Insert leaflet

Pantozol® i.v.

Active ingredient:
Pantoprazole sodium sesquihydrate

COMPOSITION
Each vial contains 45.1 mg Pantoprazole sodium sesquihydrate (equivalent to pantoprazole 40 mg).

PHARMACOLOGICAL PROPERTIES
ATC Code : A02BC02

MECHANISM OF ACTION
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells.
Pantoprazole is converted to its active form in the acidic environment in the parietal cells where its 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. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in 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, the substance can affect hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given orally or intravenously.

INDICATIONS
- Duodenal ulcer
- Gastric ulcer
- Moderate and severe cases of inflammation of the oesophagus (reflux esophagitis)
- For the treatment of pathological hypersecretory condition associated with Zollinger-Ellison-Syndrome and other neoplastic conditions

POSOLOGY AND METHOD OF ADMINISTRATIONS
The intravenous administration of Pantozol® i.v. is recommended only if oral application is not appropriate.

- **Recommended dosage**

Duodenal ulcer, gastric ulcer, moderate and severe reflux esophagitis
The recommended intravenous dosage is one vial (40 mg pantoprazole) Pantozol® i.v. per day.

Long-term management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions
Patients should start their treatment with a daily dose of 80 mg Pantozol® i.v. Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion to guide.

With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control.
In case a rapid acid control is required, a starting dose of 2 x 80 mg Pantozol® i.v. 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 oral to i.v. and from i.v to oral formulations of gastric acid inhibitors should be performed in such manner to ensure continuity of effect of suppression of acid secretion.

- **Instruction for use/ handling**

A ready-to-use solution is prepared by injecting 10 ml of physiological sodium chloride solution into the vial containing the dry substance. This solution may be administered directly or may be administered after mixing with 100 ml physiological sodium chloride solution or 5% Glucose.
After preparation the solution must be used within 12 hours.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at not more than 25°C.
Pantozol® should not be manufactured or mixed with solvents other than those stated.
As soon as oral therapy is possible, treatment with Pantozol® should be discontinued and 40 mg pantoprazole p.o. should be administered instead.
The drug should be administered intravenously over 2 - 15 minutes.
Any product that has remained in the container or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed) has to be discarded.
The contents of the vial is for single use only.

CONTRAINDICATIONS
Hypersensitivity to the active ingredient(s), or to any of the excipients of the product or the combination product.

WARNINGS AND PRECAUTIONS
The intravenous administration of Pantozol® i.v. is recommended only if oral application is not appropriate.
Pantoprazole is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

In the presence of alarm symptoms :
Symptomatic response to pantoprazole does not preclude the presence of gastric malignancy.
In the presence of any alarm symptoms (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, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

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

In patients with severe liver impairment the daily dose has to be reduced to 20 mg pantoprazole. Furthermore, in these patients the liver enzymes should be monitored during Pantozol® i.v. therapy. In case of a rise of the liver enzymes Pantozol® should be discontinued.

To date there has been no experience with treatment in children.
Therefore, Pantozol i.v. is not recommended for use in patients below 18 years of age.

Bone fracture:
PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).
Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis related fractures should be managed according to established treatment guidelines.

Clostridium difficile:
PPI therapy may be associated with an increased risk of Clostridium difficile infection.
Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Hypomagnesemia:
Has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesemia include tetany, arrhythmia, and seizure. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia *(see Undesirable Effects)*.
In most patients, treatment of hypomagnesemia (and hypomagnesemia associated hypocalcaemia and/or hypokalaemia) required magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Influence on vitamin B12 absorption :

Daily treatment with any acid-suppressing medication over a prolonged period of time (several years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Cyanocobalamin deficiency should be considered in patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, individuals with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if relevant clinical symptoms are observed.

Interference with Laboratory Tests:
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, proton pump inhibitor treatment should be stopped 14 days before CgA measurements.

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, nelfinavir; due to significant reduction in their bioavailability.

Methotrexate:
Concomitant use with high dose methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Subacute 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 the product. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Pregnancy and Lactation

Pregnancy
Clinical experience in pregnant women is limited.
Pantoprazole should only be used when the benefit to the mother is considered greater than the potential risk to this foetus/baby. The potential risk for human is unknown.
Pantoprazole should not be used during pregnancy unless clearly necessary.

Lactation
Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore a decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breastfeeding to the child and the benefit of

pantoprazole therapy to women.

Effect on the ability to drive and to use machines
Pantoprazole is not expected to adversely affect the ability to drive or 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.

