Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Protium 40 mg Gastro-resistant Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 40 mg pantoprazole (as sodium sesquihydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

Product imported from the UK:
Yellow, oval biconvex tablets marked with a ‘P40’ in brown ink on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:

- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux oesophagitis
- Zollinger-Ellison Syndrome and other pathological hypersecretory conditions
- Eradication of Helicobacter pylori, in combination with two antibiotics in patients with duodenal ulcer or gastric ulcer, in order to prevent the reoccurrence of these conditions.

Note: Protium® 40 mg is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

Prior to treatment of gastric ulcer or reflux oesophagitis, the possibility of malignancy should be excluded as treatment with Protium® 40 mg may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Diagnosis of reflux oesophagitis should be confirmed by endoscopy.

In the case of combination therapy for the eradication of *Helicobacter pylori*, the Summaries of Product Characteristics of the respective drugs should be observed.

4.2 Posology and method of administration

Recommended dosage:

Adults and adolescents 12 years of age and above:

Treatment of moderate and severe reflux oesophagitis

One tablet of Protium® per day. In individual cases the dose may be doubled (increase to 2 tablets Protium®daily) especially when there has been no response to other treatment. Protium®40 mg should not be chewed or crushed, and should be swallowed whole with water either before or during breakfast.

Adults:

Treatment of duodenal ulcer and gastric ulcer

One tablet of Protium®40 mg per day. Protium®40 mg should not be chewed or crushed, and should be swallowed whole with water either before or during breakfast.

In individual cases, a double dose (increase to 2 tablets of Protium®40 mg each day) can be given to patients with gastric and duodenal ulcer, particularly if they have not responded to other drugs.

In combination therapy for the eradication of *Helicobacter pylori*, the recommended dose is one tablet taken twice daily. Combination therapy should be implemented for 7 days. Where a daily dose of two tablets has been prescribed, the second Protium®40 mg tablet should be taken before the evening meal.

In most patients, freedom from symptoms is achieved rapidly.

Duodenal ulcer:
Duodenal ulcers generally heal within 2 weeks. If a 2-week period of treatment is not sufficient, healing will usually be achieved within a further 2 weeks.

Gastric ulcer:
A 4-week period is usually required for the treatment of gastric ulcers. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Gastro-Oesophageal Reflux:
A 4-week period is usually required for the treatment of gastro-oesophageal reflux. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Long-term management of Zollinger-Ellison syndrome and other pathological hypersecretory conditions:
Patients should start their treatment with a daily dose of 80 mg (2 tablets of Protium® 40 mg).
Thereafter, the dosage 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 dosage above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control. Treatment duration in Zollinger-Ellison Syndrome and other pathological hypersecretory conditions is not limited and should be adapted
according to clinical needs.

Eradication of *Helicobacter pylori* (*H.pylori)*

The use of Protium® 40 mg in combination with two antibiotics (triple therapy) is recommended. The following combinations have been shown to be effective:

(a) Protium® 40 mg twice daily,
plus 1000 mg amoxycillin twice daily
and 500 mg clarithromycin twice daily

(b) Protium® 40 mg twice daily,
plus 400 mg metronidazole twice daily
and 250 mg clarithromycin twice daily

The second Protium® 40 mg tablet should be taken before the evening meal. Combination therapy should be implemented for 7 days. At the end of the 7 days' combination period, pantoprazole may be continued to ensure the

healing of the ulcer. For duodenal ulcers, this may require an additional 1 to 3 weeks. For gastric ulcers, this may require an additional 3 to 7 weeks.

Elderly and renally impaired patients:
The daily dose of 40 mg pantoprazole should not be exceeded in elderly patients, or in those with impaired renal function.

Patients with hepatic cirrhosis:
In the case of severely reduced liver function, the dosage should be adjusted to one tablet (40 mg) every second day.

4.3 Contraindications

Protium® 40 mg should generally not be used in cases of known hypersensitivity to any of its constituents.

Pantoprazole, like other proton pump inhibitors (PPIs), should not be co-administered with atazanavir *(see Section 4.5).*

4.4 Special warnings and precautions for use

The safety of prolonged use is not fully established and care should be taken to keep patients on prolonged treatment under regular surveillance.

In patients with Zollinger-Ellison-Syndrome and other pathological hypersecretory 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 if respective clinical symptoms are observed.

