1.3.1.1 Professional Information for medicines for human use– January 2021

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

MYLAN PANTOPRAZOLE 20 mg (Enteric-coated tablets)

MYLAN PANTOPRAZOLE 40 mg (Enteric-coated tablets)

COMPOSITION:

MYLAN PANTOPRAZOLE 20 mg - Each tablet contains 22,550 mg pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

Contains lactose monohydrate 19,06 mg

MYLAN PANTOPRAZOLE 40 mg - Each tablet contains 45,1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

Contains lactose monohydrate 38,12 mg

Excipients for **MYLAN PANTOPRAZOLE 20 mg** and **40 mg** Tablets:

Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, silica colloidal anhydrous, purified water, a colour mixture and coating material.

PHARMACOLOGICAL CLASSIFICATION:

A02BC02 Proton pump inhibitors

A.11.4.3 Medicines acting on the gastro-intestinal tract.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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 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:

The mean inhibition of pentagastrin stimulated acid output after dosing of 7 days with pantoprazole 40 mg/day is 85 %, 2½ to 3½ hours after dosing.

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. 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.

Pharmacokinetic properties:

Absorption and distribution:

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 micrograms/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 %.

Metabolism:

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

Pharmacokinetic profile in patients with impaired liver or renal function:

In subpopulations of subjects suffering from mild to moderately severe liver cirrhosis, the half-life increases to between 7 to 9 hours. The AUC values increase by a factor of 5 to 8, while the maximum serum concentration 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 dialysable. A slight increase in AUC and C_{max} occurs in elderly volunteers compared with younger people.

INDICATIONS:

MYLAN PANTOPRAZOLE 40 mg 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, **MYLAN PANTOPRAZOLE 40 mg** used in combination with appropriate antibiotics may be useful.

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

MYLAN PANTOPRAZOLE 20 mg is indicated for the symptomatic improvement (e.g. heartburn, acid regurgitation, pain on swallowing) and healing of mild gastro-oesophageal reflux disease (GERD).

MYLAN PANTOPRAZOLE 20 mg is indicated for long-term management and prevention of relapse in gastro-oesophageal reflux disease (GERD).

MYLAN PANTOPRAZOLE 20 mg is indicated for the prevention of gastroduodenal lesions and dyspeptic symptoms induced by non selective non steroidal anti-inflammatory drugs (NSAID's) in patients at risk, and with a need for continuous NSAID treatment.

CONTRAINDICATIONS:

Hypersensitivity to pantoprazole or any of the ingredients of **MYLAN PANTOPRAZOLE** tablets.
Safety and efficacy in children have not been established.
Severely impaired liver function (see under **DOSAGE AND DIRECTIONS FOR USE).**
Co-administration with atazanavir (see **INTERACTIONS).**

WARNINGS AND SPECIAL PRECAUTIONS:

In patients with severe liver impairment the liver enzymes should be monitored regularly during treatment with **MYLAN PANTOPRAZOLE**, particularly on long-term use. In the case of a rise of the liver enzymes **MYLAN PANTOPRAZOLE** should be discontinued. **MYLAN PANTOPRAZOLE** is not indicated for mild gastro-intestinal complaints such as nervous dyspepsia.

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

Diagnosis of reflux oesophagitis should be confirmed by endoscopy.

Daily treatment with any acid-blocking medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin caused by hypo- or achlorhydria. Rare cases of cyanocobalamin deficiency under acid-blocking therapy have been reported in the literature. This should be considered when respective clinical symptoms are observed.

Use of **MYLAN PANTOPRAZOLE 20 mg** as preventative of gastroduodenal ulcers, induced by non-selective non steroidal anti-inflammatory drugs (NSAID's) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastro-intestinal complications.

MYLAN PANTOPRAZOLE 20 mg may increase the risk of subclinical acute or chronic interstitial nephritis associated with proton pump inhibitors (PPIs) leading to chronic renal inflammation and reduced renal function (tubular injury being "tubulointerstitial nephritis").

Information about the lactose content in MYLAN PANTOPRAZOLE:

MYLAN PANTOPRAZOLE contains lactose. Patients with the rare hereditary conditions of

galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **MYLAN PANTOPRAZOLE.**

INTERACTIONS:

Concomitant intake of food has no influence on the bioavailability.

Pantoprazole may reduce or increase the absorption of medicines whose bioavailability is pH-dependant e.g. ketoconazole, ampicillin esters and iron salts.

Atazanavir: It has been shown that co-administration of atazanavir/ritonavir with omeprazole or atazanavir with lansoprazole resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH-dependent. Therefore, pantoprazole must not be co-administered with atazanavir (see **CONTRA-INDICATIONS**).

Pantoprazole, although metabolised by hepatic cytochrome P450-enzyme systems, does not appear to either inhibit or induce cytochrome P450-enzyme activity. However, an interaction of **MYLAN PANTOPRAZOLE** with other medicines which are metabolised using the same enzyme system cannot be excluded.

No clinically significant interactions were observed after concomitant administration of pantoprazole with either antipyrine, diazepam, theophylline, digoxin, phenytoin, carbamazepine, diclofenac, nifedipine, piroxicam, metoprolol, glibenclamide, ethanol, caffeine, warfarin or oral contraceptives. However, the response to anti-coagulants, such as warfarin, may be affected by any concomitant medication. Therefore, monitoring the patient with additional PT (prothrombin time) / INR (International normalized ratio) determinations when **MYLAN PANTOPRAZOLE** is initiated, discontinued or taken irregularly would be a good practice.

