemic bioavailability of pantoprazole is approximately 77 %. The AUC is approximately 4,0 mg/L. Concomitant intake of food had no influence on the AUC and C_{max} of the pantoprazole 40 mg tablet and thus its bioavailability.

Distribution

The serum protein binding of pantoprazole is approximately 98 %. Volume of distribution is

approximately 0,15 L/kg and clearance is approximately 0,1 L/h/kg.

Biotransformation

Pantoprazole is extensively and almost exclusively metabolised in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. The main metabolite is desmethylpantoprazole, which is conjugated with sulphate. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g., 3 % of Caucasians and African Americans and 17 – 23 % of Asians). Although these sub-populations of slow pantoprazole metabolisers have elimination half-life values of 3,5 to 10,0 hours, they still have minimal accumulation (δ 23 %) with once daily dosing.

Elimination

Pantoprazole is rapidly eliminated from serum. Renal elimination represents the most important route of excretion (approximately 80 %) for the metabolites of pantoprazole, the rest are excreted with the faeces. The half-life of the main metabolite (approximately 1,5 hours) which is not much longer than that of pantoprazole.

Linearity/non-linearity

Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after oral administration.

Special populations

Pharmacokinetic profile in patients with impaired liver function

For patients with mild to moderately severe hepatic cirrhosis the elimination half-life values increase to between 7 to 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.

Pharmacokinetic profile in patients with impaired renal function

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:

Calcium stearate

Crospovidone

Mannitol

Silica-colloidal anhydrous

Sodium carbonate anhydrous

Sodium starch glycollate

Sub-coating:

Hypromellose

Macrogol 6000

Sodium hydroxide

Gastro-coating:

Eudragit L30 D55

Macrogol 6000

Film-coating:

Opadry AMB 80W 52172.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 ºC in the original packaging.

6.5 Nature and contents of container

PAZIPEP OTC are packed in aluminium/aluminium blisters of 14 tablets. The blister is then packaged in an outer carton to give a pack size of 14 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

PAZIPEP OTC: 48/11.4.3/1015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 June 2022

10. DATE OF REVISION OF THE TEXT

31 January 2023