ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Note: This SPC, labelling and packages leaflet is the version valid at the time of Commission Decision.

After the Commission Decision the Member State Competent Authorities, in liaison with the Reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Protium and associated names (see Annex I) 20 mg gastro-resistant tablets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient
Each gastro-resistant tablet contains 1.06 microgram soya oil.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet (tablet).
Yellow, oval biconvex film coated tablet imprinted with “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 20 mg per day is recommended, increasing to 40 mg pantoprazole per day if a relapse occurs. Protium 40 mg is available for this case. After healing of the relapse the dose can be reduced again to 20 mg 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 dose is one gastro-resistant tablet Protium 20 mg 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*.

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 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 breast-feeding 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 (≥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**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders			Thrombocytopenia; Leukopenia	

Frequency / System Organ Class	Uncommon	Rare	Very rare	Not known
Immune system disorders		Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders		Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia
Psychiatric disorders	Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination; Confusion (especially in pre-disposed patients, as well as the aggra-vation 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; Jaun-dice; Hepato-cellular failure
Skin and sub-cutaneous tissue disorders	Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-John-son syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity
Musculoskeletal and connective tissue disorders		Arthralgia; Myalgia		

Frequency / System Organ Class	Uncommon	Rare	Very rare	Not known
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: 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 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

Core:
Sodium carbonate, anhydrous
Mannitol (E421)
Crospovidone
Povidone K90
Calcium stearate

Coating:
Hypromellose
Povidone K25
Titanium dioxide (E171)
Yellow iron oxide (E172)
Propylene glycol
Methacrylic acid-ethyl acrylate copolymer (1:1)
Polysorbate 80
Sodium laurilsulfate
Triethyl citrate

Printing ink:
Shellac
Red iron oxide (E172)

Black iron oxide (E172)
Yellow iron oxide (E172)
Soya lecithin
Titanium dioxide (E171)
Antifoam DC 1510 (dimeticone emulsion)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottles with LDPE screw cap closure.

	7	gastro-resistant tablets
	10	gastro-resistant tablets
	14	gastro-resistant tablets
	15	gastro-resistant tablets
	24	gastro-resistant tablets
	28	gastro-resistant tablets
	30	gastro-resistant tablets
	48	gastro-resistant tablets
	49	gastro-resistant tablets
	56	gastro-resistant tablets
	60	gastro-resistant tablets
	84	gastro-resistant tablets
	90	gastro-resistant tablets
	98	gastro-resistant tablets
	98 (2x49)	gastro-resistant tablets
	100	gastro-resistant tablets
	112	gastro-resistant tablets
	168	gastro-resistant tablets
Hospital pack with	50	gastro-resistant tablets
	56	gastro-resistant tablets
	84	gastro-resistant tablets
	90	gastro-resistant tablets
	112	gastro-resistant tablets
	140	gastro-resistant tablets
	140 (10x14) (5x28)	gastro-resistant tablets
	150 (10x15)	gastro-resistant tablets
	280 (20x14), (10x28)	gastro-resistant tablets
	500	gastro-resistant tablets
	700 (5x140)	gastro-resistant tablets

Blister (ALU/ALU blister) without cardboard reinforcement.
Blister (ALU/ALU blister) with cardboard reinforcement (blister wallet).

	7	gastro-resistant tablets
	10	gastro-resistant tablets
	14	gastro-resistant tablets
	15	gastro-resistant tablets
	28	gastro-resistant tablets
	30	gastro-resistant tablets
	49	gastro-resistant tablets
	56	gastro-resistant tablets
	60	gastro-resistant tablets
	84	gastro-resistant tablets
	90	gastro-resistant tablets
	98	gastro-resistant tablets
	98 (2x49)	gastro-resistant tablets
	100	gastro-resistant tablets
	112	gastro-resistant tablets
	168	gastro-resistant tablets
Hospital pack with	50	gastro-resistant tablets
	56	gastro-resistant tablets
	84	gastro-resistant tablets
	90	gastro-resistant tablets
	112	gastro-resistant tablets
	140	gastro-resistant tablets
	140 (10x14) (5x28)	gastro-resistant tablets
	150 (10x15)	gastro-resistant tablets
	280 (20x14), (10x28)	gastro-resistant tablets
	500	gastro-resistant tablets
	700 (5x140)	gastro-resistant tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD/MM/YYYY}
[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}
[To be completed nationally]

Detailed information on this medicinal product is available on the website of the Heads of Medicines Agencies (HMA) http://www.hma.eu

1. NAME OF THE MEDICINAL PRODUCT

Protium and associated names (see Annex I) 40 mg gastro-resistant tablets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient
Each gastro-resistant tablet contains 1.06 microgram soya oil.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet (tablet).
Yellow, oval, biconvex film-coated tablet imprinted with “P 40” in brown ink on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and adolescents 12 years of age and above
- Reflux oesophagitis.

Adults
- Eradication of *Helicobacter pylori* (*H. pylori*) in combination with appropriate antibiotic therapy in patients with *H. pylori* associated ulcers.
- Gastric and duodenal ulcer.
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.

