1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ASPEN PANTOPRAZOLE IV 40 mg powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml vial contains 40 mg pantoprazole as pantoprazole sodium sesquihydrate.

Contains sugar: Mannitol 200 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.

ASPEN PANTOPRAZOLE IV is a white freeze dried powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ASPEN PANTOPRAZOLE IV is indicated for:

- The short-term treatment of duodenal ulcer, gastric ulcer and reflux oesophagitis.
- Intravenous administration in patients who cannot be treated orally.
- If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori*

infections, ASPEN PANTOPRAZOLE IV used in combination with appropriate antibiotics may be useful.

- The treatment of Zollinger-Ellison Syndrome.

4.2 Posology and method of administration

Posology

The recommended dose is one vial (40 mg) of ASPEN PANTOPRAZOLE IV per day.

ASPEN PANTOPRAZOLE IV is indicated for intravenous administration in patients who cannot be treated orally.

A ready-to-use solution is prepared by injecting 10 ml of a 0,9 % sodium chloride solution into the vial containing the freeze dried powder. The solution may be administered directly or may be diluted further by mixing with 100 ml 0,9 % sodium chloride or 5 % glucose ONLY.

The product should be administered intravenously over 2 to 15 minutes.
After preparing the solution in 0,9 % sodium chloride and 5 % dextrose the solution must be used immediately and any unused portion discarded.

ASPEN PANTOPRAZOLE IV may be used intravenously for up to 7 days. As soon as oral therapy is possible, treatment should be replaced with the same oral dose (of a suitable oral formulation of pantoprazole) in compliance with the approved dosage regimen as stated below.

Duodenal ulcer:

The recommended dose is 40 mg pantoprazole 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, ASPEN PANTOPRAZOLE IV or an oral pantoprazole formulation used in combination with appropriate antibiotics may be useful.

Gastric ulcer:

The recommended dose is 40 mg pantoprazole once daily. 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 the diagnosis.

Reflux oesophagitis:

The recommended dose is 40 mg pantoprazole once daily.

Zollinger-Ellison syndrome:

For management of Zollinger-Ellison syndrome, the patient should start treatment with a daily dosage of 80 mg (2 vials) of ASPEN PANTOPRAZOLE IV. 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, the dosage should be divided and given twice daily.

In case rapid acid control is required, a starting dose of 2 x 80 mg ASPEN PANTOPRAZOLE IV is sufficient to manage a decrease of acid output into the target range (< 10 mmol/h) within one hour in the majority of patients. Transition from ASPEN PANTOPRAZOLE IV to an oral formulation should be performed as soon as it is clinically justified.

Long-term treatment:

Long-term treatment with ASPEN PANTOPRAZOLE IV is currently not indicated as there is

insufficient clinical data.

Elderly patients:

No dosage adjustment is needed in the elderly.

Impaired renal and liver function:

No dosage adjustment is required in impaired renal function.

A daily dose of 20 mg pantoprazole should not be exceeded in patients with mild to moderate 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

For intravenous administration.

4.3 Contraindications

ASPEN PANTOPRAZOLE IV is contraindicated in:

- Patients with hypersensitivity to pantoprazole or to any excipients in ASPEN PANTOPRAZOLE IV (see section 6.1).
- Safety and efficacy in children have not been established.
- Severe impaired liver function (see sections 4.2 and 4.4)
- Co-administration with atazanavir and nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use

ASPEN PANTOPRAZOLE IV is for intravenous route only and must not be administered by any other route.

ASPEN PANTOPRAZOLE IV 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 IV should not be exceeded in elderly patients or in those with impaired renal function.

Clostridium difficile-associated diarrhoea (CDAD)
Published observational studies suggest that proton pump inhibitor (PPI) therapy, like ASPEN PANTOPRAZOLE IV, 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
ASPEN PANTOPRAZOLE IV may be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole 40 mg, as in ASPEN PANTOPRAZOLE IV, may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter*.

Hepatic impairment

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

Gastric malignancy

Symptomatic response to pantoprazole, as in ASPEN PANTOPRAZOLE IV, may mask the symptoms of gastric malignancy and may delay diagnosis. In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded.

Further investigation is to be considered if symptoms persist despite adequate treatment.

Daily treatment with acid-blocking medicines including ASPEN PANTOPRAZOLE IV 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.

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 or nelfinavir, due to significant reduction in their bioavailability (see sections 4.3 and 4.5).

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with PPIs such as ASPEN PANTOPRAZOLE IV 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. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia. 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 ASPEN PANTOPRAZOLE IV with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), medical practitioners should consider measuring magnesium levels before starting ASPEN PANTOPRAZOLE IV treatment and periodically during treatment.

Bone fractures

PPIs, such as ASPEN PANTOPRAZOLE IV, 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 PPIs 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)

PPIs, such as ASPEN PANTOPRAZOLE IV, are associated with 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 medical practitioner should consider

stopping ASPEN PANTOPRAZOLE IV. SCLE after previous treatment with a PPI may increase the risk of SCLE with other PPIs.

Interference with laboratory tests

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

Increased risk of subclinical acute or chronic interstitial nephritis associated with proton pump inhibitors (PPIs) 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 (PPIs) 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 proton pump inhibitors such as omeprazole, is a class effect.

