Professional Information for Medicines for Human Use:

PANTOPRAZOLE 40 mg IV AUSTELL

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PANTOPRAZOLE 40 mg IV AUSTELL lyophilised powder for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

Pantoprazole sodium sesquihydrate equivalent to pantoprazole 40 mg.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

A white to off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PANTOPRAZOLE 40 mg IV AUSTELL is indicated for intravenous administration to patients who cannot be treated orally.

PANTOPRAZOLE 40 mg IV AUSTELL 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, PANTOPRAZOLE 40 mg IV AUSTELL used in combination with appropriate antibiotics may be useful.

PANTOPRAZOLE 40 mg IV AUSTELL is indicated for the treatment of Zollinger–Ellison Syndrome.

4.2 Posology and method of administration

Posology

The recommended intravenous dose is one vial (pantoprazole 40 mg) PANTOPRAZOLE 40 mg IV AUSTELL per day. PANTOPRAZOLE 40 mg IV AUSTELL is indicated for intravenous administration to patients who cannot be treated orally. PANTOPRAZOLE 40 mg IV AUSTELL 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, in compliance with the approved dosage regimen.

Duodenal ulcer

The recommended dose is 40 mg 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* infections, PANTOPRAZOLE 40 mg IV AUSTELL used in combination with appropriate antibiotics may be useful.

Gastric ulcer

The recommended dose is 40 mg pantoprazole once daily for 4 to 8 weeks. In the case of 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 dose is PANTOPRAZOLE 40 mg IV AUSTELL once daily for 4 to 8 weeks.

If gastroesophageal reflux disease (GERD) symptom control has not been achieved after four weeks of treatment with the prescribed daily dose, especially where differentiation of diagnosis of GERD with angina and congestive heart failure is present, further investigation is recommended.

Zollinger-Ellison syndrome

For management of Zollinger-Ellison syndrome patients should start their treatment with a daily dose of 80 mg (2 vials of PANTOPRAZOLE 40 mg IV AUSTELL). Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretions 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 80 mg pantoprazole (2 vials of PANTOPRAZOLE 40 mg IV AUSTELL) is sufficient to manage a decrease of acid output into the target range (< 10 mEq/h) within one hour in the majority of patients. Transition from PANTOPRAZOLE 40 mg IV AUSTELL to the oral formulation should be performed as soon as it is clinically justified.

Long-term treatment

Long-term treatment with PANTOPRAZOLE 40 mg IV AUSTELL is currently not indicated as there are insufficient clinical data.

Special populations

Elderly population

No dosage adjustment is necessary in the elderly.

Renal impairment

No dosage adjustment is required in the presence of impaired renal function (see section 5.2).

Hepatic impairment

A daily dose of 20 mg pantoprazole should not be exceeded in patients with mild to moderate liver impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of pantoprazole 40 mg powder for solution for injection, as in PANTOPRAZOLE 40 mg IV AUSTELL in children aged under 18 years have not been established (see section 4.3). Therefore, PANTOPRAZOLE 40 mg IV AUSTELL powder for solution for injection is contraindicated for use in patients below 18 years of age.

Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Method of administration

The ready-to-use solution may be administered directly after reconstitution with sodium chloride 9 mg/mL (0,9 %) solution for injection, or it may be further diluted with sodium chloride 9 mg/mL (0,9 %) solution for injection or glucose (5 %) solution for injection before parenteral administration. For instructions for preparation and storage of solution before parenteral administration, see section 6.6.

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

4.3 Contraindications

- Hypersensitivity to pantoprazole or to any of the excipients listed in section 6.1.
- Safety and efficacy in children have not been established.
- Severely impaired liver function (see section 4.4).
- Safety in pregnancy and lactation has not been established (see section 4.6).
- Concomitant administration with atazanavir or nelfinavir (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Gastric malignancy

Symptomatic response to pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL 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.

Clostridium difficile associated diarrhoea

PPI therapy like PANTOPRAZOLE 40 mg IV AUSTELL may be associated with an increased risk of Clostridium difficile associated diarrhoea (CDAD), especially in hospitalised patients.

This diagnosis should be considered for diarrhoea that does not improve (see section 4.8).

Patients should use the lowest dose and shortest duration of PANTOPRAZOLE 40 mg IV AUSTELL therapy appropriate to the condition being treated.