There were no interactions with concomitantly administered antacids.

PREGNANCY AND LACTATION:

Safety in pregnancy and during lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

The recommended once daily dosage of pantoprazole should be taken in the morning. **MYLAN PANTOPRAZOLE 20 mg** and **MYLAN PANTOPRAZOLE 40 mg** should be swallowed whole with a little water either before or during breakfast.

Duodenal ulcer

The recommended oral dosage is 40 mg of **MYLAN PANTOPRAZOLE** once daily in the morning for 2 to 4 weeks. If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori* infection, **MYLAN PANTOPRAZOLE 40 mg** used in combination with appropriate antibiotics may be useful.

Gastric ulcer

The recommended oral dosage is 40 mg of **MYLAN PANTOPRAZOLE** once daily in the morning for 4 to 8 weeks.

In the case of a suspected gastric ulcer, malignancy of the ulcer should be excluded, as treatment could conceal the symptoms and may delay diagnosis.

Reflux oesophagitis

The recommended oral dosage is 40 mg of **MYLAN PANTOPRAZOLE** 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 **MYLAN PANTOPRAZOLE** two tablets of **MYLAN PANTOPRAZOLE 40 mg)**. Thereafter, 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 (GERD)

The recommended oral dosage is 20 mg of **MYLAN PANTOPRAZOLE** per day. A 4-week period is usually required for healing of mild GERD.

If symptom control has not been achieved after four weeks of treatment with the prescribed daily dose, further investigation is recommended.

In patients with healed reflux disease, recurring symptoms can be controlled using an on-demand regimen of 20 mg once daily when required.

Long-term management and prevention of relapse in GERD

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

For prevention of gastro-duodenal lesions and dyspeptic symptoms induced by non selective non steroidal anti-inflammatory medicines (NSAID's) in patients at risk and with a need for continuous NSAID treatment, the recommended oral dose is one **MYLAN PANTOPRAZOLE 20 mg** tablet per day.

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 **MYLAN PANTOPRAZOLE** should not be exceeded in patients with mild to moderately severe liver impairment (see **Pharmacokinetic Properties** and **WARNINGS AND SPECIAL PRECAUTIONS**).

SIDE EFFECTS:

Blood and the lymphatic system disorders:

Less frequent: Leukopenia, thrombocytopenia

Immune system disorders:

Less frequent: Anaphylactic reactions including anaphylactic shock

Metabolism and nutrition disorders:

Less frequent: Increased liver enzymes (transaminases, γ-GT), elevated triglycerides and increased body temperature

Psychiatric disorders:

Less frequent: Mental depression

Nervous system disorders:

Frequent: Headache

Less frequent: Dizziness or disturbances in vision (blurred vision)

Gastrointestinal disorders:

Frequent: Gastro-intestinal complaints such as upper abdominal pain, diarrhoea, constipation or flatulence

Less frequent: Nausea, vomiting, dry mouth

Hepato-biliary disorders:

Less frequent: Severe hepatocellular damage leading to jaundice with or without hepatic failure

Skin and subcutaneous tissue disorders:

Less frequent: Allergic reactions such as pruritus and skin rash, urticaria, angioedema and severe skin reactions such as Stevens-Johnson's Syndrome, erythema multiforme, Lyell's Syndrome and photosensitivity

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Arthralgia, myalgia

Renal and urinary disorders:

Less frequent: Interstitial nephritis (with possible progression to renal failure)

General disorders and administrative site conditions:

Less frequent: Peripheral oedema

Post-marketing exposure:

The renal effect of proton pump inhibitors (PPIs) may progress to renal failure as it is not necessarily reversed when treatment is discontinued.

There is an increased risk of subclinical acute or chronic interstitial nephritis associated with proton pump inhibitors (PPIs) leading to chronic renal inflammation and reduced renal function (tubular injury being "tubulointerstitial nephritis").

Acute tubulointerstitial nephritis is characterised by an inflammatory reaction within the tubulointerstitial space of the kidney. Acute interstitial inflammatory reactions are associated with damage to the tubulointerstitium, leading to acute kidney injury.
Interstitial nephritis may lead to renal failure.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

IDENTIFICATION:

MYLAN PANTOPRAZOLE 20 mg: Yellow to ochre, elongated enteric-coated tablet.

MYLAN PANTOPRAZOLE 40 mg: Pale yellow to ochre, elongated enteric-coated tablet.

PRESENTATION:

MYLAN PANTOPRAZOLE 20 mg and **MYLAN PANTOPRAZOLE 40 mg** tablets are available in white HDPE bottles or blister packs of 7, 14, 15, 28, 30, 50, 56, 60, 100 and 250 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Keep container well closed. KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBERS:

MYLAN PANTOPRAZOLE 20 mg: 43/11.4.3/0843

MYLAN PANTOPRAZOLE 40 mg: 43/11.4.3/0844

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

XIXIA PHARMACEUTICALS (PTY) LTD

4 Brewery Street,

Isando, Johannesburg,

1600

Republic of South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

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