Panzolec Powder for Solution for Injection 40mg (Pantoprazole)

1. NAME AND DOSAGE FORM OF PRODUCT :

Panzolec Powder for Solution for Injection 40mg (Pantoprazole)

2. NAME AND STRENGTH OF ACTIVE INGREDIENT :

Each vial contains Pantoprazole 40mg (equivalent to Pantoprazole Sodium Sesquihydrate 45.1mg)

3. LIST OF EXCIPIENTS:

Mannitol

4. DESCRIPTION :

It occurs as a white to off white lyophilization powder in vial.

5. THERAPEUTIC CLASS :

Selective proton pump inhibitor.

6. INDICATIONS :

Short term use for symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:

- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux esophagitis

7. DOSAGE AND ADMINISTRATION :

Panzolec Powder for Solution for Injection 40mg (Pantoprazole) is recommended only if oral administration is not appropriate.

Recommended Dosage:

- Treatment for Duodenal ulcer, gastric ulcer, moderate/severe reflux esophagitis:

The adult recommended dosage is Pantoprazole 40mg daily by IV injection.

This medicine should be administered by a healthcare professional and under the appropriate medical supervision. Data are available on intravenous use for up to 7 days.

Special Patient Populations

Pediatric patients:

The experience in children is limited. Therefore, Pantoprazole 40 mg powder for solution for injection is not recommended for use in patients below 18 years of age.

Hepatic Impairment:

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 Panzolec Powder for Solution for Injection 40mg (Pantoprazole) therapy. In the case of a rise of the liver enzymes, the treatment should be discontinued.

In addition, pantoprazole 40 mg must not be used in combination treatment (e.g. amoxicillin, clarithromycin,) for eradication of H. pylori in patients with moderate to severe hepatic dysfunction since currently no data are available on the efficacy and safety of pantoprazole in combination

treatment of these patients.

Elderly patients and impaired renal function:
No dose adjustment is necessary and the daily dose of 40 mg Pantoprazole should not be exceeded in elderly patients or in those with impaired renal function. In addition, pantoprazole 40 mg must not be used in combination treatment (e.g. amoxicillin, clarithromycin) for eradication of H. pylori in patients with impaired renal function, since currently no data are available on the efficacy and safety of pantoprazole in combination treatment for these patients.

8. CONTRAINDICATIONS :
Panzolec Powder for Solution for Injection 40mg (Pantoprazole) is contraindicated in patients with known hypersensitivity to the formulation.

9. PRECAUTIONS AND WARNINGS :
The intravenous administration of Panzolec Powder for Solution for Injection 40mg (Pantoprazole) is recommended only if oral application is not appropriate.

In presence of alarm symptoms
In the presence of any alarm symptom (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.

Clostridium difficile
PPI therapy may be associated with an increased risk of Clostridium difficile infection.
Published observational studies suggest that proton pump inhibitor (PPI) therapy like pantoprazole may be associated with an increased risk of Clostridium difficile-associated diarrhoea (CDAD), especially in hospitalized patients. This diagnosis should be considered for diarrhoea that does not improve (see 4.8 Undesirable Effects). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with Panzolec Powder for Solution for Injection 40mg (Pantoprazole) may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as Salmonella and Campylobacter, and in hospitalized patients, possibly also Clostridium difficile.
Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with Panzolec Powder for Solution for Injection 40mg (Pantoprazole), refer to Warnings and Precautions sections of those package inserts.

Gastrointestinal infections caused by bacteria
Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with Panzolec Powder for Solution for Injection 40mg (Pantoprazole) may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as Salmonella and Campylobacter and in hospitalized patients.

Hypomagnesaemia
Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated

with PPIs for at least three months, in most cases after a year of therapy. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmias can occur but they begin insidiously and can be overlooked. In most patients, treatment of hypomagnesaemia 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 hypomagnesaemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Bone Fractures
Several published observational studies suggest that proton pump inhibitor (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-dose, 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.

Concomitant use with Methotrexate
Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients.

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.

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.

10. SYMPTOMS AND TREATMENT FOR OVERDOSAGE AND ANTIDOTE(S) :
There are no known symptoms of overdosage in humans.
In the case of overdosage with clinical signs of intoxication, the usual rules of intoxication therapy apply.