Acute interstitial nephritis (AIN) leading to acute kidney injury (AKI) and/or chronic kidney disease

PANTOPRAZOLE 40 mg IV AUSTELL may increase the risk of subclinical acute interstitial nephritis (AIN) associated with proton pump inhibitors (PPIs) leading to chronic renal inflammation and reduced renal function (tubular injury being “tubulointerstitial nephritis” also called “Acute interstitial nephritis (AIN)”) (see section 4.8).

AIN has been observed in patients taking PPIs, such as PANTOPRAZOLE 40 mg IV AUSTELL, and may occur at any point during PPI therapy. AIN is characterised by an inflammatory reaction within the tubulointerstitial space of the kidney. Acute interstitial inflammatory reactions are associated with damage to the tubulointerstitium and can progress to acute kidney injury (AKI) (acute renal failure).

AIN may be drug-related, infectious, systemic, autoimmune, genetic, and idiopathic with the most common cause being related to a medicine or drug exposure.

Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decrease renal function (e.g., malaise, nausea, anorexia). A delay in diagnosis and continued use of the PPI can lead to chronic renal failure.

Patients on treatment with PPIs must be frequently monitored for renal function and the urine checked for haematuria and/or proteinuria. Patients should be advised to report any decrease in urine volumes or if they suspect that there is blood in their urine. Treatment with PPIs, such as PANTOPRAZOLE 40 mg IV AUSTELL should be discontinued in patients with AIN.

Concomitant administration with atazanavir or nelfinavir

Co-administration of PANTOPRAZOLE 40 mg IV AUSTELL with atazanavir or nelfinavir is contraindicated. Their absorption is dependent on acidic intragastric pH, and concomitant administration with pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL causes a significant reduction in their bioavailability (see sections 4.3 and 4.5).

Hepatic impairment

Liver function should be monitored regularly during treatment with PANTOPRAZOLE 40 mg IV AUSTELL, particularly on long-term use.
In the case of a rise of the liver enzymes, PANTOPRAZOLE 40 mg IV AUSTELL should be discontinued (see section 4.2).

Hepatic impairment may require a reduction in dose (see sections 4.2 and 5.2).

Bone fractures

Proton pump inhibitors, especially if used in high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture (see section 4.8), predominantly in older people or in the presence of other recognised risk factors.

Observational studies suggest that proton pump inhibitors, such as pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL may increase the overall risk of fracture by 10 – 40 %. Some of this increase may be due toother risk factors.

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. 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.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with PPIs like pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular dysrhythmia can occur, but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors, such as pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL are associated with very infrequent 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 PANTOPRAZOLE 40 mg IV AUSTELL. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Vitamin B12 (cyanocobalamin) absorption

Daily treatment with PANTOPRAZOLE 40 mg IV AUSTELL 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.

Atrophic gastritis

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL, particularly in patients who were *H. pylori* positive.

Gastrointestinal infections caused by bacteria

Treatment with PANTOPRAZOLE 40 mg IV AUSTELL may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* (see section 4.8).

Interactions with diagnostic investigations for neuroendocrine tumours

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, PANTOPRAZOLE 40 mg IV AUSTELL 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, such as PANTOPRAZOLE 40 mg IV AUSTELL treatment.

Concomitant use of PANTOPRAZOLE 40 mg IV AUSTELL with methotrexate

Concomitant use of PPIs such as PANTOPRAZOLE 40 mg IV AUSTELL with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PANTOPRAZOLE 40 mg IV AUSTELL may be considered in some patients (see section 4.5).

Intravenous use

PANTOPRAZOLE 40 mg IV AUSTELL is for intravenous route only and must not be given by any other route.

Mild gastrointestinal complaints

PANTOPRAZOLE 40 mg IV AUSTELL is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

Reflux oesophagitis

Diagnosis of reflux oesophagitis should be confirmed by endoscopy.

4.5 Interaction with other medicines and other forms of interaction

Effects of pantoprazole on the pharmacokinetics of other substances

Active substances with pH dependent absorption

Because of profound and long-lasting inhibition of gastric acid secretion, pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL may interfere with the absorption of other medicines where gastric pH is an important determinant of oral bioavailability.

