PANTOVAL® I.V.

Pantoprazole sodium

1. Name of the Medicinal Product

1.1 Product Name: PantoVal® I.V.
1.2 Strength: 40 mg
1.3 Pharmaceutical Dosage Form: Powder for solution for injection

2. Quality and Quantitative Composition

2.1 Qualitative Declaration

Active ingredient: pantoprazole sodium

2.2 Quantitative Declaration

One vial contains pantoprazole sodium 42.3 mg (equivalent to pantoprazole 40 mg)
For excipients, see section 6.1

3. Pharmaceutical Form

Powder for solution for injection
White to off-white powder

4. Clinical Particulars

4.1 Therapeutic Indications

- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux esophagitis
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions

4.2 Posology and method of administration

The intravenous administration of **PantoVal® 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) **PantoVal® 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 **PantoVal® 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 of rapid acid control is required, a starting dose of 2 x 80 mg **PantoVal® 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 **PantoVal® i.v.** to the oral formulation of **PantoVal®** should be performed as soon as it is clinically justified.

Method of administration and General instructions

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.

PantoVal® i.v. should not be manufactured or mixed with solvents other than those stated.

As soon as oral therapy is possible, treatment with **PantoVal® i.v.** should be discontinued and 40 mg pantoprazole p.o. (by mouth) should be administered instead.

The drug should be administered intravenously over 2- 15 minutes.

Keep the vial in the outer carton in order to protect from light.

Special Patient Populations

Paediatric patients

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

Impaired hepatic function

A daily dose of 20 mg pantoprazole (half a vial of 40 mg **PantoVal® i.v.** should not be exceeded in patients with severe liver impairment (See section 4.4).

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 (see section 4.4).

Impaired renal function

No dose adjustment is necessary in patients with impaired renal function.

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.

Elderly patients

No dose adjustment is necessary in elderly patients.

4.3 Contraindications

Hypersensitivity to the active ingredients, or to any of the excipients of the product.

4.4 Special warning and precautions for use

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).

Clostridium difficile:

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

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 4.8).

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, the treatment should be discontinued (see section Posology and method of administration, 4.2).

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.

Gastric malignancy:
Symptomatic response to pantoprazole does not preclude the presence of gastric malignancy.

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.

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 Undesirable Effects, 4.8). 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 in rare cases with the occurrence of subacute cutaneous lupus erythematosus (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.

4.5 Interactions with other medicinal products and other forms of interactions
Other interaction studies:
Pantoprazole is extensively metabolized in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways which include oxidation by CYP3A4. Interaction studies with drugs also metabolized with these pathways, including carbamazepine, diazepam, glibenclamide, nifedipine, phenytoin, and an oral contraceptive containing levonorgestrel and ethinyl estradiol did not reveal clinically significant interactions.

An interaction of pantoprazole with other drugs or compounds, which are metabolized using the same enzyme system, cannot be excluded.

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) and 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.

Effects of Pantoprazole on Other Medicinal Products

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.

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.

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.

Coumarin anticoagulants (phenprocoumon or warfarin):
Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenoprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenoprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

Effects of other medicinal products on Pantoprazole
Drugs that Inhibit or Induce CYP2C19:

Inhibitors of CYP2C19, such as fluvoxamine, would likely increase the systemic exposure of pantoprazole. Inducers of CYP2C19 may decrease the systemic exposure to pantoprazole

4.6 Pregnancy and lactation
<u>Pregnancy</u>
There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity (see section “Preclinical safety data”). The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary.

<u>Lactation</u>
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.

4.7 Effects on ability to drive and use of machines
There are no known effects on the ability to drive, 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.

4.8 Undesirable effects
The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification: 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).

Frequency/ System Organ Class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorder			Agranulocytosis	Thrombocytopenia; Leukopenia; Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorder			Hyperlipidemias; Weight changes		Hyponatremia; Hypomagnesemia; Hypocalcemia*; Hypokalemia*
Psychiatric disorders		Sleep disorder	Depression	Disorientation	Hallucination; Confusion
Nervous system disorder		Headache; Dizziness;	Taste disorder		
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 subcutaneous tissue disorders		Rash/ exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome (TEN); Drug reaction with eosinophilia and systemic (DRESS); Acute generalized exanthematous pustulosis; Erythema multiforme; Photosensitivity;
Musculoskeletal, connective tissue disorders			Arthralgia; Myalgia		Fracture of wrist, hip and spine
Renal and urinary disorders					Tubulointerstitial nephritis (TIN) (with possible progression to renal failure)
Reproductive system and breast disorder			Gynecomastia		
General disorders and administration site conditions	Injection site thrombophlebitis	Asthenia, fatigue and malaise	Body temperature increased; Edema peripheral		

Postmarketing ADRs are listed with frequency Not Known.
*Hypocalcemia and/or hypokalemia may be related to the occurrence of hypomagnesemia *(see Special Warnings and Special Precautions for use, 4.4*)

4.9 Overdose
Systemic exposure with up to 240 mg i.v. were administered over two minutes and well tolerated.

In the case of overdosage with clinical sign of intoxication, the usual rules of intoxication therapy apply.

