APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PANTOPRAZOLE 40 mg PD tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PANTOPRAZOLE 40 mg PD tablet contains pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

PANTOPRAZOLE 40 mg PD contains mannitol 141.0 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet.

PANTOPRAZOLE 40 mg PD: Orangish, biconvex and oval gastro-resistant tablet. Diameter: 6,1 mm x 11,7 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PANTOPRAZOLE 40 mg PD 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 PD used in combination with appropriate antibiotics may be useful.

PANTOPRAZOLE 40 mg PD is indicated for the treatment of Zollinger-Ellison Syndrome.

4.2 Posology and method of administration

The recommended once daily dose of PANTOPRAZOLE 40 mg PD should be taken in the morning.

Duodenal ulcer

The recommended oral dose is 40 mg of PANTOPRAZOLE PD 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 PANTOPRAZOLE PD used in combination with appropriate antibiotics may be useful.

Gastric ulcer

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

Zollinger-Ellison Syndrome

For the management of Zollinger-Ellison Syndrome patients should start their treatment with a daily dose of 80 mg of PANTOPRAZOLE PD. Therefore, the dose 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 (GORD)

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

Long-term management and prevention of relapse in GORD

For long-term management a maintenance dose of one 20 mg PANTOPRAZOLE PD tablet per day is recommended, increasing to

40 mg PANTOPRAZOLE PD per day if a relapse occurs. After healing of the relapse, the dose can be reduced to 20 mg of PANTOPRAZOLE PD. Experience with long-term administration is limited.

Special populations

Elderly patients

No dosage adjustment is necessary in the elderly.

Impaired renal and liver function

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

Method of administration

For oral use.

PANTOPRAZOLE 40 mg PD should be swallowed whole with a little water either before or during breakfast.

4.3 Contraindications

- hypersensitivity to pantoprazole or to any of the ingredients of PANTOPRAZOLE 40 mg PD (see section 6.1)

- safety and efficacy in children has not been established
- severely impaired liver function (see section 4.4)
- co-administration with atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

The daily dose of PANTOPRAZOLE 40 mg PD should not be exceeded in elderly patients or those with impaired renal function.

Co-administration with anticoagulants

The response to anticoagulants such as warfarin may be affected by any concomitant medication. It is therefore good practice to monitor the patient with additional PT (prothrombin time)/INR (international normalised ratio) determinations when PANTOPRAZOLE 40 mg PD is initiated, discontinued or taken irregularly. Changes in absorption should be observed when medicines whose absorption is pH-dependent, e.g. ketoconazole, are taken concomitantly.

Gastric malignancy

Prior to treatment, or in the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena), the possibility of malignancy of gastric ulcer or a malignant disease of the oesophagus should be excluded, as the treatment with PANTOPRAZOLE 40 mg PD may

alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Diagnosis of reflux oesophagitis

Diagnosis of reflux oesophagitis should be confirmed by endoscopy.

Clostridium difficile associated diarrhoea (CDAD)

PANTOPRAZOLE 40 mg PD may be associated with an increased risk of *Clostridium difficile* associated diarrhoea (CDAD). A diagnosis of CDAD should be considered for patients taking PANTOPRAZOLE 40 mg PD who develop diarrhoea that does not improve. Patients should use the lowest dose and shortest duration of PANTOPRAZOLE 40 mg PD therapy appropriate to the condition being treated.

Gastrointestinal infections caused by bacteria

Treatment with Pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* or *C. difficile* especially in hospitalised patients. Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. This diagnosis should be considered for diarrhoea that does not improve (see section 4.8).

Hypomagnesaemia

Severe hypomagnesaemia has been rarely reported in patients treated with proton pump inhibitors (PPIs) like PANTOPRAZOLE 40 mg PD for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8). In most affected patients, hypomagnesaemia (and hypomagnesaemia associated hypocalcaemia and/or hypokalaemia) improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Bone fractures

The use of PANTOPRAZOLE 40 mg PD may be associated with an increased risk of bone fractures in the hip, wrist or spine. This effect has been reported mostly in people taking high doses, on long-term treatment, and in those who were 50 years and older or in presence of other recognised risk factors. It is not clear if PANTOPRAZOLE 40 mg

PD is the actual cause of an increased risk of bone fractures. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10 - 40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Hepatic impairment

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

Mild gastro-intestinal complaints

PANTOPRAZOLE 40 mg PD is not indicated for mild gastro-intestinal complaints such as nervous dyspepsia.

Vitamin B_{12} absorption

Daily treatment with acid-blocking medicines including PANTOPRAZOLE 40 mg PD over a long period of time (e.g. longer than 3 years) may lead to malabsorption of vitamin B12 caused by hypo- or achlorhydria. Cases of vitamin B12 deficiency under acid-blocking therapy have been reported. This should be considered when

respective clinical symptoms are observed.

Co-administration with HIV protease inhibitors

Co-administration of PANTOPRAZOLE 40 mg PD is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, due to significant reduction in their bioavailability (see section 4.5).

