1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ASPEN PANTOPRAZOLE 20 mg enteric-coated tablets

ASPEN PANTOPRAZOLE 40 mg enteric-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ASPEN PANTOPRAZOLE 20:

Each enteric-coated tablet of ASPEN PANTOPRAZOLE 20 contains 20 mg of pantoprazole as pantoprazole sodium sesquihydrate equivalent.

Contains sugar: Mannitol 53,08 mg

ASPEN PANTOPRAZOLE 40:

Each enteric-coated tablet of ASPEN PANTOPRAZOLE 40 contains 40 mg of pantoprazole as pantoprazole sodium sesquihydrate equivalent.

Contains sugar: Mannitol 106,17 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

ASPEN PANTOPRAZOLE 20 is a light yellow, oval, normal biconvex enteric-coated tablet.

ASPEN PANTOPRAZOLE 40 is a dark yellow, oval, normal biconvex enteric-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ASPEN PANTOPRAZOLE 40 is indicated 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, ASPEN PANTOPRAZOLE 40 used in combination with appropriate antibiotics may be useful.
- the treatment of Zollinger-EIlison Syndrome.

ASPEN PANTOPRAZOLE 20 is indicated for:

- the symptomatic improvement (e.g. heartburn, acid regurgitation, pain on swallowing) and healing of mild gastro-oesophageal reflux disease (GERD).
- long-term management and prevention of relapse in gastro-oesophageal reflux disease (GERD).

4.2 Posology and method of administration

Posology

The recommended once daily dose of ASPEN PANTOPRAZOLE should be taken in the morning. ASPEN PANTOPRAZOLE should be swallowed whole with a little water either before or during breakfast.

Duodenal ulcer:

The recommended oral dose is 40 mg of ASPEN PANTOPRAZOLE once daily. The total treatment with intravenous and oral pantoprazole should be 2 to 4 weeks. If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori* infection, 40 mg of ASPEN PANTOPRAZOLE used in combination with appropriate antibiotics may be useful.

Gastric ulcer:

The recommended oral dose is 40 mg of ASPEN PANTOPRAZOLE once daily for 4 to 8 weeks. In the case of a 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 oral dose is 40 mg of ASPEN PANTOPRAZOLE once daily in the morning for 4 to 8 weeks.

Zollinger-Ellison Syndrome:

For the management of Zollinger-EIlison Syndrome patients should start their treatment with a daily dose of 80 mg of ASPEN PANTOPRAZOLE (two ASPEN PANTOPRAZOLE 40 tablets). 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.

Mild Gastro-oesophageal reflux disease (GERD):

The recommended oral dose is 20 mg of ASPEN PANTOPRAZOLE per day. A 4-week period is usually required for healing of mild GERD. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Long-term management and prevention of relapse in GERD:

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

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 of ASPEN PANTOPRAZOLE should not be exceeded in patients with mild to moderately severe liver impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of ASPEN PANTOPRAZOLE in children has not been established (see section 4.3).

Method of administration

For oral administration.

4.3 Contraindications

ASPEN PANTOPRAZOLE is contraindicated in:

- Patients with hypersensitivity to pantoprazole or to any of the excipients in ASPEN PANTOPRAZOLE (see section 6.1).
- Co-administration with atazanavir and nelfinavir (see section 4.5).
- Severely impaired liver function (see section 4.4).

Safety and efficacy in children has not been established.

4.4 Special warnings and precautions for use

Clostridium difficile-associated diarrhoea (CDAD)

Published observational studies suggest that proton pump inhibitor (PPI) therapy, like ASPEN PANTOPRAZOLE, may be associated with an increased risk of *Clostridium difficile*-associated diarrhoea, especially in hospitalised patients. This diagnosis should be considered for diarrhoea that does not improve (see section 4.8).

Gastrointestinal infections caused by other bacteria

Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as Salmonella and Campylobacter and *C. difficile*.

Increased risk of subclinical acute or chronic interstitial nephritis associated with proton pump inhibitors (PPI's) leading to chronic renal inflammation and reduced renal function

There is an increased risk of subclinical acute or chronic interstitial nephritis associated with proton pump inhibitors (PPI's) leading to chronic renal inflammation and reduced renal function. The preferred term to describe the histological findings of 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 tubulointerstitium, leading to acute kidney injury. Tubulointerstitial nephritis may be medicine-related, infectious, systemic, autoimmune, genetic, and idiopathic with the most common cause being related to a medication or medicine exposure.

The risk of tubulointerstitial nephritis leading to chronic inflammation and reduced renal function associated with the use of PPIs such as omeprazole, is a class effect.

