PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PRAZTEK 20 mg gastro-resistant tablets

PRAZTEK 40 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar – mannitol 39,354 mg

Each gastro-resistant tablet contains 40 mg pantoprazole (as sodium sesquihydrate).

Contains sugar – mannitol 78,708 mg

This medicine contains less than 1 mmol sodium per tablet, that is to say it is essentially “sodium-free”.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Enteric-coated tablets.

PRAZTEK 20 mg: Yellow, oval, biconvex, enteric-coated tablets plain on both sides.

PRAZTEK 40 mg: Yellow, oval, biconvex, enteric-coated tablets plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PRAZTEK 20 mg is indicated for the symptomatic improvement (e.g., heartburn, acid regurgitation, pain on swallowing) and healing of mild gastro-oesophageal reflux disease. In patients with healed reflux disease, recurring symptoms can be controlled using an on-demand regimen of 20 mg once daily when required.

PRAZTEK 20 mg is indicated for long-term management and prevention of relapse in gastro-oesophageal reflux disease.

PRAZTEK 20 mg is indicated for the prevention of gastroduodenal lesions and dyspeptic symptoms induced by non-selective non-steroidal anti-inflammatory drugs (NSAID's) in patients at risk, and with a need for continuous NSAID treatment.

PRAZTEK 40 mg is used for the short-term treatment of duodenal ulcer, gastric ulcer and reflux oesophagitis. If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori* infection, **PRAZTEK 40 mg** should be used in combination with appropriate antibiotics.

PRAZTEK 40 mg is indicated in adults for the treatment of Zollinger-Ellison syndrome.

4.2 Posology and method of administration

Posology

Mild gastro-oesophageal reflux disease

The recommended oral dose is **PRAZTEK 20 mg** per day. A 4-week period is usually required for healing of mild gastro-oesophageal reflux disease. If this is not sufficient, healing will usually be achieved within a further 4 weeks. In patients with healed reflux disease, reoccurring symptoms can be controlled using an on-demand regimen of **PRAZTEK 20 mg** once daily when required.

Long-term management and prevention of relapse in gastro-oesophageal reflux disease

For long-term management a maintenance dose of one **PRAZTEK 20 mg** tablet per day is recommended, increasing to 40 mg **PRAZTEK** per day if a relapse occurs. After healing of the relapse, the dose can be reduced to **PRAZTEK 20 mg**. Experience with long-term administration is limited.

For prevention of gastro-duodenal lesions and dyspeptic symptoms induced by non-selective non-steroidal anti-inflammatory drugs (NSAID's) in patients at risk and with a need for continuous NSAID treatment, the recommended oral dose is one **PRAZTEK 20 mg** per day.

Duodenal ulcer:

The recommended dose is **PRAZTEK 40 mg** once daily. The total treatment should be 2 to 4weeks.If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori* infection, **PRAZTEK** should be used in combination with appropriate antibiotics.

Gastric ulcer:

The recommended dose is **PRAZTEK 40 mg**, one tablet, once daily for 4 to 8 weeks.

In case of suspected gastric ulcer, malignancy of the gastric ulcer should be excluded as treatment could conceal the symptoms and may delay diagnosis.

Reflux oesophagitis:

The recommended dose is **PRAZTEK 40 mg**, one tablet, once daily for 4 to 8 weeks.

If gastro-oesophageal reflux disease (GORD) symptom control has not been achieved after four weeks of treatment with the prescribed daily dose, especially where differentiation of diagnosis of GORD with angina and congestive heart failure is present, further investigation is recommended.

Zollinger-Ellison Syndrome:

For management of Zollinger-Ellison syndrome, patients should start their treatment with daily dose of 80 mg (2 tablets of **PRAZTEK 40 mg**). Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion as a guide. With doses of above 80 mg daily, the dose should be divided and given twice daily.

Special Populations

Elderly patients:

No dosage adjustment is necessary in the elderly.