Atazanavir or nelfinavir

Co-administration of atazanavir and other HIV medicines whose absorption is pH-dependent with proton-pump inhibitors might result in a substantial reduction in the bioavailability of these HIV medicines and might impact the efficacy of these medicines (see section 4.4). Therefore, the co-administration of proton pump inhibitors, such as PANTOPRAZOLE 40 mg IV AUSTELL with atazanavir or nelfinavir is contraindicated.

If the combination of HIV protease inhibitors with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole dose of 20 mg per day should not

be exceeded. Dosage of the HIV protease inhibitor may need to be adjusted.

Other active substances

The absorption of medicines whose absorption is pH dependent, e.g. ketoconazole, itraconazole, posaconazole, ampicillin esters, iron salts and other medicines such as erlotinib is significantly reduced and thus clinical efficacy may be impaired when they are taken concomitantly with PPIs such as pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL.

Substances metabolised by CYP2C19 and CYP3A4

Pantoprazole, the active ingredient of PANTOPRAZOLE 40 mg IV AUSTELL 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 metabolized with these pathways, like carbamazepine, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol, did not reveal clinically significant interactions.

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

Substances metabolised by CYP2C19

The metabolism of concomitant pro-drugs or active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these active substances decreased or increased, respectively. Examples of such a pro-drug is clopidogrel and of active substances are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Clopidogrel

Clopidogrel is metabolised to its active metabolite in part by CYP2C19. Co-administration of clopidogrel

and proton pump inhibitors like pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL, which inhibits CYP2C19 metabolism may result in a significant decreased exposure to the active metabolite of clopidogrel with a resultant decrease in inhibition of platelet aggregation and thus reduce the antiplatelet effect of clopidogrel.

As a precaution, concomitant use of pantoprazole and clopidogrel should be discouraged.

Diazepam

Pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL may prolong the elimination of diazepam.

Phenytoin

Pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL may prolong the elimination of phenytoin. Monitoring phenytoin plasma concentration is recommended.

Coumarin anticoagulants

The response to anticoagulants such as warfarin may be affected by any concomitant medication.

Co-administration of pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL with warfarin or phenoprocoumon did not affect the pharmacokinetics of warfarin, phenoprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenoprocoumon concomitantly as pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL may prolong the elimination of warfarin. 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 PANTOPRAZOLE 40 mg IV AUSTELL is initiated, discontinued or taken irregularly.

Active substances metabolised by CYP3A4

Tacrolimus

Concomitant administration of pantoprazole, as in PANTOPRAZOLE 40 mg IV AUSTELL may decrease the CYP3A4 metabolism and increase the blood levels of tacrolimus in some people.

A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

Unknown mechanism

Methotrexate

Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors, such as pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL has been reported to elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate in some patients (see section 4.4). Therefore, in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

Effects of other active substances on the pharmacokinetics of pantoprazole

Inhibitors of CYP2C19 and/or CYP3A4

Since pantoprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as voriconazole, fluvoxamine) may lead to increased pantoprazole serum levels by decreasing pantoprazole's rate of metabolism.

A dose reduction may be considered for patients treated long-term with high doses of pantoprazole, or those with hepatic impairment.

The plasma concentration of both pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL and voriconazole may be increased.

Inducers of CYP2C19 and/or CYP3A4

Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John´s wort (Hypericum perforatum) may reduce the plasma concentrations of PPIs such as pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL that are metabolized through these enzyme systems.

Other interactions

Concomitant administration with medicines that may cause hypomagnesaemia

Proton pump inhibitors including, pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL, can cause hypomagnesaemia when used for a prolonged period, and the risk may be further increased when combined with other medicines that also have this effect.

For patients expected to be on prolonged treatment or who take PANTOPRAZOLE 40 mg IV AUSTELL with medicines that may cause hypomagnesaemia such as digoxin, tacrolimus or diuretics, measuring of magnesium levels before starting PANTOPRAZOLE 40 mg IV AUSTELL treatment and periodically during treatment should be considered (see section 4.4).

False Positive Urine Tests for THC

There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving proton pump inhibitors, such as pantoprazole as in PANTOPRAZOLE 40 mg IV AUSTELL. An alternative confirmatory method should be considered to verify positive results.

Food

Concomitant intake of food has no influence on the bioavailability.