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
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. A 4-week period is usually required for the treatment of reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Adults
Eradication of *H. pylori* in combination with two appropriate antibiotics
In *H. pylori* positive patients with gastric and duodenal ulcers, eradication of the germ by a combination therapy should be achieved. Considerations should be given to official local guidance (e.g. national recommendations) regarding bacterial resistance and the appropriate use and prescription of antibacterial

agents. Depending upon the resistance pattern, the following combinations can be recommended for the eradication of *H. pylori*:

a) twice daily one tablet Protium
+ twice daily 1000 mg amoxicillin
+ twice daily 500 mg clarithromycin

b) twice daily one tablet Protium
+ twice daily 400 - 500 mg metronidazole (or 500 mg tinidazole)
+ twice daily 250 - 500 mg clarithromycin

c) twice daily one tablet Protium
+ twice daily 1000 mg amoxicillin
+ twice daily 400 - 500 mg metronidazole (or 500 mg tinidazole)

In combination therapy for eradication of *H. pylori* infection, the second Protium tablet should be taken 1 hour before the evening meal. The combination therapy is implemented for 7 days in general and can be prolonged for a further 7 days to a total duration of up to two weeks. If, to ensure healing of the ulcers, further treatment with pantoprazole is indicated, the dose recommendations for duodenal and gastric ulcers should be considered.

If combination therapy is not an option, e.g. if the patient has tested negative for *H. pylori*, the following dose guidelines apply for Protium monotherapy:

Treatment of gastric ulcer
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. 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.

Treatment of duodenal ulcer
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. A duodenal ulcer generally heals within 2 weeks. If a 2-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

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 (2 tablets of Protium 40 mg). 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.
Treatment duration in Zollinger-Ellison syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.

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 (1 tablet of 20 mg pantoprazole) should not be exceeded in patients with severe liver impairment. Protium must not be used in combination treatment for eradication of *H. pylori* in patients with moderate to severe hepatic dysfunction since currently no data are available on the efficacy and safety of Protium in combination treatment of these patients (see section 4.4).

Renal Impairment
No dose adjustment is necessary in patients with impaired renal function. Protium must not be used in combination treatment for eradication of *H. pylori* in patients with impaired renal function since currently no data are available on the efficacy and safety of Protium in combination treatment for these patients.

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 or of the combination partners.

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).

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

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
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 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*.

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 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 breast-feeding 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 (≥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**	**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
Psychiatric disorders	Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination; Confusion (especially in

Frequency / System Organ Class	Uncommon	Rare	Very rare	Not known
				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 and connective tissue disorders		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: 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 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 40 mg oral dose. On average at about 2.5 h p.a. the maximum serum concentrations of about 2 - 3 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 - 3 h), 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 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.

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

Core:
Sodium carbonate, anhydrous
Mannitol (E421)
Crospovidone
Povidone K90
Calcium stearate

Coating:
Hypromellose
Povidone K25
Titanium dioxide (E171)
Yellow iron oxide (E172)
Propylene glycol
Methacrylic acid-ethyl acrylate copolymer (1:1)
Polysorbate 80
Sodium laurilsulfate
Triethyl citrate

Printing ink:
Shellac
Red iron oxide (E172)
Black iron oxide (E172)
Yellow iron oxide (E172)
Soya lecithin
Titanium dioxide (E171)
Antifoam DC 1510 (dimeticone emulsion)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottles with LDPE screw cap closure.

7 gastro-resistant tablets
10 gastro-resistant tablets
14 gastro-resistant tablets
15 gastro-resistant tablets
24 gastro-resistant tablets
28 gastro-resistant tablets
30 gastro-resistant tablets
48 gastro-resistant tablets
49gastro-resistant tablets
56 gastro-resistant tablets
60 gastro-resistant tablets
84 gastro-resistant tablets
90 gastro-resistant tablets
98 gastro-resistant tablets
98 (2x49) gastro-resistant tablets
100 gastro-resistant tablets
112 gastro-resistant tablets
168 gastro-resistant tablets

Hospital pack with
50 gastro-resistant tablets
90 gastro-resistant tablets
100 gastro-resistant tablets
140 gastro-resistant tablets
140 (10x14) gastro-resistant tablets
150 (10x15) gastro-resistant tablets
700 (5x140) gastro-resistant tablets

Blister (ALU/ALU blister) without cardboard reinforcement.
Blister (ALU/ALU blister) with cardboard reinforcement (blister wallet).

7 gastro-resistant tablets
10 gastro-resistant tablets
14 gastro-resistant tablets
15 gastro-resistant tablets
28 gastro-resistant tablets
30 gastro-resistant tablets
49gastro-resistant tablets
56 gastro-resistant tablets
60 gastro-resistant tablets
84 gastro-resistant tablets
90 gastro-resistant tablets
98 gastro-resistant tablets
98 (2x49) gastro-resistant tablets
100 gastro-resistant tablets
112 gastro-resistant tablets
168 gastro-resistant tablets

Hospital pack with
50 gastro-resistant tablets

90 gastro-resistant tablets
100 gastro-resistant tablets
140 gastro-resistant tablets
140 (10x14) gastro-resistant tablets
150 (10x15) gastro-resistant tablets
700 (5x140) gastro-resistant tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD/MM/YYYY}
[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}
[To be completed nationally]

Detailed information on this medicinal product is available on the website of the Heads of Medicines Agencies (HMA) http://www.hma.eu

1. NAME OF THE MEDICINAL PRODUCT

Protium and associated names (see Annex I) 40 mg powder for solution for injection
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients
Each vial contains 1 mg disodium edetate and 0.24 mg sodium hydroxide.
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. is essentially 'sodium-free'.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.
White to off-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 Protium 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 Protium i.v. should be discontinued and 40 mg pantoprazole p.o. should be administered instead.

