PACKAGE INSERT

PANTOLOC RANGE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

PANTOLOC® 20 Enteric-coated tablets

PANTOLOC® 40 Enteric-coated tablets

PANTOLOC® IV Lyophilised powder for injection

COMPOSITION

PANTOLOC® 20 Each tablet contains 22,6 mg pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole and is sugar-free.

Excipients include: sodium carbonate, mannitol, crospovidone, polyvidone K90, calcium stearate, hypromellose 2910, polyvidone K25, titanium dioxide, yellow ferric oxide, propylene glycol, methacrylic acid-ethyl and triethyl citrate.

PANTOLOC® 40 Each tablet contains 45,1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole and is sugar-free.

Excipients include: sodium carbonate, mannitol, crospovidone, polyvidone K90, calcium stearate, hypromellose 2910, polyvidone K25, titanium dioxide, yellow ferric oxide, propylene glycol, methacrylic acid-ethyl and triethyl citrate.

PANTOLOC® IV Each vial contains 42,3 mg pantoprazole sodium equivalent to 40 mg pantoprazole.

Excipients include: edentate disodium dehydrate, sodium hydroxide

PHARMACOLOGICAL CLASSIFICATION

A 11.4.3 Medicines acting on the gastro-intestinal tract.

PHARMACOLOGICAL ACTION

Site and 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 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

Following oral or intravenous administration, pantoprazole inhibits the pentagastrin-stimulated gastric acid secretion. The mean acid inhibition was 85 %, 2½ to 3½ 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 administering 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.

Pharmacokinetics

Absorption and distribution

Oral:

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 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 %.

Intravenous:

Following intravenous administration of pantoprazole, plasma concentrations decline biexponentially. The terminal half-life ($t_{½}$) is about 1 hour. The total serum clearance is approximately 0,1 l/h/kg and the volume of distribution is about 0,15 l/kg, respectively.

The plasma kinetics for pantoprazole after both oral and intravenous administration are linear over the dose range 10-80 mg.

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

For patients with mild to moderately severe hepatic cirrhosis the elimination half-life values increase to between 7 to 9 hours. The AUC values increase by a factor of 5 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.

INDICATIONS

PANTOLOC® IV is indicated for intravenous administration to patients who cannot be treated orally.

PANTOLOC® 40 and **PANTOLOC® IV** are 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, **PANTOLOC® 40** or **PANTOLOC® IV** used in combination with appropriate antibiotics may be useful.

PANTOLOC® 40 and **PANTOLOC® IV** are indicated for the treatment of Zollinger-Ellison Syndrome.

PANTOLOC® 20 is indicated for the symptomatic improvement (e.g. heartburn, acid regurgitation, pain on swallowing) and healing of mild gastro-oesophageal reflux disease. In patients with healed reflux disease, recurring symptoms can be controlled using an on-demand regimen of 20 mg once daily when required.

PANTOLOC® 20 is indicated for long-term management and prevention of relapse in gastro-oesophageal reflux disease.

PANTOLOC® 20 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.

CONTRA-INDICATIONS

Hypersensitivity to pantoprazole.

Severely impaired liver function (**see SPECIAL PRECAUTIONS**).

Safety and efficacy in children have not been established.

PANTOLOC®, should not be co-administered with atazanavir **(see INTERACTIONS).**

WARNINGS

PANTOLOC® IV is for intravenous route only, and must not be given by any other route.

PANTOLOC® is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

Further investigation is to be considered if symptoms persist despite adequate treatment.

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

Clostridium difficile-associated diarrhoea

Published observational studies suggest that proton pump inhibitor therapy, like **PANTOLOC®**, may be associated with an increased risk of *Clostridium difficile*-associated diarrhoea, especially in hospitalised patients. This diagnosis should be considered for diarrhoea that does not improve (**see SIDE FFECTS AND SPECIAL PRECAUTIONS, Post-marketing reports)**

INTERACTIONS

Concomitant intake of food has no influence on the bioavailability.

The active ingredient of **PANTOLOC®** is metabolised in the liver via the cytochrome P450 enzyme system. An interaction of **PANTOLOC®** 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, phenprocoumon, phenytoin, piroxicam, theophylline, warfarin and oral contraceptives.

Coumarin anticoagulants

However, the response to anticoagulants such as warfarin, phenprocoumon and acenocoumarol 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 **PANTOLOC®** is initiated, discontinued or taken irregularly.

Due to long lasting inhibition of gastric acid secretion **PANTOLOC®** may reduce the absorption of medicines with a gastric pH-dependent bioavailability, e.g. some azole antifungals like ketoconazole, itraconazole, posaconazole and other medicines like erlotinib.

HIV medications

It has been shown that co-administration of atazanavir 300 mg/ ritonavir 100 mg with proton pump inhibitors (PPIs) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore PPIs, including **PANTOLOC®**, should not be co-administered with atazanavir (**see CONTRA-INDICATIONS**).

There were no interactions with concomitantly administered antacids.

Methotrexate

Concomitant use of PPIs, including **PANTOLOC®,** with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities.

PREGNANCY AND LACTATION

Safety in pregnancy and during lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

PANTOLOC® 20 and **PANTOLOC® 40**

PANTOLOC® 20 and **PANTOLOC® 40** should be swallowed whole with a little water either before or during breakfast.

PANTOLOC® IV is indicated for intravenous administration to patients who cannot be treated orally.

A ready-to-use solution is prepared by injecting 10 ml of physiological sodium chloride (0,9 %) solution into the vial containing the dry substance. **PANTOLOC® IV** may be used intravenously for up to 7 days. After preparation the solution in physiological sodium chloride solution and 5 % glucose must be used within 12 hours and any unused portion discarded after 12 hours.
The solution may be administered directly or it may be further diluted by mixing with 100 ml physiological sodium chloride solution or 5 % glucose **ONLY**. The medicine should be administered intravenously over 2 - 15 minutes.

