RBC PHARMACEUTICALS (PTY) LTD.

PANTAKIND-40 (Pantoprazole sodium, Delayed release tablets)

PROFESSIONAL INFORMATION FOR PANTAKIND-40

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PANTAKIND-40, Delayed release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric coated tablet contains 42,280 mg pantoprazole sodium equivalent to 40 mg pantoprazole.

Sugar free.

For the full list of excipients, (see section 6.1)

3. PHARMACEUTICAL FORM

Tablets: Light brown to brown, round, biconvex, delayed-release tablets imprinted with ‘L9’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PANTAKIND-40 is indicated for the short-term treatment of duodenal ulcer, gastric ulcer and reflux oesophagitis.

If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori* infection, PANTAKIND-40 used in combination with appropriate antibiotics may be useful.

PANTAKIND-40 is indicated for the treatment of Zollinger-Ellison Syndrome.

4.2 Posology and method of administration

Posology

Duodenal ulcer

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

Gastric ulcer

The recommended oral dose is 40 mg PANTAKIND-40 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 PANTAKIND-40 once daily for 4 to 8 weeks.

Zollinger-Ellison Syndrome

For management of Zollinger-Ellison Syndrome patients should start their treatment with a daily dose of 80 mg (2 tablets of PANTAKIND-40). 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.

Long-term management and prevention of relapse in gastro-oesophageal reflux disease

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

Special population

Elderly patients

No dosage adjustment is necessary for 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 PANTAKIND-40 should not be exceeded in patients with mild to moderately severe liver impairment (see sections 4.4 and 5.2).

Method of administration

For oral administration

PANTAKIND-40 should be swallowed whole with a little water either before or during breakfast.

4.3 Contraindications

PANTAKIND-40 is contraindicated in:

Hypersensitivity to pantoprazole sodium.

Severely impaired liver function (see section 4.4).

Safety and efficacy in children have not been established.

PANTAKIND-40 should not be co-administered with atazanavir and nelfinavir (see section 4.4).

4.4 Special warnings and precautions for use

Hepatic impairment

In patients with severe liver impairment, the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise in the liver enzymes, the treatment should be discontinued (see section 4.2).

Combination therapy

In the case of combination therapy, the Professional Information of the respective medicines should be observed.

Gastric malignancy

Symptomatic response to pantoprazole 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.

Co-administration with HIV protease inhibitors

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

Influence on vitamin B12 absorption

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

Long-term treatment

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

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*.

Hypomagnesaemia

Severe hypomagnesaemia has been rarely reported in patients treated with proton pump inhibitors (PPIs) like pantoprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8). In most affected patients, hypomagnesaemia (and hypomagnesaemia associated with hypocalcaemia and/or hypokalaemia) improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who takes 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

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, predominantly in the elderly or in the presence of other recognised risk factors.

Observational studies suggest that proton pump inhibitors 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.

Sub-acute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the healthcare professional should consider stopping Pantoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Acute tubulointerstitial nephritis

Acute Tubulointerstitial Nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. TIN 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. TIN may be drug-related, infectious, systemic, autoimmune, genetic, and idiopathic with the most common cause being

related to a medication 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). In reported case series, some patients were diagnosed on biopsy and in the absence of extrarenal manifestations (e.g. fever rash or arthralgia). Discontinue PANTAKIND-40 and evaluate patients with suspected acute TIN.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, Pantoprazole treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to the reference range after the initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Pantoprazole contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Interference with Antiretroviral Therapy

Concomitant use of atazanavir or nelfinavir with proton pump inhibitors is not recommended. Coadministration of atazanavir or nelfinavir with proton pump inhibitors is expected to substantially decrease atazanavir or nelfinavir plasma concentrations and may result in a loss of therapeutic effect and development of medicine resistance. 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.

Coumarin Anticoagulants

Study reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including PANTAKIND-40, and warfarin concomitantly. Increases in INR and prothrombin time

may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly should be monitored for increases in INR and prothrombin time.

Clopidogrel

In a study concomitant administration of pantoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of PANTAKIND-40.

Medicines for which gastric pH can affect bioavailability

Pantoprazole causes long-lasting inhibition of gastric acid secretion. Therefore, pantoprazole may interfere with the absorption of medicines where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

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. An alternative confirmatory method should be considered to verify positive results.

Methotrexate

Studies published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose, see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted (see section 4.4).

Medicinal products that inhibit or induce CYP2C19

Inhibitors of CYP2C19 such as fluvoxamine could increase the systemic exposure of pantoprazole. A dose reduction may be considered for patients treated long-term with high doses of 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

Pregnancy

The safety in pregnant women has not been established. Animal studies have shown reproductive toxicity.

Breastfeeding

Safety during lactation has not been established. Animal studies have shown the 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. Therefore, a decision on whether to discontinue breastfeeding or to discontinue/abstain from Pantoprazole therapy takes into account the benefit of breastfeeding for the child and the benefit of Pantoprazole therapy for the woman.

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

Pantoprazole has no or negligible influence on the ability to drive and use machines.

Adverse drug reactions, 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

Adverse reactions are listed according to MedDRA primary system organ class. Within each system organ class, adverse reactions are ranked by frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Blood and lymphatic system disorders

Less frequent: Agranulocytosis, thrombocytopenia, leukopenia, pancytopenia.