Interaction with Other Medications and Other Forms of Interaction

Drugs with pH-Dependent Absorption Pharmacokinetics:
Pantoprazole may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability. (e.g. some azole antifungals as ketoconazole, itraconazole, posaconazole and other medicine as erlotinib).

Clopidogrel :
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 pantoprazole.

Other Interaction Studies
The active ingredient of Pantozol® i.v. is metabolized in the liver via the cytochrome P450 enzyme system. An interaction of pantoprazole with other drugs or compounds which are metabolized using the same enzyme system can not be excluded.

No clinically significant interactions were, however, observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, warfarin and an oral contraceptive.

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in INR have been reported during concomitant treatment in the post-marketing period. Therefore, in patients being treated with coumarin anticoagulants, monitoring of prothrombin time/INR is recommended after initiation, termination or during irregular use of pantoprazole.

There were also no interactions with concomitantly administered antacids.

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, nelfinavir; due to significant reduction in their bioavailability.

Methotrexate:
Concomitant use with high dose methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (fluvoxamine):
Inhibitors of CYP2C19, such as fluvoxamine, would likely increase the systemic exposure of pantoprazole.
Inducers of CYP2C19 would likely decrease the systemic exposure to pantoprazole.

Nonclinical Safety Data

Carcinogenesis, Mutagenesis, Impairment of Fertility
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.
In the two-year carcinogenicity studies in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and it can be concluded that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high dose treatment. In the two-year rodent studies, an increased number of liver tumors was observed in rats and in female mice and was interpreted as being due to the high metabolic rate of pantoprazole in the liver.

Animal Toxicology and/or Pharmacology
A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg). The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no side effects to the thyroid glands are expected.
In animal reproduction studies, signs of fetotoxicity were observed at doses above 3 mg/kg. Investigations revealed no evidence of impaired fertility or teratogenic effects. Crossing of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, the concentration of pantoprazole in the fetus is increased shortly before birth.

OVERDOSAGE
There are no known symptoms of overdosage in man.
Doses up to 240 mg i.v. were administered over two minutes and were well tolerated.
In the case of overdosage with clinical signs of intoxication, the usual rules of intoxication therapy apply.

PRESENTATION PANTOZOL i.v.

Box, 1 vial @ 40 mg

Reg. No. DKI1553300844A1

Keep below 25°C

Keep container in the outer carton.

Shelf life: 24 months.

On Medical Prescription Only
HARUS DENGAN RESEP DOKTER

Keep out of reach of children!

Imported by: PT Takeda Indonesia

Manufactured by Takeda GmbH
Production Site Singen
Robert Bosch Strasse 8
78244 Singen
Germany

Takeda GmbH
Byk Gulden Strasse 2
D-78467 Konstanz
Germany

Based on CCDS version 7.0 dtd 23 Apr 2020.

Table 1 lists adverse drug reactions reported with pantoprazole in clinical studies and postmarketing experience. The following convention is used for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table Undes

Frequency / System	common (>1/100, <1/10)	uncommon (>1/1,000, <1/100)	rare (<1/1,000, >1/10,000)	Very rare (<1/10,000, incl. isolated reports)	Not Known
Blood and lymphatic system			Agranulocytosis	Leukopenia; Thrombocytopenia ; Pancytopenia	
Gastrointestinal disorders		Nausea/vomiting; Diarrhoea; constipation; dry mouth; abdominal pain; flatulence; abdominal distension and bloating; discomfort			
General disorders and administration site conditions	Injection site Thrombophlebitis	Asthenia; fatique and malaise	Body temperature increased; oedema pheripheral		
Hepatobiliary disorders		Liver enzymes increases (transamines, γ-GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Musculoskeletal, connective tissue disorders			Arthralgia; Myalgia		Fracture of wrist, hip and spine
Nervous system disorders		Headache; Dizziness	Taste disorder		
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation	Hallucination; confusion
Renal and urinary disorders					Interstitial nephritis
Skin and subcutaneous tissue disorders		Allergic reactions such as pruritus and skin rash exanthema/ eruption	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity; DRESS
Metabolism and Nutrition disorders			Elevated triglycerides; weight changes; hyperlipidemias		Hypomagnesemia; hyponatremia; Hypocalcemia*; Hypokalemia*
Eye disorders			Disturbances in visions / blurred vision		
Reproductive system and breast disorders			Gynecomastia		

*Hypocalcemia and/or hypokalemia may be related to the occurrence of hypomagnesemia (see Warnings and Precautions)