Recommended dose
Gastric and duodenal ulcer, reflux oesophagitis
The recommended intravenous dose is one vial of Protium (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 Protium. 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 Protium 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

Paediatric patients
The experience in children is limited. Therefore, Protium 40 mg powder for solution for injection is not recommended for use in patients below 18 years of age until further data become available.

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).

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

Elderly
No dose adjustment is necessary in elderly patients.

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 55 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 - 15 minutes.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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.

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 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.
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*.

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

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 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 breast-feeding 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 (≥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				Thrombo-cytopenia; Leukopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggrava-	Hallucination; Confusion (especially in

Frequency / System Organ Class	Common	Uncommon	Rare	Very rare	Not known
				tions)	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 subcutaneous tissue disorders		Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity
Musculoskeletal and connective tissue disorders			Arthralgia; Myalgia		
Renal and urinary disorders					Interstitial nephritis
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions	Injection site thrombophlebitis	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: 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 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

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.

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 (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.
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.

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

Children
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

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

Disodium edetate
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, or reconstitution and dilution, chemical and physical in use stability has been demonstrated for 12 hours at 25 °C.
From a microbiological point of view, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25 °C.
Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted and diluted medicinal product see section 6.3.

6.5 Nature and contents of container

10 ml clear glass (type I) vial with aluminum cap and grey rubber stopper containing 40 mg powder for solution for injection.
Pack sizes of 1 vial and 5 (5x1) vials with powder for solution for injection.
Hospital packs: 1 vial, 5 (5x1) vials, 10 (10x1) vials and 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 powder. The appearance of the product after reconstitution is a clear yellowish 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 55 mg/ml (5 %) solution for injection. Glass or plastic containers should be used for dilution.

After reconstitution, or reconstitution and dilution, chemical and physical in use stability has been demonstrated for 12 hours at 25 °C.
From a microbiological point of view, the product should be used immediately.
Protium 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 or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed) should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD/MM/YYYY}
[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}
[To be completed nationally]

Detailed information on this medicinal product is available on the website of the Heads of Medicines Agencies (HMA) http://www.hma.eu

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Protium and associated names (see Annex I) 20 mg gastro-resistant tablets
[See Annex I - To be completed nationally]

Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg of pantoprazole (as sodium sesquihydrate).

3. LIST OF EXCIPIENTS

Contains soya oil. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Pack with 7, 10, 14, 15, 24, 28, 30, 48, 49, 56, 60, 84, 90, 98, 98 (2x49), 100, 112, 168 gastro-resistant tablets.
Hospital pack with 50, 56, 84, 90, 112, 140, 140 (10x14 or 5x28), 150 (10x15), 280 (20x14 or 10x28), 500, 700 (5x140) gastro-resistant tablets.

(Part of a) hospital pack - not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Swallow whole, do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Blister wallet

1. NAME OF THE MEDICINAL PRODUCT

Protium and associated names (see Annex I) 20 mg gastro-resistant tablets
[See Annex I - To be completed nationally]

Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains soya oil. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Pack with 5 gastro-resistant tablets.
Pack with 7 gastro-resistant tablets.

(Part of a) hospital pack - not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Swallow whole, do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Protium and associated names (see Annex I) 20 mg tablets
[See Annex I - To be completed nationally]

Pantoprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle label

1. NAME OF THE MEDICINAL PRODUCT

Protium and associated names (see Annex I) 20 mg gastro-resistant tablets
[See Annex I - To be completed nationally]

Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains soya oil. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Pack with 7, 10, 14, 15, 24, 28, 30, 48, 49, 56, 60, 84, 90, 98, 100, 112, 168 gastro-resistant tablets.
Hospital pack with 50, 56, 84, 90, 112, 140, 140 (10x14 or 5x28), 150 (10x15), 280 (20x14 or 10x28), 500, 700 (5x140) gastro-resistant tablets.

(Part of a) hospital pack - not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Swallow whole, do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Protium and associated names (see Annex I) 40 mg gastro-resistant tablets
[See Annex I - To be completed nationally]

Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains soya oil. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Pack with 7, 10, 14, 15, 24, 28, 30, 48, 49, 56, 60, 84, 90, 98, 98 (2x49), 100, 112, 168 gastro-resistant tablets.
Hospital pack with 50, 90, 100, 140, 140 (10x14), 150 (10x15), 700 (5x140) gastro-resistant tablets.

(Part of a) hospital pack - not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Swallow whole, do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Blister wallet

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Protium and associated names (see Annex I) 40 mg gastro-resistant tablets
[See Annex I - To be completed nationally]

Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains soya oil. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Pack with 5 gastro-resistant tablets.
Pack with 7 gastro-resistant tablets.

(Part of a) hospital pack - not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Swallow whole, do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Protium and associated names (see Annex I) 40 mg tablets
[See Annex I - To be completed nationally]

Pantoprazole

2. NAME OF THE MARKETING AUTHORISATION

[See Annex I - To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. PHARMACEUTICAL FORM AND CONTENTS

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle Label

1. NAME OF THE MEDICINAL PRODUCT

Protium and associated names (see Annex I) 40 mg gastro-resistant tablets
[See Annex I - To be completed nationally]

Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains soya oil. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Pack with 7, 10, 14, 15, 24, 28, 30, 48, 49, 56, 60, 84, 90, 98, 100, 112, 168 gastro-resistant tablets.
Hospital pack with 50, 90, 100, 140, 140 (10x14), 150 (10x15), 700 (5x140) gastro-resistant tablets.

