Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Patmac Lyophilized powder solution for injection

2. Qualitative and quantitative composition

Each vial contains:
Pantoprazole Sodium Equivalent to Pantoprazole.....40mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder for solution for injection.

A White to almost white color cake/powder on reconstitution form clear colorless transparent liquid free from particles and fibers.

4. Clinical particulars

4.1 Therapeutic indications

Pantoprazole is indicated in adults for:

Reflux oesophagitis.
Gastric ulcer and duodenal ulcer.
Zollinger-Ellison Syndrome and other pathological hypersecretory conditions.

4.2 Posology and method of administration

Posology

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

An intravenous administration is only indicated if oral administration is not appropriate. Data are available for the intravenous administration up to 7 days. Therefore, as soon as oral therapy is possible, treatment with Pantoprazole should be switched to 40 mg pantoprazole oral therapy.

Reflux oesophagitis, gastric ulcer, duodenal ulcer

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

Zollinger-Ellison Syndrome and other pathological hypersecretory conditions

For long-term management of Zollinger-Ellison Syndrome and other pathological hypersecretory conditions, patients should start with a dose of 80 mg pantoprazole per day. Thereafter, this dose can be titrated up or

down as needed using gastric acid secretion measurements to guide monitoring. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the pantoprazole dose above 160 mg is possible but should not be maintained longer than clinically necessary. As rapid acid control is required, a starting dose of 2 x 80 mg pantoprazole is sufficient to bring down acid output within one hour to below 10 mEq/h in the majority of patients.

Special populations

Hepatic impairment: in patients with severe liver impairment, the daily dose should be reduced to 20 mg pantoprazole (half a vial of 40 mg pantoprazole).
Renal impairment: no dose adjustment is necessary in patients with impaired renal function, including those on dialysis.
Elderly: no dose adjustment is necessary in elderly patients.

Paediatric population

The safety and efficacy of Pantoprazole in children aged under 18 years have not been established. Therefore, Pantoprazole is not recommended for use in patients below 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. 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. After preparation the solution must be used within 12 hours. The medicinal product should be administered intravenously over 2 to 15 minutes.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation should be considered if symptoms persist despite adequate treatment.

In patients with severe hepatic impairment, liver enzymes should be monitored regularly during pantoprazole therapy. Treatment should be discontinued if liver enzymes are increased.

Co-administration of pantoprazole with atazanavir is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended.

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

Severe hypomagnesaemia has been reported rarely in patients treated with proton pump inhibitors like pantoprazole for at least three months, 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. In most affected patients, hypomagnesaemia (and hypomagnesaemia-associated hypocalcaemia and/or hypokalaemia) improved after magnesium replacement and discontinuation of the proton pump inhibitor. For patients expected to be on prolonged treatment or who take proton pump inhibitors with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals should consider measuring magnesium levels before starting proton pump inhibitor treatment and periodically during treatment.

Proton pump inhibitors, especially if used in high doses and over long duration (>1 year), may modestly increase the risk of fracture of the hip, wrist or spine, predominantly in the elderly or in the 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.

Cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS) and erythema multiforme, some of them fatal, have been reported in association with pantoprazole treatment. Patients should be advised of the signs and symptoms and monitored closely for skin reactions at the start of treatment. If signs and symptoms suggestive of these reactions appear, pantoprazole should be withdrawn immediately and an alternative treatment considered.

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

Pantoprazole may lead to a false positive result in the urine screening test for tetrahydrocannabinol (THC) in some cases. An alternative confirmatory method should be considered to verify positive results.

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. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after discontinuation of proton pump inhibitor treatment.

This medicinal product contains less than 1 mmol sodium (23 mg) per maximum daily dose, 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

Pantoprazole leads to a profound and long-lasting inhibition of gastric acid production. The absorption of medicinal products with a pH-dependent bioavailability (e.g. ketoconazole, itraconazole, posaconazole, erlotinib) can be reduced due to the acid suppressive effect of pantoprazole.