The response to anticoagulants such as warfarin, phenprocoumon or acenocoumarol may be affected by any concomitant medication. It is therefore good practice to monitor the patient with additional PT (Prothrombin time) /INR (International Normalized Ratio) determinations when Protium® is initiated, discontinued or taken irregularly.

4.5 Interaction with other medicinal products and other forms of interaction

Changes in absorption may be observed when drugs whose absorption is pH-dependent, e.g ketoconazole, are taken concomitantly.

It has been shown that co-administeration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore PPIs, including pantoprazole, should not be co-administered with atazanavir *(see Section 4.3).*

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. An interaction of pantoprazole with other drugs which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenprocoumon, phenytoin, piroxicam, theophylline, warfarin and an oral contraceptive. There were also no interactions with concomitantly administered antacids.

4.6 Pregnancy and lactation

During pregnancy and breast-feeding, Protium® 40 mg should only be used after the diagnosis has been clearly established, since so far there is no information about its safety during pregnancy and lactation in humans. Animal experiments revealed no signs of foetal damage. In an animal study, small amounts of the drug were detected in breast milk.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive and use machines.

4.8 Undesirable effects

Frequency	Common	Uncommon	Rare	Very rare
Organ system	(>1/100, <1/10)	(>1/1,000,<1/100)	(>1/10,000, <1/1,000)	(<1/10,000, incl Isolated reports)
Blood and lymphatic system				Leukopenia; Thrombocytopenia
Gastrointestinal Disorders	Upper abdominal pain; Diarrhoea; Constipation; Flatulence	Nausea / Vomiting	Dry mouth	
General disorders and administration site conditions				Peripheral oedema
Hepatobiliary disorders				Severe hepatocellular damage leading to jaundice with or without hepatic failure
Immune system disorders				Anaphylactic reactions including anaphylactic shock
Investigations				Increased liver enzymes (transaminases, γ-GT); Elevated triglycerides; Increased body temperature
Musculoskeletal, connective tissue disorders				Arthralgia, Myalgia
Nervous system disorders	Headache	Dizziness; Disturbances in vision (blurred vision)		
Psychiatric disorders			Depression, Hallucination,	

		Disorientation and Confusion, especially in predisposed patients, as well as the aggravation of these symptoms in case of preexistence	
Renal and urinary Disorders			Interstitial nephritis
Skin and subcutaneous tissue disorders	Allergic reactions such as pruritus and skin rash		Urticaria; Angioedema; Severe skin reactions such as Stevens-Johnson Syndrome, Erythema multi-forme, Lyell-Syndrome; Photosensitivity

4.9 Overdose

There are no known symptoms of overdose in man. Doses up to 240 mg i.v. have been administered and were well tolerated. The treatment of overdose is symptomatic. Haemodialysis is of no benefit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pantoprazole is a proton pump inhibitor, i.e. it inhibits specifically and dose-proportionally the gastric H^+/K^+-ATPase enzyme which is responsible for acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There it is converted into the active form, a cyclic sulphenamide, which binds to the H^+/K^+-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distally to the receptor level, it can inhibit gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Following intravenous or oral administration, pantoprazole inhibits pentagastrin-stimulated gastric acid secretion. With an oral dose of 40 mg, inhibition was 51% on day 1 and 85% on day 7. Basal 24 hour acidity was reduced by 37% and 98%, respectively.

The special selectivity of pantoprazole is due to the fact that it only exerts its full effect in a strongly acidic environment (pH<3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological and thus therapeutic effect can only be achieved in the acid-secretory parietal cells. By means of a feedback mechanism, this effect is diminished at the same rate as acid secretion is inhibited

The fasting gastrin values increased under pantoprazole, but in most cases they did not exceed the normal upper limit.

Following completion of a course of oral treatment, the median gastrin values clearly declined again.

Enhanced gastrin secretion caused by acid inhibition can lead to an increase in the number of ECL cells in the gastric

mucosa.

5.2 Pharmacokinetic properties

General pharmacokinetics
Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40 mg oral dose. On average at about 2.5 hours post administration, the maximum serum concentration is about 2-3 µg/ml, and this value remains constant after multiple administration.

Volume of distribution is about 0.15 L/kg and clearance is about 0.1 L/h/kg. Terminal half-life is about 1 hour. There were a few cases of subjects with delayed elimination. Because of the specific activation within the parietal cell, the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

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

Pantoprazole's serum protein binding is about 98%. The substance is almost exclusively metabolised in the liver. Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole, the rest are excreted in the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolites (about 1.5 hours) is not much longer than that of pantoprazole.