(Part of a) hospital pack - not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Swallow whole, do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[See Annex I - To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Protium and associated names (see Annex I) 40 mg powder for solution for injection
[See Annex I - To be completed nationally]

Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Each vial contains 1 mg disodium edetate and 0.24 mg sodium hydroxide.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection.

Pack with 1 vial.
Pack with 5 (5x1) vials.

Hospital pack with 1 vial.
Hospital pack with 5 (5x1) vials.
Hospital pack with 10 (10x1) vials.
Hospital pack with 20 (20x1) vials.

(Part of a) hospital pack - not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Shelf life after reconstitution (and dilution): 12 hours

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Vial Label

1. NAME OF THE MEDICINAL PRODUCT

Protium and associated names (see Annex I) 40 mg powder for solution for injection.
[See Annex I - To be completed nationally]

Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.

4. EXPIRY DATE

EXP
Shelf life after reconstitution: 12 hours

5. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Keep the vial in the outer carton in order to protect from light.

6. BATCH NUMBER

Batch

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Protium and associated names (see Annex I) **20 mg gastro-resistant tablets**
[See Annex I - To be completed nationally]

Pantoprazole

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT PROTIUM IS AND WHAT IT IS USED FOR

Protium is a selective "proton pump inhibitor", a medicine which reduces the amount of acid produced in your stomach. It is used for treating acid-related diseases of the stomach and intestine.

Protium is used for:

Adults and adolescents 12 years of age and above:

- Treating symptoms (e.g. heartburn, acid regurgitation, pain on swallowing) associated to gastro-oesophageal reflux disease caused by reflux of acid from the stomach.

- Long-term management of reflux oesophagitis (inflammation of the oesophagus accompanied by the regurgitation of stomach acid) and preventing its return.

Adults:

- Preventing duodenal and stomach ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs, for example, ibuprofen) in patients at risk who need to take NSAIDs continuously.

2. BEFORE YOU TAKE PROTIUM

Do not take Protium
- If you are allergic (hypersensitive) to pantoprazole, soya oil or to any of the other ingredients of Protium (see section 6).
- If you are allergic to medicines containing other proton pump inhibitors.

Take special care with Protium

- If you have severe liver problems. Please tell your doctor if you have ever had problems with your liver. He will check your liver enzymes more frequently, especially when you are taking Protium as a long-term treatment. In the case of a rise of liver enzymes the treatment should be stopped.
- If you need to take medicines called NSAIDs continuously and receive Protium because you have an increased risk of developing stomach and intestinal complications. Any increased risk will be assessed according to your own personal risk factors such as your age (65 years old or more), a history of stomach or duodenal ulcers or of stomach or intestinal bleeding.
- If you have reduced body stores or risk factors for reduced vitamin B12 and receive pantoprazole long-term treatment. As with all acid reducing agents, pantoprazole may lead to a reduced absorption of vitamin B12.
- If you are taking a medicine containing atazanavir (for the treatment of HIV-infection) at the same time as pantoprazole, ask your doctor for specific advise.

Tell your doctor immediately if you notice any of the following symptoms:
- an unintentional loss of weight
- repeated vomiting
- difficulty in swallowing
- vomiting blood
- you look pale and feel weak (anaemia)
- you notice blood in your stools
- severe and/or persistent diarrhoea, as Protium has been associated with a small increase in infectious diarrhoea.

Your doctor may decide that you need some tests to rule out malignant disease because pantoprazole also alleviates the symptoms of cancer and could cause delay in diagnosing it. If your symptoms continue in spite of your treatment, further investigations will be considered.

If you take Protium on a long-term basis (longer than 1 year) your doctor will probably keep you under regular surveillance. You should report any new and exceptional symptoms and circumstances whenever you see your doctor.

Taking other medicines
Protium may influence the effectiveness of other medicines, so tell your doctor if your are taking

- Medicines such as ketoconazole, itraconazole and posaconazole (used to treat fungal infections) or erlotinib (used for certain types of cancer) because Protium may stop these and other medicines from working properly.
- Warfarin and phenprocoumon, which affect the thickening, or thinning of the blood. You may need further checks.
- Atazanavir (used to treat HIV-infection).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
There are no adequate data from the use of pantoprazole in pregnant women. Excretion into human milk has been reported.If you are pregnant, or think you may be pregnant, or if you are breast-feeding, you should use this medicine only if your doctor considers the benefit for you greater than the potential risk for your unborn child or baby.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
If you experience side effects like dizziness or disturbed vision, you should not drive or operate machines.

Important information about some of the ingredients of Protium
Protium contains soya oil. If you are allergic to peanut or soya, do not use this medicine.

3. HOW TO TAKE PROTIUM

Always take Protium exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

When and how should you take Protium?
Take the tablets 1 hour before a meal without chewing or breaking them and swallow them whole with some water.

Unless told otherwise by your doctor, the usual dose is:

Adults and adolescents 12 years of age and above:

To treat symptoms (e.g. heartburn, acid regurgitation, pain on swallowing) associated to gastro-oesophageal reflux disease
The usual dose is one tablet a day.This dose usually brings relief within 2 - 4 weeks – at most after another 4 weeks. Your doctor will tell you how long to continue taking the medicine. After this any recurring symptoms can be controlled by **taking one tablet daily**, when required.

