

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Protium 20 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 20mg pantoprazole (as sodium sesquihydrate).

Excipients: contains soya lecithin as part of the printing ink.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

Product imported from the UK and Italy:

Yellow, oval biconvex film coated tablets marked 'P20' in brown ink on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults and adolescents 12 years of age and above

Symptomatic gastro-oesophageal reflux disease.

For long-term management and prevention of relapse in reflux oesophagitis.

Adults

Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment (see section 4.4).

4.2 Posology and method of administration

Tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

Recommended dose:

Adults and adolescents 12 years of age and above:

Symptomatic gastro-oesophageal reflux disease

The recommended oral dose is one gastro-resistant tablet Protium 20 mg per day. Symptom relief is generally accomplished within 2-4 weeks. If this is not sufficient, symptom relief will normally be achieved within a further 4 weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment.

Long-term management and prevention of relapse in reflux oesophagitis

For long-term management, a maintenance dose of one gastro-resistant tablet Protium 20mg per day is recommended, increasing to 40mg pantoprazole per day if a relapse occurs. Protium 40mg is available for this case. After healing of the relapse the dosage can be reduced again to 20mg pantoprazole.

Adults

Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment

The recommended oral dosage is one gastro-resistant tablet Protium 20mg per day.

Special populations

Children below 12 years of age

Protium is not recommended for use in children below 12 years of age due to limited data on safety and efficacy in this age group.

Hepatic Impairment

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

Renal Impairment

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

Elderly

No dose adjustment is necessary in elderly patients.

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles, soya oil or to any of the other excipients.

4.4 Special warnings and precautions for use

Hepatic Impairment

In patients with severe liver impairment the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise of the liver enzymes the treatment should be discontinued (see section 4.2).

Co-administration with NSAIDs

The use of Protium 20 mg as a preventive of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

In presence of alarm symptoms

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 is to be considered if symptoms persist despite adequate treatment.

Co-administration with atazanavir

Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir. A pantoprazole dose of 20 mg per day should not be exceeded.

Influence on vitamin B12 absorption

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.

Long term treatment

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

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

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with PPI'S 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.

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, predominately 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. Patient at risk of osteoporosis should received care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Soya oil

This medicinal product contains soya oil. If the patient is allergic to peanut or soya, do not use this medicinal product (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

Effect of pantoprazole on the absorption of other medicinal products

Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may reduce the absorption of drugs with a gastric pH dependent bioavailability, e.g some azole antifungals as ketoconazole, itraconazole, posaconazole and other medicine as erlotinib.

HIV medications (atazanavir)

Co-administration of atazanavir and other HIV medications whose absorption is pH-dependent with proton-pump inhibitors might result in a substantial reduction in the bioavailability of these HIV medications and might impact the efficacy of these medicines. Therefore, the co-administration of proton pump inhibitors with atazanavir is not recommended (see section 4.4).

Coumarin anticoagulants (phenprocoumon or warfarin)

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed 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. Therefore, in patients treated with coumarin anticoagulants (e.g. phenprocoumon or warfarin), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

Other interactions 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Protium should not be used during pregnancy unless clearly necessary.

Lactation
Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported.

Therefore a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Protium should be made taking into account the benefit of breastfeeding to the child and the benefit of Protium therapy to women.

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 are diarrhoea and headache, both occurring in approximately 1 % of patients.

The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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	Uncommon	Rare	Very rare	Not Known
Blood and lymphatic system disorders			Thrombocytopenia; Leukopenia	
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 special warnings and precautions for use (4.4))

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			
Eye disorders		Disturbances in vision / blurred vision		
Gastrointestinal Disorders	Diarrhoea; Nausea / Vomiting; abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			
Hepatobiliary disorders	Liver enzymes increased (transaminases, γ -GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and sub-cutaneous tissue disorders	Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity
Musculoskeletal, connective tissue disorders	Fracture of the hip, wrist or spine (see section 4.4)	Arthralgia; Myalgia		
Renal and urinary disorders				Interstitial nephritis
Reproductive system and breast disorders		Gynaecomastia		
General disorders and administration site conditions	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

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: AO2BC02

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 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.

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.

5.2 Pharmacokinetic properties

Absorption

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 20 mg oral dose. On average at about 2.0 h - 2.5 h p.a. the maximum serum concentrations of about 1-1.5 µg/ml are achieved, and these values remain constant after multiple administration.

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.

The absolute bioavailability from the tablet was found to be about 77 %. Concomitant intake of food had no influence on AUC, maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

Distribution

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

Elimination

The substance is almost exclusively metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathway include oxidation by CYP3A4. 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.

Characteristics in patients/special groups of subjects

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.

No dose reduction is recommended when pantoprazole is administered 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 dialyzed. Although the main metabolite has a moderately delayed half-life (2 - 3h), excretion is still rapid and thus accumulation does not occur.

Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 3 and 6 h and the AUC values increased by a factor of 3-5, the maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

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

Children

Following administration of single oral doses of 20 or 40 mg pantoprazole to children aged 5 – 16 years AUC and $C_{\max}$ were in the range of corresponding values in adults.

Following administration of single i.v. 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

Preclinical 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate
Mannitol (E421)
Crospovidone
Povidone K90
Calcium stearate
Hypromellose
Povidone K25
Titanium dioxide (E171)
Yellow iron oxide (E172)
Propylene glycol
Methacrylic acid-Ethylacrylate copolymer (1:1)
Polysorbate 80
Sodium laurilsulfate
Triethyl citrate

Printing ink (shellac, iron oxides (E172), soya lecithin, titanium dioxide E171, with antifoam DC1510 or Dimeticone emulsion)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

UK: Aluminium blisters in a cardboard carton containing 28 tablets.
Italy: Re-boxed carton containing blister strips. Pack size 28

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Imbat Limited
Unit L2
North Ring Business Park
Santry
Dublin 9

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1151/16/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th September 2006

Date of last renewal: 8th September 2011

10 DATE OF REVISION OF THE TEXT

October 2012