Long-term treatment

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

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of Subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care provider should consider stopping PANTOPRAZOLE 40 mg PD. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations

for neuroendocrine tumours. To avoid this interference, PANTOPRAZOLE 40 mg PD treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Combination therapy

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

Information on excipients of PANTOPRAZOLE 40 mg PD:

PANTOPRAZOLE 40 mg PD contains mannitol. Patients with rare hereditary conditions of fructose intolerance should not take PANTOPRAZOLE 40 mg PD.

PANTOPRAZOLE 40 mg PD contains sodium. To be taken into consideration in patients on a sodium controlled diet.

4.5 Interaction with other medicines and other forms of interaction

Concomitant intake of food has no influence on the bioavailability.

PANTOPRAZOLE 40 mg PD may reduce or increase the absorption of medicines whose bioavailability is pH-dependent, e.g. ketoconazole,

itraconazole, posaconazole and other medicines like erlotinib.

HIV protease inhibitors

It has been shown that atazanivir 300 mg/ritonavir 100 mg with a proton pump inhibitors (PPIs) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanivir. The absorption of atazanavir is pH-dependent. Therefore PPIs, including pantoprazole should not be co-administered with atazanavir (see section 4.3).
If the combination of HIV protease inhibitors with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A PANTOPRAZOLE 40 mg PD dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitor may need to be adjusted.

Coumarin anticoagulants (phenprocoumon or warfarin)

The response to anticoagulants such as warfarin, phenprocoumon and acenocoumarol may be affected by any concomitant medicine. There have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. It is therefore good practice to monitor the patient with additional PT (prothrombin time) /INR (international normalised ratio) determinations when PANTOPRAZOLE 40 mg PD is initiated,

discontinued or taken irregularly.

Methotrexate

Concomitant use of high-dose methotrexate (e.g. 300 mg) and proton pump inhibitors including PANTOPRAZOLE 40 mg PD has been reported to increase methotrexate levels in some patients. Therefore in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

Inhibitors of CYP2C19

Inhibitors of CYP2C19, such as fluvoxamine, could increase the systemic exposure of pantoprazole. A dose reduction may be considered for patients treated long-term with high doses of PANTOPRAZOLE 40 mg PD, or those with hepatic impairment.

Enzyme inducers affecting CYP2C19 and CYP3A4

Enzyme inducers affecting CYP2C19 and CYP3A4, such as rifampicin and St John´s wort (*Hypericum perforatum*), may reduce the plasma concentrations of PPIs that are metabolized through these enzyme systems.

Other interactions studies:

The active ingredient of PANTOPRAZOLE 40 mg PD is metabolised in the liver via the cytochrome P450 enzyme system. An interaction of PANTOPRAZOLE 40 mg PD 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, phenytoin, piroxicam, theophylline, warfarin and oral contraceptives.

There were no interactions with concomitantly administered antacids.

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

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and during lactation has not been established.

Pregnancy

Animal studies have shown reproductive toxicity.

As a precautionary measure, it is preferable to avoid the use of PANTOPRAZOLE 40 mg PD during pregnancy.

Breastfeeding

There is insufficient information on the excretion of pantoprazole in human milk but excretion into human milk has been reported. A risk to the newborns/infants cannot be excluded. Therefore, breastfeeding while on PANTOPRAZOLE 40 mg PD is not recommended.

Fertility

There was no evidence of impaired fertility following the administration of pantoprazole in animal studies. There is no data on fertility in humans with PANTOPRAZOLE 40 mg PD.

4.7 Effects on ability to drive and use machines

PANTOPRAZOLE 40 mg PD may have a minor or moderate influence on the ability to drive.

PANTOPRAZOLE 40 mg PD may affect the ability to drive in that adverse effects, such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.

4.8 Undesirable effects

Summary of the safety profile

Approximately 5 % of patients can be expected to experience adverse drug reactions (ADRs).

Tabulated list of adverse effects

System Organ Class	Frequency	Side effects
Infections and Infestations	Frequency unknown	*Clostridium difficile*-associated diarrhoea*
Blood and lymphatic system disorders	Less frequent	Leukopenia, thrombocytopenia, pancytopenia, agranulocytosis
Immune system disorders	Less frequent	Anaphylactic reactions including anaphylactic shock and angioedema
Metabolism and nutrition disorders	Less frequent Frequency unknown	Increased bilirubin, elevated triglycerides and increased body temperature, lipid increases, hyperlipidaemia, weight changes Hyponatraemia, hypomagnesaemia, hypocalcaemia in association with hypomagnesaemia
Psychiatric disorders	Less frequent	Mental depression, sleep disorders, depression, hallucination*, confusion*, disorientation
Nervous system disorders	Frequent Less frequent	Headache Dizziness, taste disorders