For long-term management and for preventing the return of reflux oesophagitis
The usual dose is one tablet a day. If the illness returns, your doctor can double the dose, in which case you can use Protium 40 mg tablets instead, one a day. After healing, you can reduce the dose back again to one tablet 20 mg a day.

Adults:

To prevent duodenal and stomach ulcers in patients who need to take NSAIDs continuously
The usual dose is one tablet a day.

Special patient groups:

- If you suffer from severe liver problems, you should not take more than one 20 mg tablet a day.

- Children below 12 years. These tablets are not recommended for use in children below 12 years.

If you take more Protium than you should
Tell your doctor or pharmacist. There are no known symptoms of overdose.

If you forget to take Protium
Do not take a double dose to make up for the forgotten dose. Take your next normal dose at the usual time.

If you stop taking Protium
Do not stop taking these tablets without first talking to your doctor or pharmacist.

If you have any further questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Protium can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

If you get any of the following side effects, stop taking these tablets and tell your doctor immediately, **or contact the casualty department at your nearest hospital:**

- **Serious allergic reactions (frequency rare):** swelling of the tongue and/or throat, difficulty in swallowing, hives (nettle rash), difficulties in breathing, allergic facial swelling (Quincke's oedema / angioedema), severe dizziness with very fast heartbeat and heavy sweating.

- **Serious skin conditions (frequency not known):** blistering of the skin and rapid deterioration of your general condition, erosion (including slight bleeding) of eyes, nose, mouth/lips or genitals (Stevens-Johnson-Syndrome, Lyell-Syndrome, Erythema multiforme) and sensitivity to light.

- **Other serious conditions (frequency not known):** yellowing of the skin or whites of the eyes (severe damage to liver cells, jaundice) or fever, rash, and enlarged kidneys sometimes with painful urination and lower back pain (serious inflammation of the kidneys).

Other side effects are:

- **Uncommon** (affects 1 to 10 users in 1,000)
  headache; dizziness; diarrhoea; feeling sick, vomiting; bloating and flatulence (wind); constipation; dry mouth; abdominal pain and discomfort; skin rash, exanthema, eruption; itching; feeling weak, exhausted or generally unwell; sleep disorders.
- **Rare** (affects 1 to 10 users in 10,000)
  disturbances in vision such as blurred vision; hives; pain in the joints; muscle pains; weight changes; raised body temperature; swelling of the extremities (peripheral oedema); allergic reactions; depression; breast enlargement in males.
- **Very Rare** (affects less than 1 user in 10,000)
  disorientation.
- **Not known** (frequency cannot be estimated from the available data)
  Hallucination, confusion (especially in patients with a history of these symptoms); decreased sodium level in blood.

Side effects identified through blood tests:
- **Uncommon** (affects 1 to 10 users in 1,000)
  an increase in liver enzymes.
- **Rare** (affects 1 to 10 users in 10,000)
  an increase in bilirubin; increased fats in the blood.
- **Very Rare** (affects less than 1 user in 10,000)
  a reduction in the number of blood platelets, which may cause you to bleed or bruise more than normal; a reduction in the number of white blood cells, which may lead to more frequent infections.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PROTIUM

Keep out of the reach and sight of children.

Do not use Protium after the expiry date, which is stated on the carton and the container after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions**.**

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Protium contains

- The active substance is pantoprazole. Each gastro-resistant tablet contains 20 mg of pantoprazole (as sodium sesquihydrate).

- The other ingredients are:
  Core: sodium carbonate (anhydrous), mannitol, crospovidone, povidone K90, calcium stearate.
  Coating: hypromellose, povidone K25, titanium dioxide (E171), yellow iron oxide (E172), propylene glycol, methacrylic acid-ethyl acrylate copolymer (1:1), polysorbate 80, sodium laurilsulfate, triethyl citrate.
  Printing ink: shellac, red, black and yellow iron oxide (E172), soya lecithin, titanium dioxide (E171) and antifoam DC 1510 (dimeticone emulsion).
  [To be completed nationally]

What Protium looks like and contents of the pack

Yellow, oval, biconvex gastro-resistant tablet imprinted with “P 20” on one side.

Packs: bottles (high density polyethylene container with low density polyethylene screw cap closure) and blister (ALU/ALU blister) without cardboard reinforcement or with cardboard reinforcement (blister wallet).

Protium is available in the following pack sizes:

Packs with 7, 10, 14, 15, 24, 28, 30, 48, 49, 56, 60, 84, 90, 98, 98 (2x49), 100, 112, 168 gastro-resistant tablets.
Hospital packs with 50, 56, 84, 90, 112, 140, 140 (10x14 or 5x28), 150 (10x15), 280 (20x14 or 10x28), 500, 700 (5x140) gastro-resistant tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicine is authorised in the Member States of the EEA under the following names:

