PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PANTOCID® 40 mg INJECTION Lyophilised Powder for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PANTOCID® 40 mg INJECTION: Each vial contains pantoprazole sodium equivalent to 40 mg pantoprazole.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilised Powder for Injection.

PANTOCID® 40 mg INJECTION: A white to off-white lyophilised cake in a 10 mL colourless glass vial for intravenous injection.

The reconstituted solution is a clear yellowish solution**.**

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PANTOCID® 40 mg INJECTION 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 Heliocobacter pylori infection, **PANTOCID® 40 mg INJECTION** used in combination with appropriate antibiotics may be useful.
- Treatment of Zollinger-Ellison syndrome.

4.2 Posology and method of administration

Posology

PANTOCID® 40 mg INJECTION is indicated for intravenous administration to patients who cannot be treated with oral pantoprazole.

The recommended dosage is one vial **PANTOCID® 40 mg INJECTION** per day administered intravenously over 2 to15 minutes.

Duodenal ulcer:

The recommended dose is one vial **PANTOCID® 40 mg INJECTION** once daily. The total duration of treatment with intravenous and oral pantoprazole should be 2 to 4 weeks. If the duodenal ulcer was demonstrated to be associated with Helicobacter pylori infection, **PANTOCID® 40 mg INJECTION** used in combination with appropriate antibiotics may be useful.

Gastric ulcer:

The recommended dose is one vial **PANTOCID® 40 mg INJECTION** once daily. The total duration of treatment with intravenous and oral pantoprazole should be 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 intravenous dose is one vial **PANTOCID® 40 mg INJECTION** once daily. The total duration of treatment with intravenous and oral pantoprazole should be 4 to 8 weeks.

Zollinger-Ellison syndrome:

For management of Zollinger-Ellison syndrome treatment should be started with a daily dose of 80 mg (2 vials of **PANTOCID® 40 mg INJECTION**). 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.

In case rapid acid control is required, a starting dose of 2 x 80 mg (2 x 2 vials of **PANTOCID® 40 mg INJECTION**) is sufficient to manage a decrease of acid output into the target range (< 10 mEq/h) within 1 hour in the majority of patients.

Long-term management:

Long-term treatment with **PANTOCID® 40 mg INJECTION** is currently not indicated as there are

insufficient clinical data.

Special populations

Elderly patients:

No dosage adjustment is necessary in the elderly.

Impaired renal function

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

Impaired liver function

A daily dose of 20 mg of **PANTOCID® 40 mg INJECTION** should not be exceeded in patients with mild to moderately severe liver impairment (see Section 5.2 and 4.4).

Method of administration

PANTOCID® 40 mg INJECTION should be reconstituted with 10 ml of physiological sodium chloride (0,9 %) solution into the vial containing the dry substance. **PANTOCID® 40 mg INJECTION** may be used intravenously for up to 7 days.

After preparation the physiological sodium chloride (0,9 %) solution and 5 % glucose must be used within 12 hours and any unused portion discarded after 12 hours.

The solution may be administered directly or it may be further diluted by mixing with 100 ml physiological sodium chloride solution or 5 % glucose ONLY.

The medicine should be administered intravenously over 2 - 15 minutes.

Patients should be switched to oral therapy as soon as possible.

4.3 Contraindications

- Hypersensitivity to pantoprazole, or to any of the ingredients of **PANTOCID® 40 mg INJECTION** (see Section 6.1).
- 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

PANTOCID® 40 mg INJECTION should only be administered intravenously, and must not be given by any other route.

Mild gastro-intestinal complaints

PANTOCID® 40 mg INJECTION is not indicated for mild gastro-intestinal complaints such as nervous dyspepsia.

Diagnosis of reflux oesophagitis should be confirmed by endoscopy.

Hepatic impairment

PANTOCID® 40 mg INJECTION should not be used in patients with severely impaired liver function (see Section 4.3).

In patients with severe liver impairment the liver enzymes should be monitored regularly during treatment with **PANTOCID® 40 mg INJECTION**, particularly on long-term use. In the case of a rise of the liver enzymes **PANTOCID® 40 mg INJECTION** should be discontinued.

Gastric Malignancy

Prior to treatment the possibility of malignancy of gastric ulcer or a malignant disease of the oesophagus should be excluded, as the treatment with **PANTOCID® 40 mg INJECTION** may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Diagnosis of reflux oesophagitis should be confirmed by endoscopy.

