Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pantoprazole 40 mg powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 40 mg pantoprazole (as sodium sesquihydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.
White or almost white uniform porous cake.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pantoprazole is indicated for use in adults for:

- reflux oesophagitis.
- gastric and duodenal ulcer.
- Zollinger-Ellison syndrome and other pathological hypersecretory conditions.

4.2 Posology and method of administration

This medicine should be administered by a healthcare professional and under appropriate medical supervision.

Intravenous administration of pantoprazole is recommended only if oral administration is not appropriate. Data are available on intravenous use for up to 7 days. Therefore, as soon as oral therapy is possible, intravenous treatment with pantoprazole should be discontinued and 40 mg of pantoprazole should be administered orally instead.

Posology

Gastric and duodenal ulcer, reflux oesophagitis
The recommended dose is 40 mg pantoprazole daily.

Zollinger-Ellison syndrome and other pathological hypersecretory conditions
For the long-term management of Zollinger-Ellison syndrome and other pathological hypersecretory conditions the recommended initial dose is 80 mg pantoprazole daily. Thereafter, the dose can be adjusted according to measurements of gastric acid secretion. With daily doses above 80 mg, the dose should be divided and given twice daily. A temporary increase of the dose 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, an initial dose of 2 x 80 mg pantoprazole is sufficient to manage a decrease of acid output into the target range (< 10 mEq/h) within one hour in the majority of patients.

Special populations
Patients with hepatic impairment
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment (see section 4.4).

Patients with renal impairment
No dose adjustment is necessary in patients with impaired renal function (see section 5.2).

Elderly
No dose adjustment is necessary in the elderly (see section 5.2).

Paediatric population
The safety and efficacy of intravenous pantoprazole in children aged under 18 years of age have not been established. Therefore, this medicine is not recommended in children under 18 years of age. The currently available data are described in section 5.2. However, no dose recommendation can be made based on these data.

Method of administration

Intravenous use.

This medicinal product should be reconstituted, or reconstituted and diluted, before use. It should be administered intravenously over 2-15 minutes.

For instructions on reconstitution, or reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Gastric malignancy
Symptomatic response to pantoprazole may mask the symptoms of gastric malignancy and may delay diagnosis. 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.
Further investigation is to be considered if symptoms persist despite adequate treatment.

Hepatic impairment
In patients with severe liver impairment, the liver enzymes should be monitored during therapy. In the case of a rise of the liver enzymes, the treatment should be discontinued (see section 4.2).

Co-administration with HIV protease inhibitors
The simultaneous use of pantoprazole with HIV protease inhibitors (such as atazanavir), the absorption of which is dependent on an acidic gastric pH value, is not recommended due to its significantly reduced bioavailability (see section 4.5).

Gastrointestinal infections caused by bacteria
Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as Salmonella, Campylobacter or *C. difficile*.

Hypomagnesaemia
Severe hypomagnesaemia has been rarely reported in patients treated with proton pump inhibitors (PPIs) such as pantoprazole for at least three months, but in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur, but they may begin insidiously and be overlooked. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8). In most affected patients, the hypomagnesaemia (and hypomagnesaemia associated hypocalcaemia and/or hypokalaemia) improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or medicinal products that may cause hypomagnesaemia (e.g. diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Bone fractures
Proton pump inhibitors, especially when used in high doses and for a long time (over 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

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

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, Pantoprazole treatment should be discontinued for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products with pH-dependent absorption pharmacokinetics
Because of profound and long-lasting inhibition of gastric acid secretion, pantoprazole may reduce the absorption of medicinal products for which an acidic gastric pH value is an important factor for oral bioavailability (e.g. some azole antifungals as ketoconazole, itraconazole, posaconazole and other medicines, e.g. erlotinib).

HIV protease inhibitors
The simultaneous use of pantoprazole with HIV protease inhibitors (such as atanazavir), the absorption of which is dependent on an acidic gastric pH value, is not recommended due to the significantly reduced bioavailability (see section 4.4). If the combination of HIV protease inhibitors with a proton pump inhibitor cannot be avoided, close clinical monitoring (e.g. viral load) is recommended. Pantoprazole dose of 20 mg per day should not be exceeded. Adjustment of the dose of HIV protease inhibitors may be necessary.