Hepatic impairment

Patients with severe liver impairment: liver enzymes should be monitored regularly during treatment with ASPEN PANTOPRAZOLE, particularly on long-term use. In the case of a rise of liver enzymes, ASPEN PANTOPRAZOLE should be discontinued.

Gastric malignancy

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or malaena) and prior to treatment, the possibility of malignancy of gastric ulcer or a malignant disease of the oesophagus should be excluded, as treatment with ASPEN PANTOPRAZOLE may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.
Further investigation is to be considered if symptoms persist despite adequate treatment.

Daily treatment with acid blocking medicines, including ASPEN PANTOPRAZOLE, over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin caused by hypo- or achlorhydria. Cases of cyanocobalamin deficiency under acid-blocking therapy have been reported in the literature. This should be considered when respective clinical symptoms are observed (see section 4.5).

Use of ASPEN PANTOPRAZOLE as preventative of gastroduodenal ulcers, induced by non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications.
ASPEN PANTOPRAZOLE is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

Further investigation is to be considered if symptoms persist despite adequate treatment. The daily dose of 40 mg ASPEN PANTOPRAZOLE should not be exceeded in elderly patients or in those with impaired renal function.

Diagnosis of reflux oesophagitis should be confirmed by endoscopy.

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, due to significant reduction in their bioavailability (see section 4.5).

Influence on vitamin B12 absorption

In patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

Long term treatment

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

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with PPIs such as ASPEN PANTOPRAZOLE 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 improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take ASPEN PANTOPRAZOLE with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare providers should consider measuring magnesium levels before starting ASPEN PANTOPRAZOLE treatment and periodically during treatment.

Bone fractures

PPI's, such as ASPEN PANTOPRAZOLE, 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 older people or in presence of other recognised risk factors. Observational studies suggest that PPI's may increase the overall risk of fracture by 10 % to 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):

PPI's, such as ASPEN PANTOPRAZOLE, 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 provider should consider stopping ASPEN PANTOPRAZOLE. SCLE after previous treatment with a PPI may increase the risk of SCLE with other PPI's.

Interference with laboratory tests

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

Excipients

ASPEN PANTOPRAZOLE contains mannitol which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Concomitant intake of food has no influence on the bioavailability.

Due to long lasting inhibition of gastric acid secretion ASPEN PANTOPRAZOLE may reduce the absorption of medicines with a gastric pH-dependent bioavailability, e.g. some azole antifungals like ketoconazole, itraconazole, posaconazole and other medicines such as erlotinib.

Atazanavir and nelfinavir:

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

The active ingredient of ASPEN PANTOPRAZOLE is metabolised in the liver via the cytochrome P450 enzyme system. An interaction of ASPEN PANTOPRAZOLE 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, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenprocoumon, phenytoin, piroxicam, theophylline, warfarin and oral contraceptives.

However, the response to anti-coagulants, such as warfarin, may be affected by any concomitant medication. Therefore, monitoring the patient with additional PT (prothrombin time)/INR (International normalised ratio) determinations when ASPEN PANTOPRAZOLE is initiated, discontinued or taken irregularly would be a good practice.

There were no interactions with concomitantly administered antacids.

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

Methotrexate

Concomitant use of PPIs, including ASPEN PANTOPRAZOLE**,** 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 pantoprazole may need to be considered.

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

Medicines 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 ASPEN PANTOPRAZOLE, 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.

4.6 Fertility, pregnancy and lactation

The safety of ASPEN PANTOPRAZOLE in pregnancy and during lactation has not been established.

Pregnancy

Data on pregnant women (between 300 to 1 000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of pantoprazole, as in ASPEN PANTOPRAZOLE.
Animal studies have shown reproductive toxicity.
As a precautionary measure, it is preferable to avoid the use of ASPEN PANTOPRAZOLE during pregnancy.

Breastfeeding

Animal studies have shown excretion of pantoprazole, as in ASPEN PANTPRAZOLE, 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. Therefore, a decision should be taken by the medical practitioner on whether to discontinue breastfeeding or to discontinue/abstain from ASPEN PANTOPRAZOLE therapy.

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

ASPEN PANTOPRAZOLE has moderate influence on the ability to drive and use machines. Since adverse reactions such as blurred vision and dizziness have been reported in patients receiving ASPEN PANTOPROZOLE, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that ASPEN PANTOPRAZOLE does not adversely affect their ability to do so (see section 4.8).