Bioavailability
Pantoprazole is completely absorbed after oral administration. The absolute bioavailability of the tablet is 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.

Characteristics in patients/special groups of subjects
No dose reduction is required when pantoprazole is administered to patients with impaired kidney 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 moderately delayed half-life (2 to 3 hours), excretion is still rapid and thus accumulation does not occur.

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

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

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

In the rat, no more than 0.02% of the administered dose is excreted via the breast milk.

In humans, there are no data available on excretion via the breast milk.

Children
Following administration of single oral doses of 20 or 40 mg pantoprazole to children aged 5 – 16 years AUC and Cmax 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

Acute toxicity
In acute toxicity studies in mice, the LD_{50} values were found to be 370 mg/kg bodyweight for i.v. administration and around 700 mg/kg bodyweight for oral administration.

In the rat, the corresponding values were around 240 mg/kg for i.v. administration and 900 mg/kg for oral administration.

Chronic toxicity
Hypergastrinaemia and morphologic changes of the mucosa (ECL cell hyperplasia) were observed in studies investigating repeated administration for up to 12 months in the rat and dog. Most of the effects were reversible and attributable solely to the drug action, i.e. suppression of acid secretion.

In long-term studies in the rat and dog, there was an increase in stomach and liver weights, the increase being reversible after the substance was discontinued. The increase in liver weight following highly toxic doses was seen as a result of the induction of drug-metabolising enzymes. After chronic administration of pantoprazole to rats for 1 and 2 years, liver cell hypertrophy and nephropathy were observed. In the 12-month rat study, a solitary gastric carcinoid was found.

Thyroid activation in two rat experiments is due to the rapid metabolism of thyroid hormones in the liver and has also been described in a similar form for other rugs. Changes in the thyroid and associated reduced degradation of cholesterol have been observed in one-year studies in the rat and dog. Hypertrophy of the thyroid and increases in cholesterol levels are reversible.

In studies in the dog, a species-specific pulmonary oedema was observed. The animal-specific metabolite which was responsible for the oedema could not be identified in man.

Carcinogenicity
In a 2-year carcinogenicity study in rats (which corresponds to lifetime treatment for rats), neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the stomachs of the 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 treatment. In addition, rats have more ECL cells in the mucosa of the glandular stomach than man, so that a larger number of responder cells for the increased gastrin values can become active.ECL cell neoplasms were not observed in either a long-term study in mice (24 months) or in chronic studies in dogs.

In the two year studies, an increased number of neoplastic changes of the liver was observed in rats and female mice and was interpreted as being due to pantoprazole's high rate of metabolism in the liver. It can be ruled out that pantoprazole has genotoxic potential because mutagenicity studies gave no indication that pantoprazole reacts with cellular DNA and liver neoplasms only occurred after high doses. Cell transformation tests and a DNA-binding study preclude that DNA plays a role in tumour formation. Such non-genotoxic substances do not present a carcinogenic risk for man.

A slight increase in neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose. The occurrence of these neoplasms is associated with pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. In man, no changes in the thyroid hormones T3, T4 and TSH were observed in the first two weeks of treatment. This high dose phenomenon in the rat is therefore not relevant for man.

Mutagenicity
In mutagenicity studies, there was no indication of a mutagenic action *in vivo* or *in vitro.*

Reproduction toxicology
Investigations revealed no evidence of impaired fertility or teratogenic effects.

Daily doses above 15 mg/kg led to delayed development of the skeleton in rats.

In humans, there is no experience of the use of the drug during pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Anhydrous sodium carbonate
Mannitol (E421)
Crospovidone
Povidone K90
Calcium stearate

Coating:

Hypromellose 2910
Povidone K25
Titanium dioxide (E171)
Yellow iron oxide (E172)
Propylene glycol
Poly(ethylacrylate, methacrylic acid) 1:1
Polysorbate 80
Sodium laurilsulfate
Triethyl citrate

Printing Ink:

Shellac
Iron oxide (E172)
Soya lecithin
Titanium dioxide (E171)
Dimeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Alu/alu blisters of 28 tablets contained in an outer cardboard carton.

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

Not to be chewed or crushed, swallow whole.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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HA4 0NU
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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1328/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 August 2006

10 DATE OF REVISION OF THE TEXT

January 2009