SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pantoprazole 40mg, Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect: each vial contains 2.44 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection

White to almost white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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, treatment with Pantoprazole i.v. should be discontinued and 40 mg pantoprazole p.o. should be administered instead.

Posology

Gastric and duodenal ulcer, reflux oesophagitis:

The recommended intravenous dose is one vial of Pantoprazole (40 mg of pantoprazole) per day.

Long-term management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions:

For the long-term management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions, patients should start their treatment with a daily dose of 80 mg of Pantoprazole i.v.. Thereafter, the dose can be titrated up or down as needed using measurements of gastric acid secretion to guide. Doses above 80 mg daily should be divided and given twice daily. A temporary increase of the dose above 160 mg of pantoprazole is possible but should not be applied longer than required for adequate acid control.

In case a rapid acid control is required, a starting dose of 2 x 80 mg of Pantoprazole 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.

Patients with hepatic impairment

A daily dose of 20 mg pantoprazole (half a vial of 40 mg pantoprazole) should not be exceeded in patients with severe liver impairment (see section 4.4).

The change from intravenous to oral formulation must be made as soon as the patient's clinical situation allows.

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 elderly patients (see section 5.2).

Paediatric population

The safety and efficacy of Pantoprazole 40 mg powder for solution for injection in children under 18 years of age have not been established. Therefore, Pantoprazole 40 mg powder for solution for injection is not recommended for use in patients under 18 years of age. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Method of administration

A ready-to-use solution is prepared in 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. For instructions on preparation, see section 6.6. The prepared solution may be administered directly or may be administered after mixing it with 100 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 55 mg/ml (5%) solution for injection.

After preparation, the solution must be used as indicated in section 6.3.

The medicinal product should be administered intravenously over 2 - 15 minutes.

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

Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, due to significant reduction in their bioavailability (see section 4.5).

Gastrointestinal infections caused by bacteria

Treatment with Pantoprazole may lead to an increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* or *C. difficile*.

Hypomagnesaemia

Cases of severe hypomagnesaemia have been reported in patients treated with proton pump inhibitors (PPIs) like pantoprazole for at least three months, and 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. In most affected patients, hypomagnesaemia 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), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Bone fractures

Proton pump inhibitors, especially if used in high doses and over long durations (> 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 healthcare 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 stopped 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.

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 Protium may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as Salmonella and Campylobacter.”

This medicinal product contains sodium. This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. is 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 interfere with the absorption of other medicinal products where gastric pH is an important determinant of oral bioavailability, e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other drugs such 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, due to significant reduction in their bioavailability (see section 4.4).

If the combination of HIV protease inhibitors with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitor may need to be adjusted.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or INR (International Normalised Ratio). However, there have been 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, in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

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 include oxidation by CYP3A4.

Interaction studies with medicinal products also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, and oral contraceptives containing levonorgestrel and ethinylestradiol did not reveal clinically significant interactions.

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

Results from a range of interaction studies demonstrated 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 no interactions with concomitantly administered antacids.

Interaction studies have been performed administering pantoprazole concomitantly with the following antibiotics: clarithromycin, metronidazole, amoxicillin. No clinically relevant interactions were found.

Medicinal products that inhibit or induce CYP2C19:

Inhibitors of CYP2C19 such as fluvoxamine could 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 metabolized through these enzyme systems.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of Pantoprazole.

Animal studies have shown reproductive toxicity (see section 5.3).

As a precautionary measure**,** it is preferable to avoid the use of Pantoprazole during pregnancy.

Breastfeeding

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 breast milk has been reported. A risk to the newborns/infants cannot be excluded. Therefore, a decision on whether to discontinue breast-feeding or to discontinue/abstain from Pantoprazole therapy should take 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.

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 (ADRs). The most commonly reported ADR is injection site thrombophlebitis. Diarrhoea and headache occurred in approximately 1% of patients.

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). 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 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			Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia Hypomagnesaemia (see section 4.4) Hypocalcaemia (1) Hypokalaemia
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucinations; 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 increased (transaminases, γ-GT)	Bilirubin 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; Subacute cutaneous lupus erythematosus – SCLE (see section 4.4).
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 in association with hypomagnesaemia
2) Muscle spasm as a consequence of electrolyte disturbances

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 reactions via the national reporting system:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

There are no known symptoms of overdose in man.

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 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: 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. 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 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 is the same whether the product 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) 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.

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

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 (PPIs) 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 do 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.

Absorption

Distribution

Pantoprazole’s serum protein binding is about 98%. Volume of distribution is 0.15 l/kg.

Metabolism and Biotransformation

The substance is almost exclusively metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation. Other metabolic pathways include 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 and are called 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 AUC is 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentration was increased by about 60%. These findings have no implications for the posology of pantoprazole.

Renal impairment

No dose reduction is recommended when pantoprazole is administered to patients with impaired renal 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 moderately delayed half-life (2 - 3 h), excretion is still rapid and thus accumulation does not occur.

Hepatic impairment

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, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.

Elderly patients

A slight increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is 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 for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In the two-year carcinogenicity studies in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and 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 pantoprazole's high metabolic rate 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 man is low, no harmful effects on the thyroid glands are expected.

In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg. Investigations revealed no evidence of impaired fertility or teratogenic effects.

Penetration on 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 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

Unopened vial: 2 years.

After reconstitution (and dilution)

Chemical and physical in-use stability has been demonstrated for 12 hours at 25ºC and for 24 hours at 2ºC – 8ºC.

From a microbiological point of view, the product should be used immediately. If not used immediately, the in-use storage time and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 - 8ºC.

6.4 Special precautions for storage

Do not store above 25ºC.

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

For storage conditions after reconstitution (and dilution) of the medicinal product, see section 6.3

6.5 Nature and contents of container

Pantoprazole 40 mg powder for solution for injection is packed in colourless type I borosilicate glass vials and is sealed with a cap consisting of two components, an aluminium frame and a polypropylene cap, and closed with a grey bromobutyl rubber stopper. The vials are packed in cardboard boxes.

Pantoprazole is available in packs of 1 vial, 5 (5x1) vials, 10 (10x1) vials or 20 (20x1) vials with powder for solution for injection.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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 dry powder. The appearance of the product after reconstitution is a clear, possibly slightly yellowish, solution. This solution may be administered directly or may be administered after mixing it with 100 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 55 mg/ml

(5%) solution for injection. Type I Glass or plastic containers must be used for the dilution.

After reconstitution (and dilution), chemical and physical in use stability has been demonstrated for 12 hours at 25ºC and for 24 hours at 2ºC – 8ºC. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours, at 2 - 8ºC.

Pantoprazole should not be prepared or mixed with solvents other than those stated.

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

Any product that has remained in the container or whose visual appearance has changed (e.g. if cloudiness or precipitation is observed) must be discarded.

The content of the vial is for single intravenous use only.

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

7 MARKETING AUTHORISATION HOLDER

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Portugal

8 MARKETING AUTHORISATION NUMBER(S)

PL 15413/0091

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23/04/2019

10 DATE OF REVISION OF THE TEXT

04/11/2019