Name of Member State	Name of the medicine
Austria	Pantoloc 20 mg-Filmtabletten, Zurcal 20 mg-Filmtabletten
Belgium	Pantozol, Zurcale
Bulgaria	Controloc
Cyprus	Controloc
Czech Republic	Controloc 20 mg
Denmark	Pantoloc
Estonia	Controloc 20 mg
Finland	Somac 20 mg
France	Eupantol 20 mg, Inipomp 20 mg, Pantec 20 mg, Pantipp 20 mg
Germany	Pantozol 20 mg, Pantoprazol NYC 20 mg, Pantoprazol 20 mg Byk, Rifun 20 mg, Pantoprazole Lomberg 20 mg, PantoLomberg 20 mg, Zurcal S 20 mg
Greece	Controloc 20 mg, Zurcazol 20 mg
Hungary	Controloc 20 mg
Ireland	Protium 20 mg
Italy	Pantorc, Pantopan, Pantecta, Peptazol
Latvia	Controloc 20 mg
Lithuania	Controloc 20 mg
Luxembourg	Pantozol-20, Panto-Byk-20
Netherlands	Pantozol 20 mg
Norway	Somac
Poland	Controloc 20
Portugal	Pantoc, Zurcal, Apton, Pantoprazole ALTANA 20 mg
Romania	Controloc 20 mg
Slovakia	Controloc 20 mg
Slovenia	Controloc 20 mg
Spain	Pantecta 20 mg comprimidos gastrorresistentes Blister, Anagastra 20 mg Blister, Ulcotenal 20 mg comprimidos gastrorresistentes Blister
Sweden	Pantoloc
United Kingdom	Protium 20 mg

[See Annex I - To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicinal product is available on the website of the Heads of Medicines Agencies (HMA) http://www.hma.eu

PACKAGE LEAFLET: INFORMATION FOR THE USER

Protium and associated names (see Annex I) **40 mg gastro-resistant tablets**
[See Annex I - To be completed nationally]

Pantoprazole

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT PROTIUM IS AND WHAT IT IS USED FOR

Protium is a selective "proton pump inhibitor", a medicine which reduces the amount of acid produced in your stomach. It is used for treating acid-related diseases of the stomach and intestine.

Protium is used for treating:

Adults and adolescents 12 years of age and above:

- Reflux oesophagitis.An inflammation of your oesophagus (the tube which connects your throat to your stomach) accompanied by the regurgitation of stomach acid.

Adults:

- An infection with a bacterium called *Helicobacter pylori* in patients with duodenal ulcers and stomach ulcers in combination with two antibiotics (Eradication therapy). The aim is to get rid of the bacteria and so reduce the likelihood of these ulcers returning.

- Stomach and duodenal ulcers.

- Zollinger-Ellison-Syndrome and other conditions producing too much acid in the stomach.

2. BEFORE YOU TAKE PROTIUM

Do not take Protium
- If you are allergic (hypersensitive) to pantoprazole, soya oil or to any of the other ingredients of Protium (see section 6).

- If you are allergic to medicines containing other proton pump inhibitors.

Take special care with Protium
- If you have severe liver problems. Please tell your doctor if you ever had problems with your liver in the past. He will check your liver enzymes more frequently, especially when you are taking Protium as a long-term treatment. In the case of a rise of liver enzymes the treatment should be stopped.
- If you have reduced body stores or risk factors for reduced vitamin B12 and receive pantoprazole long-term treatment. As with all acid reducing agents, pantoprazole may lead to a reduced absorption of vitamin B12.
- If you are taking a medicine containing atazanavir (for the treatment of HIV-infection) at the same time as pantoprazole, ask your doctor for specific advise.

Tell your doctor immediately if you notice any of the following symptoms:
- an unintentional loss of weight
- repeated vomiting
- difficulty in swallowing
- vomiting blood
- you look pale and feel weak (anaemia)
- you notice blood in your stools
- severe and/or persistent diarrhoea, as Protium has been associated with a small increase in infectious diarrhoea.

Your doctor may decide that you need some tests to rule out malignant disease because pantoprazole also alleviates the symptoms of cancer and could cause delay in diagnosing it. If your symptoms continue in spite of your treatment, further investigations will be considered.

If you take Protium on a long-term basis (longer than 1 year) your doctor will probably keep you under regular surveillance. You should report any new and exceptional symptoms and circumstances whenever you see your doctor.

Taking other medicines
Protium may influence the effectiveness of other medicines, so tell you doctor if you are taking

- Medicines such as ketoconazole, itraconazole and posaconazole (used to treat fungal infections) or erlotinib (used for certain types of cancer) because Protium may stop these and other medicines from working properly.
- Warfarin and phenprocoumon, which affect the thickening, or thinning of the blood. You may need further checks.
- Atazanavir (used to treat HIV-infection).
-

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
There are no adequate data from the use of pantoprazole in pregnant women. Excretion into human milk has been reported.If you are pregnant, or think you may be pregnant, or if you are breast-feeding, you should use this medicine only if your doctor considers the benefit for you greater than the potential risk for your unborn child or baby.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
If you experience side effects like dizziness or disturbed vision, you should not drive or operate machines.

Important information about some of the ingredients of Protium
Protium contains soya oil. If you are allergic to peanut or soya, do not use this medicine.

3. HOW TO TAKE PROTIUM

Always take Protium exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

When and how should you take Protium?
Take the tablets 1 hour before a meal without chewing or breaking them and swallow them whole with some water.

Unless told otherwise by your doctor, the usual dose is:

Adults and adolescents 12 years of age and above:

To treat reflux oesophagitis
The usual dose is one tablet a day. Your doctor may tell you to increase to 2 tablets daily. The treatment period for reflux oesophagitis is usually between 4 and 8 weeks. Your doctor will tell you how long to take your medicine.

Adults:

For the treatment of an infection with a bacterium called *Helicobacter pylori* in patients with duodenal ulcers and stomach ulcers in combination with two antibiotics (Eradication therapy).
One tablet, two times a day plus two antibiotic tablets of either amoxicillin, clarithromycin and metronidazole (or tinidazole), each to be taken two times a day with your pantoprazole tablet. Take the first pantoprazole tablet 1 hour before breakfast and the second pantoprazole tablet 1 hour before your evening meal. Follow your doctor's instructions and make sure you read the package leaflets for these antibiotics. The usual treatment period is one to two weeks.