Antacids

There are no interactions with concomitantly administered antacids.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

Excretion of pantoprazole into human milk has been reported. Safety during lactation has not been established (see section 4.3).

Fertility

It has been reported that 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

Adverse reactions such as dizziness and visual disturbances and somnolence may occur. Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents.

4.8 Undesirable effects

a) Summary of the safety profile

It is reported that the most common side effects are benign fundic gland polyps and injection site thrombophlebitis.

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with pantoprazole.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations		*Clostridium difficile* associated diarrhoea (CDAD)	
Blood and lymphatic system disorders		agranulocytosis, thrombocytopenia, leukopenia, pancytopenia	
Immune system disorders		hypersensitivity (including anaphylactic reactions and anaphylactic shock)	
Metabolism and nutrition disorders		hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes	Hyponatraemia, hypomagnesaemia (see section 4.4), hypocalcaemia [(1)], hypokalaemia

Psychiatric disorders		Headache, dizziness, taste disorders	Paraesthesia
Eye disorders		Disturbances in vision/blurred vision	
Gastrointestinal disorders	Fundic gland polyps (benign)	Diarrhoea, nausea/vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort	Microscopic colitis
Hepatobiliary disorders		liver enzymes increased (transaminases, γ-gt), bilirubin increased	hepatocellular injury, jaundice, hepatocellular failure
Skin and subcutaneous tissue disorders		rash/exanthema/eruption, pruritus, urticaria, angioedema	Stevens-Johnson syndrome, Lyell syndrome (toxic epidermal necrolysis), erythema multiforme, photosensitivity, subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal and connective tissue disorders		fracture of the hip, wrist or spine (see section 4.4), arthralgia, myalgia	muscle spasm [(2)]
Renal and urinary disorders			interstitial nephritis (with possible progression to renal failure)

Reproductive system and breast disorders		Gynaecomastia	
General disorders and administration site conditions	Injection site thrombophlebitis	Asthenia, fatigue and malaise, body temperature increased, peripheral oedema	

[1] Hypocalcaemia in association with hypomagnesemia

[2] Muscle spasm as a consequence of electrolyte disturbance

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za.

4.9 Overdose

There are no known symptoms of overdosage in man.

Systemic exposure with up to 240 mg administered intravenously over 2 minutes, were well tolerated.

As pantoprazole is extensively protein bound, it is not readily dialysable.

In the case of an overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A.11.4.3 Medicines acting on the gastro-intestinal tract, Other.

Pharmacotherapeutic group: Proton pump inhibitors.

ATC code: A02BC02.

Mechanism of action

Pantoprazole is a proton pump inhibitor; i.e. it inhibits specifically and dose proportionally H+, K+ - ATPase, 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 parietal cells after absorption. In the parietal cell it is protonated and chemically rearranged 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 action 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 the effect can be diminished at the same rate as acid secretion is inhibited.

Effect on gastric acid secretion

Following oral or intravenous administration, pantoprazole inhibits the pentagastrin–stimulated gastric acid secretion. The mean acid inhibition was 85 %, 2 ½ to 3 ½ hours after dosing with pantoprazole 40 mg/day for 7 days. With 30 mg pantoprazole intravenous, the mean acid inhibition after 5 days was 99 %. Basal 24 hour acidity was reduced by 98 %.

After stopping the administration of pantoprazole, there is no evidence of rebound hypersecretion and 7 days after administrating the last dose the acid output is normal.

Pantoprazole maintains the physiological pH–rhythm. The values, however, are shifted to higher levels. During the night, periods with pH values approximating placebo have been found to occur.

Although pantoprazole has a half-life of approximately 1 hour, the antisecretory effect increases during repeated once daily administration, demonstrating that the duration of action markedly exceeds the serum elimination half-life.

5.2 Pharmacokinetic properties

Absorption and distribution

Following intravenous administration of pantoprazole, serum/plasma concentrations decline bi-exponentially. Pantoprazole's serum protein binding is about 98 %. The volume of distribution is about 0,15 L/kg.

Biotransformation

Pantoprazole is almost exclusively metabolised in the liver.

The main metabolic pathway is demethylation by CYP2C19 to form desmethylpantoprazole with subsequent sulphate conjugation, other metabolic pathway includes oxidation by CYP3A4.