Atazanavir

Co-administration of atazanavir with proton pump inhibitors is not recommended, as it may substantially reduce the bioavailability of atazanavir, compromising its therapeutic effect. If the combination cannot be avoided, close clinical monitoring is recommended, together with a reduction of the atazanavir dose; a pantoprazole dose exceeding 20 mg daily should not be given.

Coumarin anticoagulants (phenprocoumon or warfarin)

Although no interaction was observed with concomitant administration in clinical pharmacokinetic studies, a few isolated cases of changes in International Normalised Ratio (INR) have been reported during concomitant treatment in the post-marketing period. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Patients treated with coumarin anticoagulants should be monitored for changes in INR and prothrombin time after starting, stopping or during irregular use of pantoprazole.

Methotrexate

Concomitant use of high dose methotrexate (e.g. 300 mg) and proton pump inhibitors has been reported to elevate and prolong serum levels of methotrexate and/or its metabolite in some patients. A temporary withdrawal of pantoprazole may need to be considered in some patients receiving high dose methotrexate.

Other interaction studies

Pantoprazole is extensively metabolised in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 with other metabolic pathways including oxidation by CYP3A4. Interaction studies with substances also metabolised via this pathway, such as carbamazepine, diazepam, glibenclamide, nifedipine and an oral contraceptive containing levonorgestrel and ethinyl estradiol, did not reveal any clinically significant interactions. Results from interaction studies show 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), or CYP2E1 (such as ethanol), nor does it interfere with p-glycoprotein related absorption of digoxin. No interaction was found with concomitantly administered antacids.

Interaction studies have also been performed with concomitant administration of pantoprazole and the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

As pantoprazole is metabolised via cytochrome P450 enzymes, interactions with medicinal products metabolised via the same enzyme system cannot be excluded. CYP2C19 inhibitors such as fluvoxamine may increase pantoprazole systemic exposure; a dose reduction may be considered in patients on long-term treatment and/or with hepatic impairment. Inducers of CYP2C19 and CYP3A4 (e.g. rifampicin, St. John's wort) may reduce plasma concentrations of proton pump inhibitors.

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

Breast-feeding

Studies in animals have shown excretion of pantoprazole in breast milk. Excretion in human milk has been reported. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from pantoprazole therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies do not indicate impairment of fertility.

4.7 Effects on ability to drive and use machines

Pantoprazole has no or negligible influence on the ability to drive and use machines. If adverse reactions such as dizziness or visual disturbance occur, patients should not drive or operate machines.

4.8 Undesirable effects

Approximately 5% of patients experience adverse reactions. The most frequently reported adverse reactions are diarrhoea and headache, both occurring in approximately 1% of patients.

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*; hypokalaemia*
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination; confusion (especially in predisposed patients, as well as

					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 (TEN); drug reaction with eosinophilia and systemic symptoms (DRESS); erythema multiforme; photosensitivity; 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†
Renal and urinary disorders					Tubulointerstitial nephritis (TIN) (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		

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

Description of selected adverse reactions

Severe cutaneous adverse reactions, subacute cutaneous lupus erythematosus and hypomagnesaemia are described further in section 4.4.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Overdosage symptoms in humans are not known. Systemic exposures 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 event of overdose with clinical signs of intoxication, other than symptomatic and supportive treatment, no specific treatment 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 through specific blocking of the proton pumps of the parietal cell. Pantoprazole is converted to its active form in the acidic environment of the parietal cell, 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.

Pharmacodynamic effects

As with other proton pump inhibitors and H2 receptor blockers, treatment with pantoprazole reduces the acidity in the stomach and, therefore, increases gastrin in proportion to the reduction of acidity. The increase in gastrin is also reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, it can inhibit hydrochloric acid secretion, independent of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the medicinal product is given orally or intravenously.

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 of the number of specific endocrine (ECL) cells in the stomach may occur during long-term treatment in a minority of cases (simple to adenomatoid hyperplasia). However, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as found in animal experimental studies, has not been observed in humans.