For the treatment of stomach and duodenal ulcers.
The usual dose is one tablet a day. After consultation with your doctor, the dose may be doubled. Your doctor will tell you how long to take your medicine. The treatment period for stomach ulcers is usually between 4 and 8 weeks. The treatment period for duodenal ulcers is usually between 2 and 4 weeks.

For the long-term treatment of Zollinger-Ellison-Syndrome and of other conditions in which too much stomach acid is produced.
The recommended starting dose is usually two tablets a day.
Take the two tablets 1 hour before a meal. Your doctor may later adjust the dose, depending on the amount of stomach acid you produce. If prescribed more than two tablets a day, the tablets should be taken twice daily.
If your doctor prescribes a daily dose of more than four tablets a day, you will be told exactly when to stop taking the medicine.

Special patient groups:
- If you have kidney problems, moderate or severe liver problems, you should not take Protium for eradication of *Helicobacter pylori*.

- If you suffer from severe liver problems, you should not take more than one tablet 20 mg pantoprazole a day (for this purpose tablets containing 20 mg pantoprazole are available).

- Children below 12 years. These tablets are not recommended for use in children below 12 years.

If you take more Protium than you should
Consult your doctor or pharmacist. There are no known symptoms of overdose.

If you forget to take Protium
Do not take a double dose to make up for the forgotten dose. Take your next, normal dose at the usual time.

If you stop taking Protium
Do not stop taking these tablets without first talking to your doctor or pharmacist.

If you have any further questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Protium can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

If you get any of the following side effects, stop taking these tablets and tell your doctor immediately, **or contact the casualty department at your nearest hospital:**

- **Serious allergic reactions (frequency rare):** swelling of the tongue and/or throat, difficulty in swallowing, hives (nettle rash), difficulties in breathing, allergic facial swelling (Quincke's oedema / angioedema), severe dizziness with very fast heartbeat and heavy sweating.

- **Serious skin conditions (frequency not known):** blistering of the skin and rapid deterioration of your general condition, erosion (including slight bleeding) of eyes, nose, mouth/lips or genitals (Stevens-Johnson-Syndrome, Lyell-Syndrome, Erythema multiforme) and sensitivity to light.

- **Other serious conditions (frequency not known):** yellowing of the skin or whites of the eyes (severe damage to liver cells, jaundice) or fever, rash, and enlarged kidneys sometimes with painful urination and lower back pain (serious inflammation of the kidneys).

Other side effects are:

- **Uncommon** (affects 1 to 10 users in 1,000)
  headache; dizziness; diarrhoea; feeling sick, vomiting; bloating and flatulence (wind); constipation; dry mouth; abdominal pain and discomfort; skin rash, exanthema, eruption; itching; feeling weak, exhausted or generally unwell; sleep disorders.
- **Rare** (affects 1 to 10 users in 10,000)
  disturbances in vision such as blurred vision; hives; pain in the joints; muscle pains; weight changes; raised body temperature; swelling of the extremities (peripheral oedema); allergic reactions; depression; breast enlargement in males.
- **Very Rare** (affects less than 1 user in 10,000)

disorientation.
- **Not known** (frequency cannot be estimated from the available data)
  Hallucination, confusion (especially in patients with a history of these symptoms); decreased sodium level in blood.

Side effects identified through blood tests:
- **Uncommon** (affects 1 to 10 users in 1,000)
  an increase in liver enzymes.
- **Rare** (affects 1 to 10 users in 10,000)
  an increase in bilirubin; increased fats in the blood.
- **Very Rare** (affects less than 1 user in 10,000)
  a reduction in the number of blood platelets, which may cause you to bleed or bruise more than normal; a reduction in the number of white blood cells, which may lead to more frequent infections.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PROTIUM

Keep out of the reach and sight of children.

Do not use Protium after the expiry date, which is stated on the carton and the container after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions**.**

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Protium contains

- The active substance is pantoprazole. Each gastro-resistant tablet contains 40 mg of pantoprazole (as sodium sesquihydrate).

- The other ingredients are:
  Core: sodium carbonate (anhydrous), mannitol, crospovidone, povidone K90, calcium stearate.
  Coating: hypromellose, povidone K25, titanium dioxide (E171), yellow iron oxide (E172), propylene glycol, methacrylic acid-ethyl acrylate copolymer (1:1), polysorbate 80, sodium laurilsulfate, triethyl citrate.
  Printing ink: shellac, red, black and yellow iron oxide (E172), soya lecithin, titanium dioxide (E171) and antifoam DC 1510 (dimeticone emulsion).
  [To be completed nationally]

What Protium looks like and contents of the pack

Yellow, oval, biconvex gastro-resistant tablet imprinted with “P 40” on one side.

Packs: bottles (high density polyethylene container with low density polyethylene screw cap closure) and blister (ALU/ALU blister) without cardboard reinforcement or with cardboard reinforcement (blister wallet).