Impaired renal and liver function

No dosage adjustment is necessary in the presence of impaired renal function. A daily dose of **PRAZTEK 20 mg** should not be exceeded in patients with mild to moderately severe liver impairment (see section 4.4 and 5.2).

Paediatric population

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

Method of administration

PRAZTEK tablets should be taken in the morning, swallowed whole with a little water either before or during breakfast.

The gastro-resistant tablet should not be crushed because coating prevents pH sensitive degradation in the gut.

4.3 Contraindications

- Hypersensitivity to 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).
- **PRAZTEK** should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir absorption (See Section 4.5).

4.4 Special warnings and precautions for use

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.

In the presence of any alarm symptoms (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, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. 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 **PRAZTEK,** particularly on long term use. In case of a rise of the liver enzymes **PRAZTEK** should be discontinued (see section 4.2).

Clostridium difficile associated diarrhoea (CDAD)

PPI therapy such as **PRAZTEK** may be associated with an increased risk of ***CDAD.***

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole 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 as **PRAZTEK** over a long period of time may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo -orachlorhydria. Cases of cyanocobalamin deficiency under acid-blocking therapy have been reported. This should be considered when respective clinical symptoms are observed.

Co-administration with non-steroidal anti-inflammatory drugs

Use of pantoprazole for prevention of gastro duodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued non-selective 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.

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.

Bone fracture

PPI such as **PRAZTEK** 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. 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 **PRAZTEK** if acute interstitial nephritis develops. Symptoms of AIN may persist even when treatment is discontinued.

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, dysrhythmia, and seizure.

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, **PRAZTEK** 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 **PRAZTEK** if they are due to have an endoscopy or urea breath test.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 enzyme

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. 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 was also no interaction with a concomitantly administered antacid(aluminium hydroxide and magnesium hydroxide).

Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John's wort (*Hypericum perforatum*) may reduce the plasma concentration of PPIs such as **PRAZTEK** that are metabolized through these enzyme systems.

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 due to the 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 intra gastric 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.

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 with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Medicines that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolisers of CYP2C19. Inhibitors of CYP2C19, such as fluvoxamine, would likely increase the systemic exposure of pantoprazole.

4.6 Fertility, pregnancy, and lactation

Safety in pregnancy and during lactation has not been established.

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 adverse drug reactions (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

Frequency **System Organ Class**	**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*
Blood and the lymphatic system		Agranulocytosis, Thrombocytopenia, Leukopenia, Pancytopenia	
Immune system disorders		Hypersensitivity (including anaphylactic reactions and anaphylactic shock)	

Metabolism and nutrition	Hyperlipidaemias and lipid increase (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; 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, 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)
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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions 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 overdosage, 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. It is converted into 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 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-secretory 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 well absorbed 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. 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 both oral and intravenous administration.
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.

Metabolism

Pantoprazole is extensively 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 (δ23%) with once daily dosing.

Elimination

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. 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 metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

Special populations

Pharmacokinetic profile in patients with impaired liver

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

Mannitol, crospovidone, sodium carbonate anhydrous, calcium stearate, hydroxypropylmethyl cellulose, povidone, propylene glycol, titanium dioxide, iron oxide yellow, methacrylic acid copolymer, triethyl citrate, black printing ink.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months from date of manufacture.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

Store in the original package in order to protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Blister pack:

Tablets are packed in cold form laminate, 25 µm OPA/45 µm Aluminum foil/60 µm PVC and plain 25 µm Aluminum foil/6-8 gsm HSL as the lidding material.

Pack size for 20 mg: 28’s

Pack size for 40 mg: 14’s and 28’s

Not all packs and pack size are necessarily marketed.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office Block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

PRAZTEK 20 mg: 51/11.4.3/1124

PRAZTEK 40 mg: 51/11.4.3/1125

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 June 2022

10. DATE OF REVISION OF THE TEXT

To be assigned