Gastrointestinal infections caused by bacteria:

Treatment with **PANTOCID® 40 mg INJECTION** may be associated with an increased risk of gastrointestinal infections caused by bacteria, such as *Salmonella, Campylobacter* or *Clostridium difficile*.

Clostridium difficile-associated diarrhoea, especially in hospitalised patients, may occur. This diagnosis should be considered for diarrhoea that does not improve (see Section 4.8).

Hypomagnesaemia:

Severe hypomagnesaemia has been reported in patients treated with **PANTOCID® 40 mg INJECTION** for at least three months, and in most cases for a year (see Section 4.8). Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of **PANTOCID® 40 mg INJECTION**.

For patients expected to be on prolonged treatment or who receive **PANTOCID® 40 mg INJECTION** with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare

professionals should consider measuring magnesium levels before starting **PANTOCID® 40 mg INJECTION** and periodically during treatment.

Bone fractures:

PANTOCID® 40 mg INJECTION is indicated for short-term use**.** If **PANTOCID® 40 mg INJECTION** is used in high doses and over long durations, it may modestly increase the risk of hip (by 10 – 40 %), wrist and spine fracture, predominantly in older people or in the presence of other recognised risk factors (see Section 4.8). 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.

Sub-acute cutaneous lupus erythematosus (SCLE):

PANTOCID® 40 mg INJECTION may be associated with cases of SCLE (see Section 4.8). 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 **PANTOCID® 40 mg INJECTION**. SCLE after previous treatment with **PANTOCID® 40 mg INJECTION** 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**, PANTOCID® 40 mg INJECTION** 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 **PANTOCID® 40 mg INJECTION** treatment.

Renal failure

Interstitial nephritis may progress to chronic renal inflammation and renal failure as it is not necessarily reversed when treatment is discontinued.

4.5 Interactions with other medicines and other forms of interaction

Concomitant intake of food has no influence on the bioavailability.

Medicines with pH dependent absorption pharmacokinetics

Because of profound and long-lasting inhibition of gastric acid secretion, **PANTOCID® 40 mg INJECTION** may reduce or increase the absorption of medicines whose bioavailability is pH-

dependent, e.g. ketoconazole, itraconazole, posaconazole and other medicines such as erlotinib.

HIV protease inhibitors

Co-administration of **PANTOCID® 40 mg INJECTION** is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir, due to the significant reduction in their bioavailability.

Close clinical monitoring (e.g. virus load) is recommended, where the combination use of HIV protease inhibitors with a proton pump inhibitor is unavoidable. The dosage of the HIV protease inhibitor may need to be adjusted (see Section 4.2 and 4.3).

Coumarin anticoagulants (e.g. warfarin):

Co-administration of **PANTOCID® 40 mg INJECTION** with warfarin did not affect the pharmacokinetics of warfarin or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving other proton pump inhibitors and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Patients treated with **PANTOCID® 40 mg INJECTION** and warfarin may need to be monitored for increase in INR and prothrombin time when **PANTOCID® 40 mg INJECTION** is initiated, discontinued or administered irregularly.

Methotrexate:

Concomitant use of high dose methotrexate (e.g. 300 mg) and **PANTOCID® 40 mg INJECTION** may elevate methotrexate levels in some patients. Therefore in settings where high dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal **of PANTOCID® 40 mg INJECTION** may need to be considered.

Other interactions

The active ingredient of **PANTOCID® 40 mg INJECTION** is metabolised in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.

Interaction studies with medicines also metabolised with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine and an oral contraceptive containing levonorgestrel and ethinylestradiol, did not reveal clinically significant interactions.

An interaction of **PANTOCID® 40 mg INJECTION** with other medicines or compounds, which are metabolised using the same enzyme system, cannot be excluded.

Results from a range of interaction studies demonstrate that **PANTOCID® 40 mg INJECTION** does not affect the metabolism of medicines metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol), and does not interfere with p-glycoprotein related absorption of digoxin.

There were also no interactions with concomitantly administered antacids.

Oxidation by CYP3A4.

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There were also no interactions with concomitantly administered antacids.

Interaction studies have also been performed by concomitantly administering pantoprazole as in **PANTOCID® 40 mg INJECTION** 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 **PANTOCID® 40 mg INJECTION**. A dose reduction may be considered for patients treated long-term with high doses of **PANTOCID® 40 mg INJECTION**, 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 **PANTOCID® 40 mg INJECTION**, which are metabolised through these enzyme systems.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established (see Section 4.3).