5. Pharmacological Properties
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02BC02

Mechanism of action
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps in the parietal cells.
Pantoprazole is converted to its active form in the acidic environment of 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 within 2 weeks. As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and consequently increases 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, it can inhibit 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.

The fasting gastrin values increase with pantoprazole. During short-term use, in most cases they do not exceed the upper limit of normal. During long-term treatment, gastrin levels double in most cases. An excessive increase has only been observed, 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 long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid based on data observed in animal studies.

5.2 Pharmacokinetic properties

Absorption
Both oral and I.V. administration of pantoprazole in the dose range of 10 mg to 80 mg result in linear serum pharmacokinetics.

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.

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.

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. $T_{1/2}$ of the main metabolite is about 1.5 hour (which is not much longer than that of pantoprazole, 1 hour).

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 adjustment is necessary in patients with impaired renal function.

Impaired hepatic function
In comparison with healthy subjects, after oral administration of 40 mg pantoprazole sodium to patients with liver cirrhosis classified as Child- Pugh A and B, serum elimination half-lives of pantoprazole increased to between 3 and 6 hours (pantoprazole 20 mg tablet) or 7 to 9 hours (pantoprazole 40 mg tablet and powder) and AUC values increased by a factor of 3 to 5 (pantoprazole 20 mg tablet) or 5 to 7-fold (pantoprazole 40 mg tablet and powder). Maximum serum concentrations, C_{max}, in these patients increased only slightly (1.3-fold after oral administration, 1.5-fold after I.V. application) relative to healthy subjects. The observed pharmacokinetic changes did not lead to relevant accumulation following once-daily dosing.

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 ($T_{1/2}$ being up to 10 hours as compared with 1 hour). 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.

Results from several studies in children/adolescents from birth to 16 years indicate that the pharmacokinetics of pantoprazole is similar to those in adults when appropriately adjusted by patient weight, despite somewhat decreased clearance in patients less than 1 year old. Similar to adults, pediatric patients who were poor metabolizers of CYP2C19, exhibited reduced clearance that was more than 70% lower than the typical value.

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.

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) and 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.

5.3 Preclinical safety data
Carcinogenesis, Mutagenesis, Impairment of Fertility
Non-clinical data reveal no special hazard to 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 pantoprazole's high metabolic rate 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 harmful 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.

6. Pharmaceutical Particulars

6.1 List of excipient
Disodium edetate; Sodium hydroxide
This medicinal product contains less than 1 mmol sodium (23 mg) per vial.

6.2 Incompatibility
PantoVal® i.v. must not be mixed with other medicinal products except those mentioned in section “Special precautions for disposal.”

6.3 Shelf life
See “expiry date” on packaging.

6.4 Special precautions for storage
PantoVal® i.v.should be stored below 25°C and protected from light.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container
Glass vial with rubber stopper and crimp-seal

Instructions for use/handling
Special precautions for disposal
A ready-to-use solution is prepared by injecting 10 mL of physiological sodium chloride (0.9%) solution for injection into the vial containing the powder. The appearance of the product after reconstitution is a clear yellowish solution. This solution may be administered directly or may be administered after mixing it with 100 mL physiological sodium chloride (0.9%) solution for injection or glucose (5%) solution for injection. Glass or plastic containers should be used for dilution.

After reconstitution, or reconstitution and dilution, chemical and physical in use stability has been demonstrated for 12 hours at 25 °C. From a microbiological point of view, the product should be used immediately. Pantoprazole should not be prepared or mixed with solvents other than those stated.

The medicinal product should be administered intravenously over 2 to 15 minutes.
The contents of the vial is for single use only. Any product that has remained in the container or whose visual appearance has changed (e.g., if cloudiness or precipitation is observed) should be disposed in accordance with local requirements.

7. Marketing Authorization Holder
Imported by: Takeda (Thailand) Ltd., Bangkok, Thailand

8. Marketing Authorization Number
1C 127/56 (N)

9. Date of Authorization

25 Dec 2013

10. Date of revision of the text
Aug 2022