PROFESSIONAL INFORMATION

PEPLOC OTC

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

PEPLOC OTC 20 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PEPLOC OTC tablet contains pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

PEPLOC OTC contains sugar (mannitol 70,50 mg/tablet).

Essentially 'sodium free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Orangish, biconvex and oval gastro-resistant tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PEPLOC OTC is indicated for the temporary short-term relief of heartburn and hyperacidity for a maximum daily dose of 20 mg and a maximum treatment period of 14 days.

4.2 Posology and method of administration

Posology

PEPLOC OTC should be taken in the morning. The recommended oral dose is 20 mg of PEPLOC OTC

per day.

Special populations

Elderly patients

No dosage adjustment is necessary in the elderly.

Impaired renal and liver function

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

Paediatric population

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

Method of administration

PEPLOC OTC should be swallowed whole with a little water either before or during breakfast.

4.3 Contraindications

PEPLOC OTC is contraindicated in:

- hypersensitivity to pantoprazole or to any of the ingredients of PEPLOC OTC (see section 6.1)
- safety and efficacy in children have not been established.
- severely impaired liver function (see section 4.4)
- co-administration with atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

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 PEPLOC 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.

Gastric malignancy

Prior to treatment, or in the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) the possibility of malignancy of a gastric ulcer or a malignant disease of the oesophagus should be excluded, as the treatment with PEPLOC OTC may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Diagnosis of reflux oesophagitis

Diagnosis of reflux oesophagitis should be confirmed by endoscopy.

Clostridium difficile associated diarrhoea (CDAD)

PEPLOC OTC may be associated with an increased risk of *Clostridium difficile* associated diarrhoea (CDAD). A diagnosis of CDAD should be considered for patients taking PEPLOC OTC who develop diarrhoea that does not improve. Patients should use the lowest dose and shortest duration of PEPLOC 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 PEPLOC 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 PEPLOC 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 PEPLOC OTC. In the case of a rise of the liver enzymes, PEPLOC OTC should be discontinued.

Mild gastro-intestinal complaints

PEPLOC OTC should not be used for mild gastrointestinal complaints such as nervous dyspepsia.

Vitamin B_{12} absorption

PEPLOC OTC, over a long period of time (e.g. longer than 3 years), may lead to malabsorption of vitamin B_{12} caused by 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.

Co-administration with nonsteroidal anti-inflammatory drugs (NSAIDs)

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

Combination therapy

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

Co-administration with human immunodeficiency virus (HIV) protease inhibitors

Co-administration of PEPLOC 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 PEPLOC 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, PEPLOC 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 PEPLOC 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 PEPLOC OTC if acute interstitial nephritis develops (see section 4.8).

Sodium:

PEPLOC OTC contains sodium.

PEPLOC OTC contains less than 1 mmol (0,023 g) sodium per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicines and other forms of interaction

Concomitant intake of food has no influence on the bioavailability.

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 PEPLOC OTC is initiated, discontinued or taken irregularly.

Medicines with pH-dependent absorption pharmacokinetics

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

HIV protease inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with proton pump

inhibitors (PPIs) such as PEPLOC OTC resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH-dependent. Therefore, PPIs, including PEPLOC 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 PEPLOC OTC 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 PPIs, including PEPLOC 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 PEPLOC OTC may need to be considered.

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 PEPLOC OTC, or those with hepatic impairment.

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 PEPLOC OTC is metabolised in the liver via the cytochrome P450 enzyme

system. An interaction of PEPLOC OTC with other medicines or compounds which are metabolised using the same enzyme system cannot be excluded.

However no clinically significant interactions were observed when used concomitantly with caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, warfarin and oral contraceptives.

There were no interactions with concomitantly administered antacids.

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

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 PEPLOC 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 PEPLOC 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 PEPLOC OTC.

4.7 Effects on ability to drive and use machines

PEPLOC OTC has no or negligible influence on the ability to drive and use machines.