Coumarin anticoagulants (phenprocoumon or warfarin)
Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or International Normalised Ratio (INR). However, there have been isolated reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon 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.

Methotrexate
Concomitant use of high-dose methotrexate (e.g. 300 mg) and proton-pump inhibitors has been reported to increase methotrexate levels in some patients. Therefore, temporary discontinuation of pantoprazole may be considered when high doses of methotrexate are used, such as for the treatment of cancer and psoriasis.

Other interactions studies
Pantoprazole is extensively metabolised in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19, other metabolic pathways include oxidation by CYP3A4.
Interaction studies with medicinal products 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.
An interaction of pantoprazole with other medicinal products or compounds that are metabolised via the same enzyme system cannot be ruled out.

Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolised 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 no interactions with concomitantly administered antacids.

In interaction studies, no clinically relevant interactions were found when pantoprazole was administered concomitantly with the corresponding antibiotics (clarithromycin, metronidazole, amoxicillin).

Medicinal products that inhibit or induce CYP2C19

Inhibitors of CYP2C19 such as fluvoxamine can increase the systemic exposure of pantoprazole. A dose reduction may be considered for patients treated long-term with high doses of pantoprazole, or those with hepatic impairment.
Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John´s wort (*Hypericum perforatum*) may reduce the plasma concentrations of PPIs that are metabolised through these enzyme systems.

4.6 Fertility, pregnancy and lactation

Pregnancy
A moderate amount of data on pregnant women (between 300 and 1 000 pregnancy outcomes) indicates no malformative foeto/neonatal toxicity of pantoprazole. Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure, the use of pantoprazole should be avoided during pregnancy.

Breast-feeding
Animal studies have shown excretion of pantoprazole in breast milk. There is insufficient information on the excretion of pantoprazole in human milk but excretion into human milk has been reported. A risk to the new-borns/infants cannot be excluded. Therefore, a decision on whether to discontinue breast-feeding or to discontinue/abstain from pantoprazole therapy should be made taking into account the benefit of breast-feeding for the child, and the benefit of pantoprazole therapy for the woman.

Fertility

There was no evidence of impaired fertility following the administration of pantoprazole in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Pantoprazole has no or negligible influence on the ability to drive and use machines. However 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

Approximately 5% of patients can be expected to experience adverse drug reactions.
The table below lists adverse reactions reported with pantoprazole, ranked under MedDRA frequency classification as follows: 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.

Frequency **System organ class**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders			Agranulocytosis	Thrombocytopenia; Leukopenia; Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemia, lipid level increase (triglycerides, cholesterol); Weight changes		Hyponatraemia; Hypomagnesaemia (see section 4.4); Hypocalcaemia[(1)]; Hypokalaemia[(1)]
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination; Confusion (especially in

					pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)
Nervous system disorders		Headache; Dizziness	Taste disorders		Paraesthesia
Eye disorders			Disturbances in vision / blurred vision		
Gastrointestinal disorders	Fundic gland polyps (benign)	Diarrhoea; Nausea / vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			Microscopic colitis
Hepatobiliary disorders		Liver enzymes level increased (transaminases, γ-GT)	Bilirubin level increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and subcutaneous tissue disorders		Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity; Sub-acute cutaneous lupus erythematosus (see section 4.4); Drug reaction with eosinophilia and systemic symptoms DRESS
Musculoskeletal and connective tissue disorders		Fracture of the hip, wrist or spine (see section 4.4)	Arthralgia; Myalgia		Muscle spasm[(2)]
Renal and urinary disorders					Interstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions	Injection site thrombophlebitis	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

(1) Hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see section 4.4)
(2) Muscle spasm as a consequence of electrolyte disturbance

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

There are no known symptoms of overdose in humans.
Systemic exposure with up to 240 mg administered intravenously over 2 minutes, were well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable.
In the case of an overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid related disorders, 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 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. Most patients are symptom-free within 2 weeks. As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby 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 of pantoprazole is the same whether it is given orally or intravenously.

