Instructions for Use

Pantozol® 20 mg

Active ingredient:
Pantoprazole sodium sesquihydrate

Composition

Each one gastro-resistant tablet/enteric coated contains 22.6 mg Pantoprazole sodium sesquihydrate (equivalent to pantoprazole 20 mg)

Mechanism of action

Pharmacodynamic properties :
Proton pump inhibitors :
ATC code : A02BC02

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 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. As with other proton pump inhibitors and H_2 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.

Pharmacokinetic properties :

- **General pharmacokinetics :**

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 20 mg oral dose. On average at about 2.5 p.a. the maximum serum concentrations of about 1 – 1.5 µg/ml are achieved, and these values remain constant after multiple administration. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg. Terminal half-life is about 1 h. There were a few cases of subjects with delayed elimination. Because of the specific activation of pantoprazole in the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition
of acid secretion).
Pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are virtually linear after both oral and intravenuos administration.
Pantoprazole's serum protein binding is about 98%. The substance is almost exclusively metabolized in the liver. Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5) is not much longer than that of pantoprazole.

- **Bioavailability**

Pantoprazole is completely absorbed after oral 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.

- **Characteristics in patients/special groups of subjects**

No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (incl. 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 moderate delayed half-life (2 – 3 h), excretion is still rapid and thus accumulation does not occur. 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-fold, the maximum serum concentration only increased slightly by a factor of 1.3 fold in moderate liver impairment subjects and 1.45-fold in severe liver impairment subjects compared with healthy subjects.
A slight increase in AUC and Cmax in elderly volunteers compared with younger counterparts is also not clinically relevant.

Nonclinical Safety Data
Non-clinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In a 2-year carcinogenicity study in rats – which corresponds to lifetime treatment for 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 allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic treatment.

In the two-year studies an increased number of liver tumors was observed in rats and female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver. From mutagenicity studies, cell transformation tests and a DNA binding study it is concluded that pantoprazole has no genotoxic potential.

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. 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 advance gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

Indications
- Symptomatic Gastro Oesophagitis Reflux Disease (GERD) or Non Erosive Reflux Disease (NERD).
- For long-term management of moderate and severe form of reflux oesophagitis.

Posology and method of administration

- Recommended dosage
Symptomatic Gastro Oesophagitis Reflux Disease (GERD) or Non Erosive Reflux Disease (NERD).
The recommended oral dosage is one gastro-resistant coated tablet Pantozol 20 mg per day. Symptom relief is generally accomplished within 2-4 weeks, and a 4-week treatment period is usually required for healing of associated oesophagitis. If this is not sufficient, healing will normally be achieved within a further 4 weeks. When symptom relief has been achieved, reoccuring symptoms can be controlled using an on-demand regimen of 20 mg once daily,when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment.

For long-term management of moderate and severe form of reflux oesophagitis
For long-term management, a maintenance dose of one gastro-resistant coated tablet Pantozol 20 mg per day is recommended, increasing to 40 mg pantoprazole per day if a relapse occurs. Pantozol 40 mg is available for this case. After healing of the relapse the dosage can be reduced again to 20 mg pantoprazole.
Note:
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment.
No dose adjustment is necessary in elderly patients or in those with impaired renal function.

- General Instructions
Pantozol 20 mg gastro-resistant coated tablets should not be chewed or crushed, and should be swallowed whole with liquid before a meal.

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

Warning and Precautions

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 of the liver enzymes, Pantozol 20 mg should be discontinued.

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.

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.

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.

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.

To date there has been no experience with treatment in children.

Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions, including erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs (*see Table Undesirable Effects)*. Discontinue pantoprazole at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

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 health care 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.
Pantozol 20mg gastro-resistant tablets should only be used when the benefit to the mother is considered greater than the potential risk to

the foetus/baby. The potential risk for humans 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.

Effects on the ability to drive and use of 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 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).

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.

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
Pantoprazole 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 cannot be excluded.

However, no clinically significant interactions were observed in specific test with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline 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.

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.

Overdosage
If you have taken too little Pantozol 20 mg or have forgotten to take it do not take the dose late, but continue with the next regular dose on your dosing schedule.

Talk to your doctor if you want to interrupt or prematurely discontinue treatment with Pantozol 20 mg. There are no known symptoms of overdosage in man. In the case of overdosage with clinical signs of intoxication, the usual rules of intoxication therapy apply.

Undesirable effects
Please see table below.

Stored:
Store below 30°C.

Shelf Life :
36 months

Harus dengan resep dokter
On medical Prescription Only

Keep out of the reach of children.

Box, 1 blister @ 7 tablets

Reg. No. DKI1553300715A1

Imported by:
PT Takeda Indonesia

Manufactured by:
Takeda GmbH
Production Site Oranienburg
Lehnitzstrasse 70-98
16151 Oranienburg Germany

Under License
Takeda GmbH
Byk-Gulden-Strasse 2
D-78476 Konstanz
Germany

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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 1 lists adverse drug reactions reported with pantoprazole in clinical studies and postmarketing experience

Frequency / System Organ Class	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		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 disorder	Depression (and all aggravations)	Disorientation	Hallucination; confusion
Renal and urinary disorders					Tubulointerstitial nephritis (TIN) (with possible progression to renal failure)
Skin and subcutaneous tissue disorders		Allergic reactions such as pruritus and skin rash/exanthema / eruption	Urticaria; Angioedema		Stevens-Johnson syndrome; Toxic epidermal necrolysis (TEN); Drug reaction with eosinophilia and systemic symptoms (DRESS); Acute generalized exanthematous pustulosis (AGEP); Erythema multiforme; Photosensitivity
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			Gynaecomastia		

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