PEPLOC OTC may affect driving ability due to potential adverse effects such as dizziness and visual disturbances (see section 4.8). If affected, patients should not drive or operate machines.

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

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	*Frequency unknown*	*Clostridium difficile*-associated diarrhoea*
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* *Frequency unknown*	Mental depression, sleep disorders, depression, disorientation Hallucination*, confusion*
Nervous system disorders	*Frequent* *Less frequent* *Frequency unknown*	Headache Dizziness, taste disorders 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* *Frequency unknown*	Allergic reactions such as pruritus and skin rash, urticaria 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* *Frequency unknown*	Arthralgia, myalgia, fracture of the hip, wrist or spine 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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

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

Pharmacotherapeutic group: Proton pump inhibitors

ATC code: A02BC02

Pharmacological classification: A.11.4.3 Medicines acting on the gastrointestinal tract

Mechanism of action:

Pantoprazole is a proton pump inhibitor, i.e. it inhibits specifically and dose-proportionally H^+, K^+-ATPase (adenosine triphosphatase), 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 sulphonamide, which binds to the H^+, K^+-ATPase, thus inhibiting the proton pump and causing suppression of stimulated and basal gastric acid secretion after single and multiple intravenous and oral pantoprazole dosing. Because pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus.

Pantoprazole exerts its full effect in a strongly acidic environment (pH < 3) and remains mostly inactive at higher pH values, which explains its selectivity for the acid secreting parietal cells of the stomach.

Therefore, the complete pharmacological and therapeutic effect for pantoprazole can only be achieved in the acid secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

Effect on gastric acid secretion

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 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 doses in healthy volunteers. The absolute systemic bioavailability of pantoprazole from single and multiple oral doses of pantoprazole is approximately 77 %.

Concomitant intake of food had no influence on AUC, maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

Distribution:

Pantoprazole's serum protein binding is about 98 %. Volume of distribution is about 0.15 L/kg.

Biotransformation:

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.

Pharmacokinetics in special patient groups

Pharmacokinetic profile in patients with impaired liver or renal function

For patients with mild to moderately severe hepatic cirrhosis, the elimination half-life values increase from 1 hour to between 7 - 9 hours. The AUC values increase by a factor of 6 - 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

A two-year carcinogenicity study in rats found both neuroendocrine neoplasms and squamous cell papillomas in the fore stomach of rats.

The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment.

In the two-year rodent study, an increased number of liver tumours was observed in rats and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg). The occurrence of these neoplasms is associated with the pantoprazole-

induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no harmful effects on the thyroid glands are expected.

In a peri-postnatal rat reproduction study designed to assess bone development, signs of offspring toxicity (mortality, lower mean body weight, lower mean body weight gain and reduced bone growth) were observed at exposures (C_{max}) approximately 2x the human clinical exposure. By the end of the recovery phase, bone parameters were similar across groups, and body weights were also trending toward reversibility after a medicine-free recovery period. The increased mortality has only been reported in pre-weaning rat pups (up to 21 days age), which is estimated to correspond to infants up to the age of 2 years old. The relevance of this finding to the paediatric population is unclear. A previous peri-postnatal study in rats at slightly lower doses found no adverse effects at 3 mg/kg compared with a low dose of 5 mg/kg in this study.

Investigations revealed no evidence of impaired fertility or teratogenic effects.

Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Carmellose sodium

Colloidal anhydrous silica

Magnesium stearate

Mannitol

Sodium carbonate anhydrous

Sodium starch glycolate type A

Tablet coating:

Hypromellose

Methacrylic acid-ethyl acrylate copolymer

Propylene glycol

Titanium dioxide (E171)

Triethyl citrate

Yellow iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store at or below 25 ºC. Protect from moisture.

Store blister in the outer carton until required for use.

6.5 Nature and contents of container

PEPLOC OTC tablets are packed in aluminium-polyamide-PVC/aluminium blister strips.

7 or 14 tablets are packed in an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

A43/11.4.3/0344

9. DATE OF FIRST AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

17 January 2025

NAM:

NS1 18/11.4/0081