Breastfeeding

Safety during lactation has not been established (see section 4.3).

Fertility

No available data.

4.7 Effects on ability to drive and use machines

PANTOCID® 40 mg INJECTION may cause side effects, such as dizziness and blurred vision. Patients should be advised not to drive a vehicle or operate machines until it is established that their ability to perform such activities is not affected.

4.8 Undesirable effects

Tabulated list of adverse reactions

Table 1

System Organ Class	Frequent	Less Frequent	Frequency Unknown
Infections and infestations			*Clostridium difficile-, Campylobacter-* or *Salmonella*-associated diarrhoea (see Section 4.4).
Blood and the lymphatic system disorders		Leukopenia, thrombocytopenia, agranulocytosis pancytopenia.	
Immune system disorders		Anaphylactic reactions including anaphylactic shock, angioedema..	
Metabolism and nutrition disorders		Hyperlipidaemias and lipid increases (elevated triglycerides, cholesterol), weight changes.	Hyponatraemia, hypomagnesemia, hypocalcaemia, hypokalaemia

Nervous system disorders		Dizziness, headache, taste disorders.	Paraesthesia
Eye disorders		Disturbances in vision (blurred vision).	
Psychiatric disorders		Mental depression, sleep disorders, disorientation (and all aggravations).	Hallucinations, confusion (especially in predisposed patients, as well as the aggravation of these symptoms in case of pre-existence).
Gastric-intestinal disorders	Fundic gland polyps (benign).	Nausea, vomiting, dry mouth, diarrhoea, constipation, flatulence, abdominal distension and bloating, abdominal pain and discomfort.	
Hepato-biliary disorders		Increased liver enzymes (transaminases gamma-glutamyltransfe-rase), increased bilirubin.	Hepatocellular injury, jaundice, hepatocellular failure.
Skin and subcutaneous tissue disorders		Allergic reactions such as pruritus, skin rash, exanthema eruption, urticaria.	Stevens-Johnson syndrome, Lyell syndrome (toxic epidermal necrosis), erythema multiforme, photosensitivity subacute cutaneous lupus erythematosus (SCLE).
Musculoskeletal and connective tissue disorders		Arthralgia, myalgia, fracture of the hip, wrist or spine.	
Renal and urinary disorders		Interstitial nephritis, renal failure	
Reproductive system and breast disorders		Gynaecomastia	
General disorders and administration site conditions	Injection site thrombophlebitis.	Increased body temperature, peripheral oedema, asthenia, fatigue, malaise.	

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. Health care 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.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors.

ATC code: A02B C02

Pharmacological classification: A 11.4.3 Medicines acting on gastric-intestinal tract. Other.

Pantoprazole is a proton pump inhibitor, i.e. it inhibits specifically and dose-proportionally H+, K+-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

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 of 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

Following intravenous administration of pantoprazole, serum/plasma concentrations decline biexponentially. The terminal half-life (t½) is about 1 hour. The total serum clearance is approximately 0,1 L/h/kg and the volume of distribution is about 0,15 L/kg.

The plasma kinetics for pantoprazole after both oral and intravenous administration are linear over the dose range 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 1,5 hours, which is slightly longer than that of pantoprazole.

Special populations

Pharmacokinetic profile in patients with impaired liver or renal function:

For patients with mild to moderate hepatic cirrhosis, the elimination half-life values increase to between 7 to 9 hours. The AUC values increase by a factor of 6 to 8, while the maximum serum concentration only increases by a factor of 1,5 in comparison with healthy subjects.

A slight increase in AUC and C_{max} occurs in elderly volunteers compared with younger patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active ingredient: Pantoprazole sodium sesquihydrate.

Inactive ingredients: Water for injection, nitrogen.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 25 °C, Protect from light.

Discard any unused solution.

Do not use after the expiry date stated on the label.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

10 mL Colourless USP type I tubular glass vial with 20 mm grey bromobutyl rubber stopper and 20 mm red flip off aluminium seal.

One, five or ten vials are packed into an outer carton.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill Ext.1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER

PANTOCID® 40 mg INJECTION: 40/11.4.3/0072

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 April 2006

10. DATE OF REVISION OF THE TEXT

12 February 2024

Namibia:

PANTOCID® 40 INJECTION: NS2 Reg. no.: 06/11.4/0332