As soon as oral therapy is possible, treatment should be replaced with the same oral dose

(**PANTOLOC® 40** tablets) in compliance with the approved dosage regimen.

Duodenal ulcer

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

Gastric ulcer

The recommended oral or IV dose is **40 mg PANTOLOC®** 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 or IV dose is **40 mg PANTOLOC®** 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 **PANTOLOC® 40** or 2 vials of **PANTOLOC® IV).** Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion as a guide. With doses above 80 mg daily, the dose should be divided and given twice daily.

In case rapid acid control is required, a starting dose of 2 x 80 mg **PANTOLOC® IV** is sufficient to manage a decrease of acid output into the target range (<10 mmol/h)within one hour in the majority of patients. Transition from **PANTOLOC® IV** to the oral formulation **PANTOLOC® 40** should be performed as soon as it is clinically justified.

Long-term treatment

Long-term treatment with **PANTOLOC® IV** is currently not indicated as there is insufficient clinical data.

Mild gastro-oesophageal reflux disease

The recommended oral dose is **20 mg PANTOLOC®** per day. A 4-week period is usually required for

healing of mild gastro-oesophageal reflux disease. If this is not sufficient, healing will usually be achieved within a further 4 weeks. In patients with healed reflux disease, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily when required.

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

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

For prevention of gastro-duodenal 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, the recommended oral dose is one **PANTOLOC® 20** 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 **PANTOLOC®** should not be exceeded in patients with mild to moderately severe liver impairment (see under **Pharmacokinetics** above and **SPECIAL PRECAUTIONS** below).

SIDE FFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS

Very common (≥1/10); common (≥1/100, ≤ 1/10); uncommon (≥1/1000, ≤ 1/100); rare (≥ 1/10 000, ≤ 1/1000) very rare (≤ 1/10 000) including isolated cases.

MedDRA System Organ class	Frequency	Side effects
Blood and lymphatic system disorders	Rare	Agranulocytosis
	Very rare	Leukopenia, thrombocytopenia, pancytopenia
Immune system disorders	Rare	Hypersensitivity (incl. anaphylactic reactions and anaphylactic shock
Metabolism and nutrition	Rare	Hyperlipidaemias and lipid increases,

disorders		weight changes
Psychiatric disorders	Uncommon	Sleep disorders
	Rare	Depression
	Very rare	Disorientation (and all aggravations)
Nervous system disorders	Common	Headache
	Uncommon	Dizziness
	Rare	Taste disorders
Eye Disorders	Uncommon	Vision disturbances (blurred vision)
Gastrointestinal disorders	Common	Upper abdominal pain, diarrhoea, constipation or flatulence
	Uncommon	Nausea, vomiting, abdominal distension and bloating, abdominal pain and discomfort
	Rare	Dry mouth
Hepato-biliary disorders	Rare	Increased bilirubin
Skin and subcutaneous tissue disorders	Uncommon	Rash/exanthema/eruption, pruritus
	Rare	Urticaria, angioedema
Musculoskeletal, connective tissue and bone disorders	Rare	Arthralgia
	Very rare	Myalgia
General disorders and administrative site conditions	Uncommon	Asthenia, fatigue, malaise
	Rare	Increased body temperature
	Very rare	Peripheral oedema, injection site thrombophlebitis
Investigations	Very rare	Increased liver enzymes (transaminases, γ-GT), elevated triglycerides

Post-marketing reports:

***Hepatobiliary disorders*:** Hepatocellular injury, jaundice, hepatocellular failure

***Psychiatric disorders*:** Hallucination, confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)

***Renal and urinary disorders*:** Interstitial nephritis

***Skin and subcutaneous tissue disorders*:** Stevens-Johnson syndrome, Lyell syndrome (Toxic epidermal necrolysis), erythema multiforme, photosensitivity

***Infections and infestations*:** *Clostridium difficile*-associated diarrhoea

SPECIAL PRECAUTIONS

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

Use of **PANTOLOC® 20** as preventative of gastroduodenal ulcers, induced by non selective non steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications.

PANTOLOC® is not indicated for mild gastro-intestinal complaints such as nervous dyspepsia.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or malaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with **PANTOLOC®** may alleviate symptoms and delay diagnosis

Daily treatment with any acid-blocking medicines including **PANTOLOC®** 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.

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

PANTOLOC® 20: Yellow, oval, biconvex enteric-coated tablet with a white to off-white core, imprinted "P20" on one side.

PANTOLOC® 40: Yellow, oval, biconvex enteric-coated tablet, with a white to off-white core, imprinted "P40" on one side.

PANTOLOC® IV: A white to almost white lyophylised powder in a glass vial for intravenous injection. The reconstituted solution is a clear yellowish solution.

PRESENTATION

PANTOLOC® 20 blister packs of 28 tablets

PANTOLOC® 40 blister packs of 14 or 28 tablets

PANTOLOC® IV vial with lyophylised powder (1 x 5 vials)

STORAGE INSTRUCTIONS

Store at or below 25 ˚C. Protect from light.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBERS

PANTOLOC® 20: 34/11.4.3/0005

PANTOLOC® 40: 28/11.4.3/0407

PANTOLOC® IV: 33/11.4.3/0041

NAME AND ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

TAKEDA (Pty) Ltd

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Namibia:
Pantoloc 20 – 05/11.4.3/0395
Pantoloc 40 – 05/11.4.3/0396
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