Pharmacodynamic effects

The fasting gastrin values increase under pantoprazole. On 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, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL - enterochromaffin-like) 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 (see section 5.3) have not been observed in humans.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also, CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.
Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

5.2 Pharmacokinetic properties

General pharmacokinetics
Pharmacokinetics does not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

Distribution
The serum protein binding of pantoprazole is about 98%. Volume of distribution is about 0.15 l/kg.

Biotransformation

Pantoprazole is almost exclusively metabolised in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, another metabolic pathway includes oxidation by CYP3A4.

Elimination
Terminal half-life is about 1 hour, and clearance is about 0.1 l/h/kg. There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole to the proton pumps of the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).
Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole, the rest is 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 hours) is not much longer than that of pantoprazole.

Special populations

Poor metabolisers
Approximately 3% of the European population lack a functional CYP2C19 enzyme (poor metabolisers). In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration time curve (AUC) was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of pantoprazole.

Patients with renal impairment
No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy volunteers, the half-life of pantoprazole is short. Only very small amounts of pantoprazole can be dialyzed. Although the main metabolite has a moderately prolonged half-life (2-3 h), excretion is still rapid and thus accumulation does not occur.

Patients with hepatic impairment
Although for patients with liver cirrhosis (classes A and B according to Child-Pugh classification) the half-life values increased to between 7 and 9 h and the AUC values increased by a factor of 5-7, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.

Elderly
A slight increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is also not clinically relevant.

Paediatric population
Following administration of single intravenous doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2-16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

5.3 Preclinical safety data

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 allows the conclusion 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 tumours was observed in rats and in female mice and was interpreted as being due to high metabolic rate of pantoprazole in the liver.

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 humans is low, no harmful effects on the thyroid gland are expected.

In a peri-postnatal rat reproduction study designed to assess bone development, signs of offspring toxicity (mortality, lower mean body weight, lower mean body weight gain and reduced bone growth) were observed at exposures (C_{max}) approximately twice the human clinical exposure. By the end of the recovery phase, bone parameters were similar across groups and body weights were also trending toward reversibility after a drug-free recovery period. The increased mortality has only been

reported in pre-weaning rat pups (up to 21 days age) which is estimated to correspond to infants up to the age of 2 years old. The relevance of this finding to the paediatric population is unclear. A previous peri-postnatal study in rats at slightly lower doses found no adverse effects at 3 mg/kg compared with a low dose of 5 mg/kg in this study.

Investigations revealed no evidence of impaired fertility or teratogenic effects.

Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Mannitol (E 421)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

Shelf life after reconstitution or reconstitution and dilution
The chemical and physical in-use stability after reconstitution, or reconstitution and dilution with sodium chloride 9 mg/ml (0.9%) solution for injection, has been demonstrated for 24 hours at 2 to 8 °C and 25 °C.
The chemical and physical in-use stability after reconstitution with sodium chloride 9 mg/ml (0.9%) solution for injection and dilution with glucose 50 mg/ml (5%) solution for injection has been demonstrated for 24 hours at 2 to 8 °C and for 12 hours at 25 °C.

From a microbiological point of view, the prepared solution should be used immediately. If not used immediately, in-use storage times and conditions prior to the use are the responsibility of the user and would not normally be longer than 24 hours at 2 to 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Keep the vials in the outer carton in order to protect from light.

For storage conditions after reconstitution, or reconstitution and dilution, of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder is filled in 10 ml capacity clear, colourless glass type I vials. Vials are closed with bromobutyl rubber stoppers and sealed with aluminium/polypropylene flip-off seals.
The vials are placed into outer cartons.

Pack sizes: 1, 5, 10 or 50 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

A ready-to-use solution is prepared by injecting 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection into the vial containing the powder. The prepared solution may be administered directly or may be administered after mixing it with 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection.

The prepared solution should be visually inspected prior to use. The appearance of the product after reconstitution is a clear yellowish solution. Only clear solutions free from particles should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

AS Kalceks
Krustpils Iela 71e
Riga
1057
Latvia

8 MARKETING AUTHORISATION NUMBER

PA2165/020/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th June 2023

10 DATE OF REVISION OF THE TEXT