Elimination

The terminal half-life (t½) is about 1 hour. The total serum clearance is approximately 0,1 L/h/kg

Renal elimination represents the major route of excretion (about 80 %) for the metabolites of pantoprazole; the rest is excreted with the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 hours) is not much longer than that of pantoprazole.

Linearity/non-linearity

The pharmacokinetics of pantoprazole after both oral and intravenous administration is linear over the dose range of 10 – 80 mg.

Special populations

Poor metabolisers

The major enzyme involved in pantoprazole metabolism is cytochrome P450 isoenzyme CYP2C19. This enzyme is polymorphically expressed, and individuals who are deficient in the enzyme are called poor metabolisers of pantoprazole. This occurs in about 3 % of Caucasians and 15 % of Chinese, Japanese, and Koreans. 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.

Renal impairment

No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (incl. dialysis patients) (see section 4.2). The half-life of pantoprazole in patients with renal impairment is comparable to the half-life of pantoprazole in healthy subjects. Only very small amounts of pantoprazole are dialyzed. Although the main metabolite has a moderately delayed half-life (2 – 3 h), excretion is still rapid and thus accumulation does not occur.

Hepatic impairment

For patients with mild to moderately severe hepatic cirrhosis (classes A and B according to Child) the elimination half-life values increase to between 7 to 9 hours. The AUC values increase by a factor of 5 to 7, while the maximum serum concentration only increases by a factor of 1,5 in comparison with healthy subjects. A dose reduction in patients with severe hepatic impairment is required (see section 4.2).

Elderly population

A slight increase in AUC and Cmax occurs in elderly volunteers compared with younger people. This is also not clinically relevant and no dose reduction is recommended when pantoprazole is administered to elderly patients (see section 4.2).

Paediatric population

Following administration of single intravenous 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Citrate Dihydrate

Mannitol

Sodium Hydroxide (alkalising agent)

6.2 Incompatibilities

PANTOPRAZOLE 40 mg IV AUSTELL must not be mixed with or reconstituted and/or diluted with other medicines before parenteral administration except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial: 24 months

Reconstituted and/or diluted solution:

After reconstitution or reconstitution and dilution, in physiological sodium chloride or 5 % glucose as indicated in section 6.6, chemical and physical in use stability of solution for injection has been demonstrated for 12 hours at 25 °C. The reconstituted and/or diluted solution must be used within 12 hours and any unused portion must be discarded after 12 hours.

From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Unopened vial:

Store at or below 25 °C.

Protect from light.

Keep the vial in the carton until required for use.

Reconstituted and/or diluted solution:

For storage conditions of the reconstituted and diluted solution for injection, see section 6.6.

6.5 Nature and contents of container

10 mL Type I amber glass vial with a grey chlorobutyl rubber stopper and yellow polypropylene flip-off cap with an aluminium seal containing 40 mg lyophilised powder for solution for injection.

Pack size: 1 x 10 mL or 5 x 10 mL vial packed into a cardboard carton together with a leaflet.

6.6 Special precautions for disposal and other handling

Preparation and storage of solution before parenteral administration

A ready-to-use solution is prepared by injecting 10 mL of physiological sodium chloride 9 mg/mL (0,9 %) solution into the vial containing the freeze-dried powder. The reconstituted solution is clear and brownish-yellow coloured.

The solution may be administered directly, or it may be further diluted by mixing with 100 mL physiological sodium chloride or 5 % glucose ONLY. Glass or plastic containers should be used for dilution.

PANTOPRAZOLE 40 mg IV AUSTELL should not be prepared or mixed with solvents other than those stated.

After preparation of the solution in physiological sodium chloride 9 mg/mL (0,9 %) solution or 5 % glucose it must be stored at or below 25 °C and used within 12 hours and any unused portion must be discarded after 12 hours. From a microbiological point of view, the product should be used immediately.

The contents of the vial are for single use only. Any product that has remained in the container or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed) should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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2193

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Tel: +27 11 611 1400 or +27 860 287 835

8. REGISTRATION NUMBER

PANTOPRAZOLE 40 mg IV AUSTELL: 60/11.4.3/0914

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 October 2025

10. DATE OF REVISION OF THE TEXT