Excipients

Patients with the rare hereditary condition of mannitol intolerance should not be administered ASPEN PANTOPRAZOLE IV.

4.5 Interaction with other medicines and other forms of interaction

pH-dependent medication

ASPEN PANTOPRAZOLE IV may reduce or increase the absorption of medicines whose bioavailability is pH-dependent, e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other medicines such as erlotinib.

HIV medicines

It has been shown that co-administration of atazanavir/ritonavir with omeprazole or atazanavir with lansoprazole resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH-dependent. Therefore, ASPEN PANTOPRAZOLE IV must not be co-administered with atazanavir (see section 4.5).

Cytochrome P450 enzyme system

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

No clinical 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, phenytoin, piroxicam, theophylline, warfarin and oral contraceptives.

Anticoagulants

The response to anticoagulants such as warfarin, phenprocoumon and acenocoumarol may be affected by concomitant medicines. It is therefore recommended to monitor the patient with additional PT (prothrombin)/INR (International normalised ratio) determinations when ASPEN PANTOPRAZOLE IV is initiated, discontinued or given irregularly.

Other antacids

There were no interactions with concomitantly administered antacids.

Methotrexate

Concomitant use of PPIs, including ASPEN PANTOPRAZOLE IV 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.

Antibiotics

Interaction studies have also been performed by concomitantly administering 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, as in ASPEN PANTOPRAZOLE IV. A dose reduction may be considered for patients treated long-term with high doses of 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

Safety and efficacy in pregnancy and lactation have not been established.

Pregnancy

Animal studies have shown reproductive toxicity.

Data on pregnant women (between 300 to 1 000 pregnancy outcomes) indicate no malformative or foetal/ neonatal toxicity.

As a precautionary measure, the use of ASPEN PANTOPRAZOLE IV should be avoided during pregnancy.

Breastfeeding

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

ASPEN PANTOPRAZOLE IV will be administered in a hospital setting. ASPEN PANTOPRAZOLE IV 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 IV, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that ASPEN PANTOPRAZOLE IV 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). The most commonly reported ADR is injection site thrombophlebitis. 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,	Hyponatraemia, hypomagnesaemia,

		hyperlipidaemias, weight changes	hypocalcaemia[1], hypokalaemia[1]
Psychiatric disorders		Mental depression, sleep disorders, disorientation	Hallucination
Nervous system disorders	Headache	Dizziness	Paraesthesia
Eye disorders		Disturbances in vision or blurred vision	Anterior ischaemic optic neuropathy
Vascular disorders		Injection site thrombophlebitis and peripheral oedema	
Gastrointestinal disorders	Abdominal pain and discomfort, diarrhoea, constipation or flatulence, fundic gland polyps (benign)	Nausea, vomiting, dry mouth, taste disorders	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, Drug reaction with eosinophilia and systemic symptoms (DRESS)
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.

Treatment

No specific therapeutic recommendation can be made in cases of overdosage. 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 – Other.

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 dosing. Because pantoprazole acts distal to receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus.

Pantoprazole exerts it full effect in a strongly acidic environment (pH < 3) and remains most inactive at higher pH values, which explains its selectivity for the acid secreting parietal cells of the stomach. Complete pharmacological and therapeutic effect for pantoprazole can therefore only be achieved in the acid-secreting parietal cells. This effect is diminished at the same rate as acid secretion is inhibited, by means of a feedback mechanism.

Effect on gastric secretion

Following intravenous administration, pantoprazole inhibits the pentagastrin-stimulated gastric acid secretion. With 30 mg pantoprazole intravenous, the mean acid inhibition after 5 days was 99 %. The basal 24 hour acidity was reduced by 98 %.

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 administration, demonstrating that the duration of action markedly exceeds the serum elimination half-life.

5.2 Pharmacokinetic properties

Absorption and distribution

Following intravenous administration of pantoprazole, serum/plasma concentrations decline exponentially. The terminal half-life is about 1 hour. The total serum clearance is approximately 0,1 L/h/kg and the volume of distribution is about 1,5 L/kg.

The plasma kinetics for pantoprazole after both oral and intravenous administration is linear over the dose range of 10 to 80 mg.

Biotransformation

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 in the faeces. The half-life of the main metabolite is approximately 1½ hours, which is slightly longer than that of pantoprazole.

Special populations

Poor metabolisers

Population groups that lack a functional CYP2C19 enzyme 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.

Hepatic and renal impairment

For patients with mild to moderately severe hepatic cirrhosis the elimination half-life values increase to between 7 to 9 hours. The AUC increases 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 in AUC and C_{max} occurs in elderly volunteers compared with younger people.

Elderly

A slight increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is also not clinically relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a cool dry place at or below 25 °C.

Protect from light.

Keep in original packaging until required for use.

The reconstituted solution must be used immediately after preparation and any remaining solution must be appropriately disposed of.

6.5 Nature and contents of container

The product is packed in a clear 10 ml amber Type I glass vial, with a grey bromobutyl rubber stopper and a purple aluminium cap.

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

42/11.4.3/0313

9 DATE OF FIRST AUTHORISATION

Date of registration: 05 August 2011

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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