It cannot be excluded that an influence of endocrine parameters of the thyroid may occur due to long-term treatment (over one year) based on results of animal experiments.

5.2 Pharmacokinetic properties

Pharmacokinetics are not different for 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 sulfation; other metabolic pathways include oxidation by CYP3A4.

Elimination

The terminal half-life is about one hour, and the clearance is about 0.1 l/h/kg. There were some cases of subjects with a delayed elimination

phase. Due to 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 main route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest being excreted with the faeces. The main metabolite in both serum and urine is desmethylpantoprazole which is conjugated with sulfate. The half-life of the main metabolite is about 1.5 hours.

Characteristics in patients / special populations

About 3% of the European population lacks a functional CYP2C19 enzyme and is called poor metabolisers. In these individuals, the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single dose of 40 mg pantoprazole orally, the mean area under the plasma concentration versus time curve was about 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%. No dose adjustment is needed.

Renal impairment: no dose reduction is needed when giving pantoprazole to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialysed. Although the main metabolite has a moderate prolonged half-life (2-3 hours), excretion is still rapid and thus no accumulation occurs.

Hepatic impairment: in cirrhotic patients (Child Class A and B), values of half-life increased to between 7 and 9 hours, and values for AUC increased by a factor of 5 to 7, while maximum serum concentration increased only by a factor of around 1.5 as compared with healthy subjects.

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

Paediatric population: after single intravenous doses of 0.8 to 1.6 mg pantoprazole/kg body weight in children aged 2 to 16 years, there was no association between the clearance of pantoprazole and age or body weight. AUC and volume of distribution were consistent 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, genotoxicity. In 2-year carcinogenicity studies in rats, findings comprised of neuroendocrine neoplasms as well as squamous cell papillomas in the forestomach. The mechanism leading to the induction of gastric carcinoid by substituted benzimidazoles has been rigorously investigated and

appears to be a secondary reaction to markedly elevated serum gastrin levels which occur in the rat during chronic high-dose treatment. In the rodent long-term studies an increased number of liver tumours were noted in rats and female mice and were interpreted as due to the high metabolic rate of pantoprazole in the liver. A slight increase of thyroid neoplasms was seen in the rat group receiving the highest dose (200 mg/kg). This increase was linked to the altered breakdown of thyroxine in the rat liver. As the therapeutic doses in humans are low, harmful effects on the thyroid gland are not expected.

Animal studies of peri-postnatal toxicity showed toxic effects such as changes of bone parameters at exposures more than 2 fold higher than clinical exposures. The pre-weaning offspring death rate in rats (from day 4 post-partum, corresponding roughly to the perinatal stage/first years of life in humans) was increased. Lower dosages, resulting in exposure levels comparable to the clinical exposure levels, did not have this effect. The relevance of this finding for children is unknown. Studies did not show any evidence for impaired fertility or teratogenic effects. Placental transfer was investigated in rats and showed an increase in pantoprazole transfer with increasing gestational age. As a result, foetal exposure of pantoprazole is increased shortly before birth.

6. Pharmaceutical particulars

6.1 List of excipients

Di sodium Edetate
Mannitol
Sodium Hydroxide
Water for Injection

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 and protect from sunlight.
Do not freeze.
Keep out of the reach of children.

6.5 Nature and contents of container

1 vial of Pantoprazole Sodium powder per pack. 10ml ampoule of 0.9% Sodium Chloride (Celine) solution for reconstitution.

6.6 Special precautions for disposal and other handling

Reconstituted solution should be administered within 12 hrs after preparation.

7. Marketing authorisation holder

Nabiqasim Industries (Pvt.) Ltd.
17/24, Korangi Industrial Area,
Korangi,
Karachi – Pakistan.

8. Marketing authorisation number

H2022/CTD6842/13095

9. Date of first authorisation/renewal of the authorisation

4th August 2022

10. Date of revision of the text

1st September 2026