11. SIDE EFFECTS AND ADVERSE REACTIONS :
Approximately 5 % of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhoea and headache, both occurring in approximately 1 % of

patients. Table 1 lists adverse drug reactions reported with pantoprazole in clinical studies and post-marketing 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).

For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a "not known" frequency.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Frequency / Organ System	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
Blood and lymphatic system			Agranulocytosis	Leukopenia; Thrombocytopenia; Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemias; Weight changes		Hyponatraemia; Hypomagnesaemia
Psychiatric disorders		Sleep disorders	Depression	Disorientation	Hallucination; Confusion
Nervous system disorders		Headache; Dizziness	Taste disorders		
Eye disorders			Disturbances in vision/ blurred vision)		
Gastrointestinal disorders		Diarrhoea; Nausea; Vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			

Hepatobiliary disorders		Liver enzymes increased	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and sub-cutaneous tissue disorders		Rash / exanthema; eruption; Pruritus	Urticaria; Angioedema		Stevens- Johnson Syndrome; Erythema multiforme, Lyell-Syndrome; Photosensitivity
Musculoskeletal, connective tissue disorders			Arthralgia; Myalgia		Fracture of the hip, wrist and spine
Renal and urinary disorders					Interstitial nephritis
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions	Injection site thrombo-phlebitis	Asthenia; Fatigue and malaise	Body temperature increased; Oedema peripheral		

12. DRUG INTERACTIONS:

Panzolec Powder for Solution for Injection 40mg (Pantoprazole) may reduce or increase the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole)

HIV medications (atazanavir)
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.

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailibility of atazanavir. The absorption of atazanavir is pH dependent. Therefore PPIs, including pantoprazole, should not be co-administered with atazanavir.

Coumarin anticoagulants (phenprocoumon or warfarin)

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in International Normalized Ratio (INR) have been reported during concomitant treatment in the post-marketing period. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients treated with coumarin anticoagulants (e.g. phenprocoumon or warfarin), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

Other interactions studies

Pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.

An interaction of pantoprazole with other drugs or compounds which are metabolized using the same enzyme system cannot be ruled out. However, no clinically significant interactions were 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 and an oral contraceptive.

Interaction studies with drugs also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol, did not reveal clinically significant interactions.

Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol), or does not interfere with p-glycoprotein related absorption of digoxin.

There were also no interactions with concomitantly administered antacids.

Interaction studies have also been performed by concomitantly administering pantoprazole with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

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.

Drugs that Inhibit or Induce CYP2C19 (Tacrolimus, Fluvoxamine):

Concomitant administration of pantoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. Inhibitors of CYP2C19, such as fluvoxamine, would likely increase the systemic exposure of pantoprazole.

13. PHARMACOLOGY

Pharmacodynamics

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 canaliculi 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. In most patients, freedom from symptoms is achieved in 2 weeks. 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 active substance is given orally or intravenously.

The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the normal upper limit. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments have not been observed in humans.

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid and liver enzymes according to results in animal studies.

Pharmacokinetics

(1) Absorption

After ingestion, pantoprazole is rapidly absorbed into the bloodstream. On average the maximum serum concentrations (C max) of 1 to 1.5 μg/mL (pantoprazole 20 mg tablet) or 2 to 3 μg/mL (pantoprazole 40 mg tablet) are achieved at about 2 to 2.5 hours after administration. After single and repeated administration of pantoprazole, the pharmacokinetic characteristics of pantoprazole are very similar. Both oral and I.V. administration of pantoprazole in the dose range of 10 mg to 80 mg result in linear serum pharmacokinetics. The absolute bioavailability from the tablet was found to be about 77%. Concomitant intake of food had no relevant influence either on the AUC or on the C max and, thus, bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

(2) Distribution

Pantoprazole's serum protein binding is about 98%, and in keeping with this, pantoprazole has a low volume of distribution (about 0.15 l/kg) and limited tissue distribution.

(3) Metabolism

Pantoprazole is rapidly eliminated from the circulation and extensively metabolized in the liver. Metabolism occurs via oxidation by the CYP enzyme system, predominantly by CYP2C19 and CYP3A4 (Phase I metabolism, which is saturable). Pantoprazole undergoes further biotransformation by conjugation with sulphate, which involves the cytoplasmic enzyme sulphotransferase (phase II metabolism, which is not saturable), and which presents the main metabolism of pantoprazole.