4.8 Undesirable effects

a) Summary of the safety profile

Approximately 5 % of patients can be expected to experience adverse drug reactions (ADRs). Diarrhoea and headache, occurred in approximately 1 % of patients.

b) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Infections and infestations	Gastrointestinal infection	*Clostridium difficile* associated diarrhoea (CDAD)	
Blood and the lymphatic system disorders		Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia	

Immune system disorders		Anaphylactic reactions including anaphylactic shock	
Metabolism and nutrition disorders		Elevated triglycerides, elevated cholesterol, hyperlipidaemias, weight changes	Hyponatraemia, hypomagnesaemia, Hypocalcaemia[1], hypokalaemia[1]
Psychiatric disorders		Mental depression, sleep disorders, disorientation	Hallucination
Nervous system disorders	Headache	Dizziness, taste disorders	Paraesthesia
Eye disorders		Disturbances in vision or blurred vision	Anterior ischaemic optic neuropathy
Gastrointestinal disorders	Abdominal pain and discomfort, diarrhoea, constipation or flatulence, fundic gland polyps (benign)	Nausea, vomiting, dry mouth	Gastric glandular cysts, microscopic colitis
Hepatobiliary disorders		Increased liver enzymes (transaminases, y-GT), severe hepatocellular damage leading to jaundice with or without hepatic failure, increased bilirubin	
Skin and subcutaneous tissue disorders		Allergic reactions such as pruritus and skin rash, urticaria, angioedema, severe skin reactions such as Stevens Johnson syndrome, erythema multiforme, Lyell syndrome, photosensitivity, exanthema, eruption	Subacute cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders		Arthralgia, myalgia, fracture of the hip, wrist or spine	Muscle spasm as a consequence of electrolyte disturbances
Renal and urinary disorders		Interstitial nephritis (may lead to renal failure)	
Reproductive system and breast disorders		Gynaecomastia	
General disorders and administrative site conditions		Asthenia, fatigue, malaise, increased body temperature	

[1]Hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see section 4.4).

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 providers are asked to report any suspected adverse reactions to **SAHPRA** via the "6.04 Adverse Drug Reactions

Reporting Form", found online under SAHPRA's

publications: https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9 Overdose

Symptoms

There are no known symptoms of overdosage in man. No specific therapeutic recommendation can be made in cases of overdosage.

Treatment

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 11.4.3. Medicines acting on the gastrointestinal tract

Pharmacotherapeutic group: Drugs for acid related disorders, Proton pump inhibitors

ATC code: A02BC02

Mechanism of action

Pantoprazole is a proton pump inhibitor (PPI), 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. 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 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 in inhibited.

Effects on gastric acid secretion:

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

Pantoprazole maintains the physiological pH-rhythm. The values, however, are shifted to higher levels. During the night, periods of 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 of pantoprazole daily, as single or multiple doses 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 are linear over the dose range 10 mg to 80 mg.

Metabolism:

Pantoprazole is almost exclusively metabolised in the liver. The main metabolite is desmethylpantoprazole, 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.

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 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.

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 AUC and C_{max} occurs in elderly volunteers compared with younger people.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium stearate, hypromellose, macrogol, mannitol, methacrylic acid copolymer, methacrylic acid-ethyl acrylate copolymer, polyethylene glycol, propylene glycol, sodium carbonate anhydrous, sodium lauryl sulphate, sodium starch glycolate, talc, titanium dioxide, yellow iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Keep in a well closed container.

Keep the blister strip in the unit carton until required for use.

Keep in original packaging until required for use.

6.5 Nature and contents of container

ASPEN PANTOPRAZOLE 20

28, 30 or 100 enteric-coated tablets are packed in a white, round HDPE container with threaded neck with a white, round PP tamper-evident screw cap with three break-points on the ring and integrated desiccant and a leaflet.

28, 30 or 100 enteric-coated tablets are packed in an aluminium push through foil and sealed with an aluminium backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

ASPEN PANTOPRAZOLE 40

14, 15, 30 or 50 enteric-coated tablets are packed in a white, round HDPE container with threaded neck with a white, round PP tamper-evident screw cap with three break-points on the ring and integrated desiccant and a leaflet.

14, 15, 30 or 50 tablets are packed in an aluminium push through foil and sealed with an aluminium backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

Not all packs or pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8 REGISTRATION NUMBER

ASPEN PANTOPRAZOLE 20: 43/11.4.3/0545

ASPEN PANTOPRAZOLE 40: 43/11.4.3/0546

9 DATE OF FIRST AUTHORISATION

Date of registration:

ASPEN PANTOPRAZOLE 20: 20 April 2012

ASPEN PANTOPRAZOLE 40: 20 April 2012

10 DATE OF REVISION OF TEXT

12 February 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

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