SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PEPTAZOL 40, 40 mg, Enteric coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PEPTAZOL 40: Each enteric coated tablet contains 45,1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

Sugar free.

Contains colouring agent as tartrazine yellow.

Each tablet contains 3,86 mg sodium.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Enteric coated tablets (Tablets)

PEPTAZOL 40: Round, biconvex, with both sides smooth, yellow enteric coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PEPTAZOL 20 mg, which is available as a different formulation, is indicated for the symptomatic improvement (e.g., heartburn, acid regurgitation, pain on swallowing) and healing of mild gastro-oesophageal reflux disease (GERD).

- for long-term management and prevention of relapse in gastro-oesophageal reflux disease (GERD).
- 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.

PEPTAZOL 40 is indicated for 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, PEPTAZOL 40 used in combination with appropriate antibiotics may be useful.
PEPTAZOL 40 is indicated for the treatment of Zollinger-Ellison syndrome.

4.2 Posology and method of administration

Posology

Mild gastro-oesophageal reflux disease (GERD)

The recommended oral dosage is one PEPTAZOL 20 tablet per day. A 4-week period is usually required for healing of mild GERD.
If symptom control has not been achieved after four weeks of treatment with the prescribed daily dose, further investigation is recommended.
In patients with healed reflux disease, recurring symptoms can be controlled using an on-demand regimen of 20 mg once daily when required. A different formulation should be used, as PEPTAZOL 40 cannot be divided.

Duodenal ulcer

The recommended oral dosage is one PEPTAZOL 40 tablet daily in the morning for 2 to 4 weeks.
If the duodenal ulcer has been demonstrated to be associated with Helicobacter pylori infection, the use of PEPTAZOL 40, in combination with appropriate antibiotics, may be useful.

Gastric ulcer

The recommended oral dosage is one PEPTAZOL 40 tablet daily in the morning for 4 to 8 weeks.
In the case of a suspected gastric ulcer, malignancy of the ulcer should be excluded, as treatment could conceal the symptoms and may delay diagnosis.

Reflux oesophagitis

The recommended oral dosage is one PEPTAZOL 40 tablet daily in the morning for 4 to 8 weeks.

Zollinger-Ellison syndrome

For management of Zollinger-Ellison syndrome patients should start their treatment with a daily dose of 80 mg (2 tablets of PEPTAZOL 40).

Thereafter the dosage can be titrated up or down as needed using measurements of gastric acid secretion as a guide. With doses above 80 mg daily, the dose should be divided and given twice daily.

Long-term management and prevention of relapse in GERD

For long-term management, a maintenance dose of one PEPTAZOL 20 per day is recommended, increasing to one PEPTAZOL 40 per day if a relapse occurs.

After healing of the relapse, the dosage can be reduced to one PEPTAZOL 20 tablet. Experience with long-term administration is limited. A different formulation should be used, as PEPTAZOL 40 cannot be divided.

Special populations

Elderly

No dosage adjustment is necessary in the elderly.

Renal and hepatic impairment

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

A daily dose of 20 mg PEPTAZOL should not be exceeded in patients with liver impairment.

Method of administration

For oral use only. PEPTAZOL 40 should be taken in the morning, swallowed whole with a little water either before or during breakfast.

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.
- Severe liver function impairment (see section 4.2, Special Populations section 4.2 and section 4.4).
- Co-administration with atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

Possible malignancy

PEPTAZOL 40 is not indicated for mild gastro-intestinal complaints such as dyspepsia. Prior to treatment, the possibility of a malignant gastric ulcer or a malignant disease of the oesophagus should be excluded, as the treatment with PEPTAZOL 40 may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Long term treatment

PEPTAZOL 40 is not indicated for long-term management and prevention of relapse in gastro-oesophageal reflux disease. Diagnosis of reflux oesophagitis should be confirmed by endoscopy. In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Influence on vitamin B_{12} absorption

PEPTAZOL 40 may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for

reduced vitamin B_{12} absorption on long-term therapy or if respective clinical symptoms are observed.

Renal inflammation

PEPTAZOL 40 may increase the 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”).

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. PEPTAZOL 40 is contraindicated in patients with severe liver impairment (see section 4.3).

Co-administration with HIV protease inhibitors

Co-administration of PEPTAZOL 40 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).

Gastrointestinal infections caused by bacteria

Treatment with PEPTAZOL 40 may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* or *C. difficile*. PEPTAZOL 40 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 proton pump inhibitors (PPIs), as in PEPTAZOL 40, 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), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Bone fractures

Proton pump inhibitors (PPIs) as in PEPTAZOL 40, 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 (PTIs), as in PEPTAZOL 40, 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 PEPTAZOL 40. 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, PEPTAZOL 40 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.

Excipients with known effect

PEPTAZOL 40 contains FD&C Yellow N°5 (tartrazine) which may cause allergic reactions.

PEPTAZOL 40 contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially sodium-free.

4.5 Interactions with other medicines and other forms of interaction

Medicinal products with pH-dependent absorption pharmacokinetics

PEPTAZOL 40 may reduce or increase the absorption of medicines whose bioavailability is pH-dependent e.g., ketoconazole.

Medicines metabolised in the liver via cytochrome P450 enzyme system

The active ingredient of PEPTAZOL 40 is metabolised in the liver via cytochrome P450 enzyme system. An interaction of PEPTAZOL 40 with other medicines or compounds which are metabolised using the same enzyme system cannot be excluded.

No clinically significant interactions were, however, observed in specific tests with a number of such medicines or compounds, namely antipyrine, diazepam, theophylline, digoxin, oral contraceptives, phenytoin, nifedipine, carbamazepine, diclofenac, naproxen, piroxicam, metoprolol, glibenclamide, ethanol and caffeine.

