PROFESSIONAL INFORMATION FOR

PRAZOLOC 40 IV

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

PRAZOLOC 40 IV (Powder for solution for IV injection/infusion)

COMPOSITION

Each vial contains pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

PHARMACOLOGICAL CLASSIFICATION

A 11.4.3 Medicines acting on the gastrointestinal tract – Other.

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 rearranged to the active inhibitor, a cyclic sulphenamide, which binds to H^+,K^+-ATPase, thus inhibiting the proton pump and causing suppression of stimulated and basal gastric acid secretion after single and multiple intravenous pantoprazole dosing.

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 of 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 intravenous administration, pantoprazole inhibits pentagastrin-stimulated gastric acid secretion. Mean acid inhibition is 85 %, 2,5 to 3,5 hours after dosing with pantoprazole 40 mg/day for 7 days. With 30 mg pantoprazole intravenous, the mean acid inhibition after 5 days is 99 %. Basal 24-hour acidity is 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.

Pharmacokinetic properties:

Absorption and distribution:

Following intravenous administration of pantoprazole, serum/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.

The plasma kinetics for pantoprazole after 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 1,5 hours, which is slightly longer than that of pantoprazole.

Pharmacokinetic profile in patients with impaired liver or renal function:

For patients with mild to moderate 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

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

PRAZOLOC 40 IV is indicated for intravenous administration to patients who cannot be treated orally. If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori* infection, **PRAZOLOC 40 IV** used in combination with appropriate antibiotics may be useful.

PRAZOLOC 40 IV is indicated for the treatment of Zollinger-Ellison syndrome.

CONTRAINDICATIONS

- Hypersensitivity to any of the ingredients in **PRAZOLOC 40 IV**.
- Safety and efficacy in children have not been established.
- Severely impaired liver function (see **WARNINGS AND SPECIAL PRECAUTIONS**).
- Co-administration with atazanavir and nelfinavir (see **INTERACTIONS**).

WARNINGS AND SPECIAL PRECAUTIONS

PRAZOLOC 40 IV is for intravenous administration only, and must not be given by any other route.

In the case of a rise in liver enzymes, **PRAZOLOC 40 IV** should be discontinued.

PRAZOLOC 40 IV is not indicated for mild gastrointestinal 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 treatment with **PRAZOLOC 40 IV** 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.

The risk of tubulointerstitial nephritis leading to chronic renal inflammation and reduced renal function is associated with the use of PPI's. Tubulointerstitial nephritis may progress to renal failure as is it not necessarily reversed when treatment is discontinued.

Effects on the ability to drive and use machines:

PRAZOLOC 40 IV may cause dizziness or disturbances in vision. Ambulatory patients should be advised to refrain from operating machinery or driving until they know how **PRAZOLOC 40 IV** affects them.

INTERACTIONS

Pantoprazole decreases the concentrations of atazanavir and nelfinavir. Co-administration of **PRAZOLOC 40 IV** and atazanavir or nelfinavir is contraindicated.

Concomitant intake of food has no influence on the bioavailability of **PRAZOLOC 40 IV**.

The active ingredient of **PRAZOLOC 40 IV** is metabolised in the liver via the cytochrome P450 enzyme system. An interaction of **PRAZOLOC 40 IV** 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. However, 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) or INR (international

normalised ratio) determinations when **PRAZOLOC 40 IV** is initiated, discontinued or used irregularly.

There are no interactions with concomitantly administered antacids.

HUMAN REPRODUCTION

Safety in pregnancy and during lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

The recommended intravenous dose is one vial (40 mg pantoprazole) **PRAZOLOC 40 IV** per day.

PRAZOLOC 40 IV is indicated for intravenous administration to patients who cannot be treated orally.

PRAZOLOC 40 IV 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 intravenous dose is **PRAZOLOC 40 IV** once daily. If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori*

infection, **PRAZOLOC 40 IV** used in combination with appropriate antibiotics may be useful.

Gastric ulcer:

The recommended intravenous dose is 40 mg **PRAZOLOC 40 IV** once daily.

Reflux oesophagitis:

The recommended intravenous dose is 40 mg **PRAZOLOC 40 IV** once daily.

PRAZOLOC 40 IV 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. If symptom control has not been achieved after four weeks of treatment with the prescribed daily dose, 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 **PRAZOLOC 40 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 **PRAZOLOC 40 IV** 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 **PRAZOLOC 40 IV** to the oral formulation should be performed as soon as it is clinically justified.