Eye disorders	Less frequent	Disturbances in vision (blurred vision)
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Gastrointestinal complaints such as upper abdominal pain, diarrhoea, constipation or flatulence Nausea, vomiting, dry mouth Microscopic colitis*
Hepatobiliary disorders	Frequent Less frequent Frequency unknown	Severe hepatocellular damage* leading to jaundice* with or without hepatic failure* and increased liver enzymes (transaminases, γ-GT)
Skin and subcutaneous tissue disorders	Less frequent	Allergic reactions such as pruritus, and skin rash, urticarial and severe skin reactions such as Stevens-Johnson Syndrome*, erythema multiforme*, toxic epidermal necrolysis* (Lyell syndrome) and photosensitivity*, Drug reaction with eosinophilia and systemic symptoms (DRESS)*, subacute cutaneous lupus erythematosus*
Musculoskeletal, connective tissue and bone disorders	Less frequent Frequency unknown	Arthralgia, myalgia, fracture of the hip, wrist or spine Muscle spasm as a consequence of electrolyte disturbance
Renal and urinary disorders	Less frequent	Interstitial nephritis*

Reproductive system and breast disorders	Less frequent	Gynaecomastia
General disorders and administrative site conditions	Less frequent	Asthenia, fatigue, malaise, and peripheral oedema, body temperature increased

*Post marketing adverse events.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link:

https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/

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

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

4.9 Overdose

Signs and symptoms:

There are no known symptoms of overdosage in man.

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

Management of overdose:

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

No specific therapeutic recommendation can be made in cases of overdosage with clinical signs of intoxication. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors

ATC code: A02BC02

Pharmacological classification: A. 11.4.3 Medicines acting on the gastro-intestinal tract.

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 the parietal cells after absorption. In the parietal

cell it is protonated and chemically re-arranged to the active inhibitor, a cyclic sulphonamide, which binds to the H+, K+-ATPase, thus inhibiting the proton pump and causing suppression of stimulated and basal gastric acid secretion after single and multiple intravenous and oral pantoprazole dosing. Because pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus.

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

Therefore, the complete pharmacological and therapeutic effect for pantoprazole can only be achieved in the acid-secreting parietal cells.

By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

Effect on gastric acid secretion

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

5.2 Pharmacokinetic properties

Absorption:

Pantoprazole is unstable in acid and is administered orally in the form of an enteric-coated tablet. Absorption takes place in the small intestine. On average, the maximum serum/plasma concentrations are approximately 2 to 3 µg/mL about 2½ hours after administration of 40 mg pantoprazole daily, as a single or multiple dose in healthy volunteers. The absolute systemic bioavailability of pantoprazole from single and multiple oral doses of pantoprazole is approximately 77 %. Concomitant intake of food had no influence on AUC, maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

Distribution

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

Biotransformation:

Pantoprazole is almost exclusively metabolised in the liver. The main metabolite is desmethylpantoprazole, which is conjugated with sulphate other metabolic pathway includes oxidation by CYP3A4.

Elimination:

Renal elimination represents the most important route of excretion (approximately 80 %) for the metabolites of pantoprazole. The balance

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

Linearity/non-linearity:

The plasma kinetics for pantoprazole administration are linear over the dose range 10 - 80 mg.

Pharmacokinetics in special patient groups

Pharmacokinetic profile in patients with impaired liver or renal function

For patients with mild to moderately severe hepatic cirrhosis the elimination half-life values increase from 1 hour to between 7 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.

In patients with renal impairment the half-life of the main metabolite is moderately increased but there is no accumulation at therapeutic doses. The half-life of pantoprazole in patients with renal impairment is comparable to the half-life of pantoprazole in healthy subjects. Pantoprazole is poorly dialysed. A slight increase in AUC and C_{max} occurs in elderly volunteers compared with younger people.

Poor metabolisers

Approximately 3 % of the European population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60 %. These findings have no implications for the posology of pantoprazole.

Elderly

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

Paediatric population

Following administration of single oral doses of 20 or 40 mg pantoprazole to children aged 5 - 16 years AUC and C_{max} were in the range of corresponding values in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 - 16 years there was no significant association between pantoprazole clearance and age or weight. AUC

and volume of distribution were in accordance with data from adults.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Carmellose sodium

Colloidal anhydrous silica

Magnesium stearate

Mannitol

Sodium carbonate anhydrous

Sodium starch glycolate type A

Coating:

Hypromellose

Methacrylic acid-ethyl acrylate copolymer

Propylene glycol

Titanium dioxide (E171)

Triethyl citrate

Yellow iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from moisture.

Store blister in the outer carton until required for use.

6.5 Nature and contents of container

PANTOPRAZOLE 40 mg PD tablets are packed in aluminium-polyamide-PVC/aluminium blister strips. 28 or 30 Tablets are packed in an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

PANTOPRAZOLE 40 mg PD: A43/11.4.3/0345

9. DATE OF FIRST AUTHORISATION

26 November 2015

10. DATE OF REVISION OF THE TEXT

05 November 2024