SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Protonix Powder for Solution or Injection for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. is essentially 'sodium-free'.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion.

White to hygroscopic 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 40 mg powder for solution for injection/infusion 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 pantoprazole) per day.

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 Pantoprazole. Thereafter, the dose 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 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, a starting 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 (half a vial of 40 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.

Elderly population

No dose adjustment is necessary in elderly patients.

Paediatric patients

The experience in children is limited. Therefore, Pantoprazole is not recommended for use in patients below 18 years of age until further data become available.

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 for preparation see section 6.6. 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 solution obtained should be administered within 12 hours (see section 6.3).

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

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles,

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).

Combination therapy

In the case of combination therapy, the summaries of product characteristics of the respective medicinal products should be observed.

Influence on vitamin B12 absorption

In patients with Zollinger-Ellison syndrome and other pathological hyper secretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

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

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. is essentially 'sodium-free'.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with 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 drugs 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 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 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 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.

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 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 medicine as erlotinib.

HIV protease inhibitors

Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir 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, 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.

Methotrexate

Concomitant use of high dose of 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 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 effect 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.

Interaction studies have also been performed administering pantoprazole concomitantly with the respective 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 40 mg powder for solution for injection.

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.

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 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

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 ADRs 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	Common	Uncommon	Rare	Very rare	Not known
System Organ Class					

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)]; Hupokalaemia
Psychiatric disorders		Sleep disorder	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		Parasthesia
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-John-son syndrome; Lyell syndrome; Erythema multiform; Photo-sensitivity; Subacute cutaneous lupus erythematosus

					(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] Hypocalcemia in association with hypomagnesemia

[2] Muscle spasm as a consequence of electrolyte disturbance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 listed in Appendix V.

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 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, Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD). 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.

Pharmacodynamic effects

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 H2 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 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 is linear after both oral and intravenous administration.

Distribution

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

Biotransformation

The substance is almost exclusively metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other 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 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 mean area under the plasma concentration-time curve 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.

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.

Older people

A slight increase in AUC and Cmax in elderly volunteers compared with younger counterparts is also not clinically relevant.

Pediatric 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

Nonclinical 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 tumors 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 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.

Data to evaluate a potential effect on the environment is currently limited (see item 6.6 – disposal of pantoprazole)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

NA

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

24 Months.

6.4 Special precautions for storage

Store below 30° C, Protect from light, heat and moisture

6.5 Nature and contents of container

Clear glass (type I) vial sealed with grey chlorobutyl stoppers and aluminium flip-off caps.

6.6 Special precautions for disposal and other handling

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 appearance of the product after reconstitution is a clear brownish solution. Do not use if any particles are present in the reconstituted solution. This 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 reconstituted solution of 40 mg/10 ml is stable for a period of 24 hours of initial puncture of stopper.

Chemical and physical in-use stability has been demonstrated for 12 hours at 25°C after dilution with sodium chloride 9 mg/ml (0.9%) solution and with glucose 50 mg/ml (5%) solution.

The diluted solutions with sodium chloride 9 mg/ml (0,9%) solution and with dextrose 50 mg/ml (5%) solution at concentrations of 80 and 160mg doses are stable during the infusion time of 15 minutes.

From a microbiological point of view, the product should be used immediately (see section 6.3).

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

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

The contents of the vial are for single use only. Any product that has remained in the container should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Wilshire Laboratories Pvt. Ltd.
124/1 industrial Estate Kot Lakhpat ,
Lahore Pakistan

8. MARKETING AUTHORISATION NUMBER(S)

TAN 20 HM 404

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25th September, 2023

10. DATE OF REVISION OF THE TEXT

Not Applicable (This is first Authorization)