The ready-to-use solution is prepared by injecting 10 ml of 0,9 % sodium chloride solution into the vial containing the dry substance. The solution may be administered directly or it may be further diluted by mixing with 100 ml 0,9 % sodium chloride solution or 5 % glucose ONLY.

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

After preparation, the solution in 0,9 % sodium chloride solution and 5 % glucose must be used within 12 hours, and any unused portion discarded after 12 hours.

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 pantoprazole should not be exceeded in patients with mild to moderate liver impairment (see **Pharmacokinetic properties** and **WARNINGS AND SPECIAL PRECAUTIONS).**

SIDE EFFECTS

The following side effects may occur:

Infections and infestations:

Less frequent: Infection, flu-like syndrome.

Blood and lymphatic system disorders:

Less frequent: Agranulocytosis.

The following side-effects have been reported and frequencies are unknown:

Thrombocytopenia, leucopenia.

Immune system disorders:

Less frequent: Anaphylactic reactions including anaphylactic shock and angioedema.

The following side-effects have been reported and frequencies are unknown:

Allergic reactions, such as pruritus and skin rash.

Metabolism and nutrition disorders:

Less frequent: Hypoglycaemia.

The following side-effects have been reported and frequencies are unknown:

Increased body temperature, elevated triglycerides.

Psychiatric disorders:

Less frequent:	Anxiety, agitation, hallucinations, somnolence.
The following side-effects have been reported and frequencies are unknown:	Depression, insomnia.

Nervous system disorders:

Frequent:	Headache.
Less frequent:	Dizziness, speech disorders, confusion, hypertonia, hypokinesia, migraine, paraesthesia.

Eye disorders:

Less frequent:	Disturbances in vision (blurred vision), anterior ischaemic optic neuropathy.

Ear and labyrinth disorders:

Less frequent:	Tinnitus, vertigo.

Cardiac disorders:

Less frequent:	Chest pain (occurs more frequently following intravenous administration).

Vascular disorders:

Less frequent:	Peripheral oedema.

Respiratory, thoracic and mediastinal disorders:

Less frequent:	Dyspnoea, bronchitis, increased coughing, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection.

Gastrointestinal disorders:

Frequent:	Diarrhoea (occurs less frequently following intravenous administration).
Less frequent:	Nausea, vomiting, abdominal pain (occurs more frequently following intravenous administration), constipation, flatulence, gastroenteritis, pancreatitis, belching, dyspepsia, rectal disorders, increased salivation, taste disturbances.
The following side-effects have been reported and frequencies are unknown:	
	Dry mouth.

Hepatobiliary disorders:

Less frequently:	Severe hepatocellular damage leading to jaundice with or without hepatic failure, and increased liver enzymes (transaminases, γ-GT), hepatitis, hepatic encephalopathy.

Skin and subcutaneous tissue disorders:

Less frequent:	Erythema multiforme, rash, pruritus, toxic epidermal necrolysis and Stevens-Johnson syndrome, alopecia, bullous eruptions.
The following side-effects have been reported and frequencies are unknown:	Urticaria and photosensitivity.

Musculoskeletal, connective tissue and bone disorders:

Less frequent:	Arthralgia, back pain, neck pain.
The following side-effects have been reported and frequencies are unknown:	Myalgia.

Renal and urinary system disorders:

Less frequent:	Urinary tract infection.
The following side-effects have been reported and frequencies are unknown:	

	Interstitial nephritis (with possible progression to renal failure as it is not necessarily reversed when treatment is discontinued).

Reproductive system and breast disorders:

Less frequent:	Impotence, gynaecomastia.

General disorders and administrative site conditions:

Frequent:	Asthenia, fatigue.
Less frequent:	Injection site thrombophlebitis, increased sweating, malaise.

Post-marketing exposure:

Frequency unknown:	Interstitial nephritis with possible progression to renal failure as it is not necessarily reversed when treatment is discontinued.

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 case of overdosage.

IDENTIFICATION

Off-white cake or powder.

Reconstituted final product: clear colourless solution free from visible particles.

PRESENTATION

10 ml capacity USP type 1 flint clear, colourless, tubular glass vial with a 20 mm bromobutyl grey rubber stopper sealed with a 20 mm white aluminium flip-off, tear-off seal containing lyophilised powder and packed in a carton.

STORAGE INSTRUCTIONS

Freeze dried powder: store at or below 25 °C.

For single use only.

Any unused portion of the reconstituted/diluted solution must be discarded.

Protect from light and moisture.

Keep in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

44/11.4.3/0305

NAME AND BUSINESS ADDRESS OF THE HOLDER OF CERTIFICATE OF REGISTRATION

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