Immune system disorders

Less frequent: Hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Metabolism and nutrition disorders

Less frequent: Hyperlipidaemias and lipid increases (triglycerides, cholesterol, generalized edema, weight changes.

Frequency unknown: Hyponatremia, hypomagnesemia, hypocalcaemia, hypokalemia.

Psychiatric disorders

Less frequent: Sleep disorders, depression, disorientation (and all aggravations).

Frequency unknown: Hallucination, confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence).

Nervous system disorders

Frequent: Headache

Less frequent: dizziness, taste disorders, vertigo.

Frequency unknown: Paraesthesia.

Eye Disorders

Less frequent: Vision disturbances (blurred vision).

Gastrointestinal disorders

Frequent: Fundic gland polyps (benign).

Less frequent: Diarrhoea, nausea, vomiting, abdominal distension and bloating, constipation or flatulence, abdominal pain and discomfort, dry mouth.

Frequency unknown: Microscopic colitis.

Hepato-biliary disorders

Less frequent: Increased liver enzymes (transaminases, y-GT), Increased bilirubin.

Frequency unknown: Hepatocellular damage leading to jaundice and hepatic failure.

Skin and subcutaneous tissue disorders

Less frequent: Rash/exanthema/eruption, pruritus, urticaria, angioedema.

Frequency unknown: Stevens-Johnson syndrome, Lyell syndrome, severe dermatologic reactions (some fatal), including erythema multiforme, toxic epidermal necrolysis (TEN, some fatal), photosensitivity reaction Sub-acute cutaneous lupus erythematosus (see section 4.4). Drug reaction with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal, connective tissue and bone disorders

Less frequent: Fracture of the hip, wrist or spine, *a*rthralgia, myalgia.

Frequency unknown: Rhabdomyolysis, muscle spasm[(2)].

Renal and urinary disorders

Frequency unknown: Tubulointerstitial nephritis (TIN) (with possible progression to renal failure).

Reproductive system and breast disorders

Less frequent: Gynaecomastia.

General disorders and administrative site conditions

Less frequent: Asthenia, fatigue, malaise, Increased body temperature, Peripheral oedema,

Investigations

Less frequent: elevated triglycerides.

Description of selected adverse reactions

[1] · Hypocalcemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia in association with hypomagnesemia (see section 4.4)

[2]· Muscle spasm as a consequence of electrolyte disturbance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine are 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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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: A02BC02

Pharmacological classification - A 11.4.3 Medicines acting on the gastrointestinal tract.

Mechanism of action

Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H+, K+ATPase enzyme, i.e., the final stage in the production of hydrochloric acid in

the stomach. The inhibition is dose dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved within 2 weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the medicine is given orally or intravenously.

Pharmacodynamic effects

The fasting gastrin values increase under pantoprazole. In short-term use, in most cases they do not exceed the upper limit of normal. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments has not been observed in humans.

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid according to results in animal studies.

During treatment with antisecretory medicines, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

5.2 Pharmacokinetic properties

Absorption

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40 mg oral dose. On average at about 2,5 h p.a. the maximum serum concentrations of about 2 - 3 µg/mL are achieved, and these values remain constant after multiple administrations.

Pharmacokinetics does not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole is linear after both oral and intravenous administration.

The absolute bioavailability from the tablet was found to be about 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 %. The volume of distribution is about 0,15 L/kg.

Biotransformation

The substance is almost exclusively metabolised in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation; other metabolic pathway includes oxidation by CYP3A4.

Elimination

Terminal half-life is about 1 hour and clearance is about 0,1 L/h/kg. There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole to the proton pumps of the parietal cell the elimination of half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

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 desmethyl pantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1,5 hours) is not much longer than that of pantoprazole.

Special populations

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.

Renal impairment

No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. 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

Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 7 and 9 h and the AUC values increased by a factor of 5 - 7, the maximum serum concentration only increased slightly by a factor of 1,5 compared with healthy subjects.

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 to 16 years AUC and C_{max} were in the range of corresponding values in adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium stearate

Crospovidone

Hypromellose

Mannitol

Polyethylene glycol

Purified Water

Silicon dioxide

Sodium carbonate anhydrous

Sucrose

Talc

Enteric coating

Methacryclic acid - Ethyl acrylate copolymer (1:1)

Triethyl citrate

FILM COATING

Isopropyl alcohol

Opadry brown 00B565003 containing HPMC 2910/Hypromellose, MACROGOL/PEG, Talc, Iron Oxide Red and Ferrosoferric Oxide NF/ Black Iron Oxide

Opacode black S-1-17823 (Ink) containing Shellac Glaze, Isopropyl Alcohol, Black Iron Oxide, n-Butyl Alcohol, Propylene Glycol and Ammonium Hydroxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Delayed release tablets

2 years

6.4 Special precautions for storage

PANTAKIND-40 Delayed release tablets

Do Not Store above 30 ºC.

Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of the container

PANTAKIND-40 Delayed-release tablets:

10 tablets are packed in Alu-Alu Blister. 3 such blisters are packed in cartons.

6.6 Special precautions for disposal and other handling

This medicine does not require any special storage conditions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

RBC PHARMACEUTICALS (PTY) LTD.

23 Kiaat Street, ERF 926, Extension 7,

Noordwyk, Midrand, Gauteng,

South Africa, 1687

Tel: 010 224 0999.

8. REGISTRATION NUMBERS

57/11.4.3/0571

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 August 2025

10. DATE OF REVISION OF TEXT

TBA