Warfarin or phenprocoumon

Concomitant administration of warfarin or phenprocoumon has no influence on its effect on coagulation factors. However, the response to anticoagulants such as warfarin may be affected

by any concomitant medications. Monitoring the patient with additional PT (prothrombin time)/INR (international normalised ratio) determinations when PEPTAZOL 40 is initiated, discontinued, or taken irregularly is advised.

HIV protease inhibitors

Co-administration of PEPTAZOL 40 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.

Methotrexate

Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors, as in PEPTAZOL 40, 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.

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 PEPTAZOL 40, 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.

Antacids

There were no interactions with concomitantly administered antacids.

Antibiotics

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

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

Animal studies have shown reproductive toxicity.

As a precautionary measure, it is preferable to avoid the use of PEPTAZOL 40 during pregnancy.

Breastfeeding

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.

4.7 Effects on ability to drive and use machines

PEPTAZOL 40 may influence the ability to drive and to use machinery. Possible side effects (see section 4.8), such as dizziness and disturbances in vision e.g. blurred vision may occur.

It is not always possible to predict to what extent PEPTAZOL 40 may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which PEPTAZOL 40 affects them.

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

System Organ Class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia
Immune system disorders	Less frequent	Anaphylactic reactions including anaphylactic shock, allergic reactions such as skin rash, pruritus, and 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,

System Organ Class	Frequency	Adverse reactions
		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	Frequent	Headache
	Less frequent	Dizziness, taste disorders
Eye disorders	Less frequent	Disturbances in vision (blurred vision)
Gastrointestinal disorders	Frequent	Upper abdominal pain, diarrhoea, nausea, constipation, flatulence, vomiting, dry mouth, Fundic gland polyps (benign)
	Frequency unknown	Microscopic colitis
Hepato-biliary disorders	Less frequent	Increase in liver enzymes (transaminases, γ-GT), severe hepatocellular damage leading to jaundice with or without hepatic failure, bilirubin increased
Skin and subcutaneous tissue disorders	Less frequent	Urticaria, rash, pruritis, severe skin reactions such as Stevens-Johnson syndrome, erythema multiforme and Lyell-syndrome, photosensitivity
	Frequency unknown	Subacute cutaneous lupus erythematosus (see section 4.4)

System Organ Class	Frequency	Adverse reactions
Musculoskeletal, connective tissue and bone disorders	Less frequent	Myalgia subsiding after termination of therapy, arthralgia. Fracture of the hip, wrist or spine (see section 4.4)
	Frequency unknown	Muscle spasm as a consequence of electrolyte disturbances
Renal and urinary disorders	Less frequent	Interstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders	Less frequent	Gynaecomastia
General disorders and administrative site conditions	Less frequent	Increased body temperature and peripheral oedema, both subsiding after termination of treatment

c. Description of selected adverse reactions

Renal effects

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 characterised by an inflammatory reaction within the tubulointerstitial space of the kidney. Acute interstitial inflammatory reactions are associated with damage to the tubulointerstitial, 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. 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.

In addition, side-effects can also be reported to info@pharmacorp.co.za.

4.9 Overdose

There are no known symptoms of overdosage in humans. No specific recommendation can be made in cases of overdosage. Treatment is symptomatic and supportive. As pantoprazole is extensively protein bound, it is not readily dialysable.

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 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 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 and multiple 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.

Effect on Gastric Acid Secretion

Following oral administration, pantoprazole inhibits the pentagastrin-stimulated gastric acid secretion. The mean acid inhibition is 85 %, 2½ to 3½ hours after dosing with pantoprazole 40 mg/day for 7 days.

After the administration of pantoprazole was stopped, there is no evidence of rebound hypersecretion and 7 days after administrating 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 and distribution

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

Absorption takes place in the small intestine. 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(s) in healthy volunteers. The absolute systemic bioavailability of pantoprazole from single and multiple oral doses of pantoprazole is

approximately 77 %. The plasma kinetics for pantoprazole after oral administration is linear over the dose ranges 10 – 80 mg.

Biotransformation

Pantoprazole is almost exclusively metabolised in the liver. The main metabolite is desmethyl-pantoprazole, which is conjugated with sulphate.

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.

Characteristics in specific groups

Pharmacokinetic profile in patients with impaired liver or renal function.

In sub-populations of patients suffering from mild to moderately severe liver cirrhosis, the half-life increases from 1 hour to between 7 to 9 hours. The AUC values are increased by a factor of 6 to 8, while the maximum serum concentration increases by a factor of only 1½ 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 the elderly compared with younger people.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium stearate (E470a)

Crospovidone (E1202)

Mannitol (E421)

Povidone K 90 (E1201)

Sodium carbonate (E500(i))

Base coating

Opadry QX White (321A180025), containing glyceryl monocaprylocaprate, macrogol copolymer (PEG), polyvinyl alcohol, talc, titanium dioxide.

Enteric coating

Acryl-Eze II White (493Z180022), containing calcium silicate, methacrylic acid copolymer, poloxamer, sodium bicarbonate, sodium lauryl sulphate, talc, titanium dioxide.

Simethicone

Tartrazine yellow (CI 19140) (E 102).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in unit carton until before use.

6.5 Nature and contents of container

PEPTAZOL 40 is packaged in an OPA-aluminium foil blister containing 15 tablets. Two blisters

are packed in a carton box.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACORP (PTY) LTD

29 Victoria Link

Route 21 Corporate Park

Irene, 0178, RSA

8. REGISTRATION NUMBER(S)

41/11.4.3/0099

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 August 2013

10. DATE OF REVISION OF THE TEXT: 9 April 2024