(4) Excretion and elimination

About 80% of the metabolites of pantoprazole are eliminated via the renal route, the rest via the feces. None of the metabolites are considered as biologically active. The main metabolite in both the serum and urine is desmethylpantoprazole, which is conjugated with sulphate. T1/2 of the main metabolite is about 1.5 hour (which is not much longer than that of pantoprazole, 1 hour).

(5) Special populations

Impaired renal function

In patients with impaired renal function (including dialysis), pantoprazole showed no prolonged elimination half-life and no accumulation when compared with healthy subjects. No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (including dialysis patients). As with healthy subjects, pantoprazole‘s half-life is short. Only very small amounts of pantoprazole can be dialyzed. Although the main metabolite has a moderately delayed half-life (2 -3h), excretion is still rapid and thus accumulation does not occur.

Impaired hepatic function

Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 3 and 6 h and the AUC values increased by a factor of 3 -5, the maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects. A slight increase in AUC and C max in elderly volunteers compared with younger counterparts is also not clinically relevant.

Age, Gender, Race

As with other clinically used PPIs, a small percentage of the population (about 3% Caucasians, 20% Asians) shows slower elimination of pantoprazole (T1/2 being up to 10 hours as compared with 1hour).

Such persons are known as poor metabolizers as a result of a deficiency of the CYP2C19 enzyme. In these individuals the metabolism of pantoprazole is probably mainly catalyzed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration- time curve was approximately 6 times higher in poor metabolizers than in subjects having a functional CYP2C19 enzyme (extensive metabolizers). Mean peak plasma concentrations were increased by about 60 %. These findings have no implications for the posology of pantoprazole.

Compared with younger subjects, slight increases in AUC and C max were noted after single and repeated oral administration of pantoprazole to healthy elderly subjects (age >65 years). However, no dose adjustment is necessary in elderly patients.

(6) Drug Interactions

Pantoprazole is metabolized in the liver via the CYP enzyme system. An interaction of pantoprazole with other drugs or compounds, which are metabolized using the same enzyme system, cannot be ruled out.

Nevertheless, in specific tests pantoprazole did not affect the clearance of several compounds metabolized by CYP enzymes. Vice-versa, all drugs that were tested regarding their potential influence on the pharmacokinetics of pantoprazole had no relevant effect.

No detectable interactions between pantoprazole and any other commonly prescribed co-medication tested so far were found.

Metabolism of pantoprazole occurs via oxidation by the CYP enzyme system, predominantly by CYP2C19 and CYP3A4. Interaction studies with drugs also metabolized by these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, phenytoin, and an oral contraceptive containing levonorgestrel and ethinyl estradiol did not reveal clinically

significant interactions. Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), or CYP2E1 (such as ethanol) does not interfere with p-glycoprotein related absorption of digoxin. There were no interactions with concomitantly administered antacids. Interaction studies have also been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

Pantoprazole, like other PPIs, should not be co-administered with atazanavir (see Interaction with other medicinal products and other forms of interaction).

14. PREGNACY AND LACTATION:

Pregnancy

The limited data on the use of pantoprazole in pregnant women does not indicate fetal /neonatal toxicity. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Panzolec Powder for Solution for Injection 40mg (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 breast-feeding or to continue/discontinue therapy with Panzolec Powder for Solution for Injection 40mg (Pantoprazole) should be made taking into account the benefit of breast-feeding to the child, and the benefit of Panzolec Powder for Solution for Injection 40mg (Pantoprazole) therapy to women.

15. EFFECT 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. If affected, patients should not drive or operate machines.

16. INSTRUCTIONS FOR USAGE:

A ready-to-use solution is prepared by injecting 10-mL 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 injection.

Panzolec Powder for Solution for Injection 40mg (Pantoprazole) must not be prepared or mixed with solvents other than those stated.

The reconstituted solution must be used immediately after preparation. If not for immediate use, the reconstituted solution should be stored under 25℃ and used within 3 hours.

Panzolec Powder for Solution for Injection 40mg (Pantoprazole) should be administered IV injection over 2-15 minutes.

17. INCOMPATIBILITIES:

This medicinal product must not be mixed with other medicinal products except those mentioned in the section “Instruction for usage”.

18. **ATC CODE:** A02BC02

19. PACKING AND PACK SIZES :

10 vials /Box.

20. STORAGE CONDITIONS :

Store at or below 30˚C. Protect from light.

21. MANUFACTURED BY :

STANDARD CHEM & PHARM CO., LTD.
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