Protium is available in the following pack sizes:

Packs with 7, 10, 14, 15, 24, 28, 30, 48, 49, 56, 60, 84, 90, 98, 98 (2x49), 100, 112, 168 gastro-resistant tablets.
Hospital packs with 50, 90, 100, 140, 140 (10x14), 150 (10x15), 700 (5x140) gastro-resistant tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicine is authorised in the Member States of the EEA under the following names:

Name of Member State	**Name of the medicine**
Austria	Pantoloc 40 mg-Filmtabletten, Zurcal 40 mg-Filmtabletten
Belgium	Pantozol, Zurcale
Bulgaria	Controloc
Cyprus	Controloc
Czech Republic	Controloc 40 mg
Denmark	Pantoloc
Estonia	Controloc 40 mg
Finland	Somac 40 mg
France	Eupantol 40 mg, Inipomp 40 mg, Pantec 40 mg, Pantipp 40 mg
Germany	Pantozol 40 mg, Pantoprazol NYC 40 mg, Rifun 40 mg, Zurcal S 40 mg
Greece	Controloc, Zurcazol
Hungary	Controloc 40 mg
Ireland	Protium
Italy	Pantorc, Pantopan, Pantecta, Peptazol
Latvia	Controloc 40 mg
Lithuania	Controloc 40 mg
Luxembourg	Pantozol-40, Panto-Byk-40
Netherlands	Pantozol, Pantoprazol Nycomed 40 mg
Norway	Somac
Poland	Controloc 40
Portugal	Pantoc 40 mg, Zurcal 40 mg, Apton 40 mg, Pantoprazole ALTANA 40 mg
Romania	Controloc 40 mg
Slovakia	Controloc 40 mg
Slovenia	Controloc 40 mg
Spain	Pantecta 40 mg Blister, Anagastra 40 mg Blister, Ulcotenal 40 mg Blister
Sweden	Pantoloc
United Kingdom	Protium 40 mg

[See Annex I - To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicinal product is available on the website of the Heads of Medicines Agencies (HMA) http://www.hma.eu

PACKAGE LEAFLET: INFORMATION FOR THE USER

Protium and associated names (see Annex I) **40 mg powder for solution for injection**
[See Annex I - To be completed nationally]

Pantoprazole

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT PROTIUM IS AND WHAT IT IS USED FOR

Protium is a selective "proton pump inhibitor", a medicine which reduces the amount of acid produced in your stomach. It is used for treating acid-related diseases of the stomach and intestine.
This preparation is injected into a vein and will only be given to you if your doctor thinks pantoprazole injections are more suitable for you at the moment than pantoprazole tablets. Tablets will replace your injections as soon as your doctor sees fit.

Protium is used for treating:

- Reflux oesophagitis. An inflammation of your oesophagus (the tube which connects your throat to your stomach) accompanied by the regurgitation of stomach acid.

- Stomach and duodenal ulcers.

- Zollinger-Ellison-Syndrome and other conditions producing too much acid in the stomach.

2. BEFORE YOU USE PROTIUM

Do not use Protium
- If you are allergic (hypersensitive) to pantoprazole or any of the other ingredients of Protium (see section 6).
- If you are allergic to medicines containing other proton pump inhibitors.

Take special care with Protium
- If you have severe liver problems. Please tell your doctor if you ever had problems with your liver in the past. He will check your liver enzymes more frequently. In the case of a rise of liver enzymes the treatment should be stopped.
- If you are taking a medicine containing atazanavir (for the treatment of HIV-infection) at the same time as pantoprazole, ask your doctor for specific advise.

Tell your doctor immediately if you notice any of the following symptoms:
- an unintentional loss of weight
- repeated vomiting
- difficulty in swallowing
- vomiting blood
- you look pale and feel weak (anaemia)
- you notice blood in your stools
- severe and/or persistent diarrhoea, as Protium has been associated with a small increase in infectious diarrhoea.

Your doctor may decide that you need some tests to rule out malignant disease because pantoprazole also alleviates the symptoms of cancer and could cause delay in diagnosing it. If your symptoms continue in spite of your treatment, further investigations will be considered.

Taking other medicines
Protium injections may influence the effectiveness of other medicines, so tell your doctor if you are taking

- Medicines such as ketoconazole, itraconazole and posaconazole (used to treat fungal infections) or erlotinib (used for certain types of cancer) because Protium may stop these and other medicines from working properly.
- Warfarin and phenprocoumon, which affect the thickening, or thinning of the blood. You may need further checks.
- Atazanavir (used to treat HIV-infection).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
There are no adequate data from the use of pantoprazole in pregnant women. Excretion into human milk has been reported.If you are pregnant, or think you may be pregnant, or if you are breast-feeding, you should use this medicine only if your doctor considers the benefit for you greater than the potential risk for your unborn child or baby.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
If you experience side effects like dizziness or disturbed vision, you should not drive or operate machines.

Important information about some of the ingredients of Protium
This medicine contains less than 1 mmol sodium (23 mg) per vial, i.e. is essentially ‘sodium- free’.

3. HOW TO USE PROTIUM

Your nurse or your doctor will administer the daily dose to you as an injection into a vein over a period of 2 - 15 minutes.

The usual dose is:
For gastric ulcers, duodenal ulcers and reflux oesophagitis.
One vial (40 mg pantoprazole) a day.

For the long-term treatment of Zollinger-Ellison syndrome and other conditions in which too much stomach acid is produced.

Two vials (80 mg pantoprazole) a day.

Your doctor may later adjust the dose, depending on the amount of stomach acid you produce. If you are prescribed more than two vials (80 mg) a day, the injections will be given in two equal doses. Your doctor may prescribe a temporary dose of more than four vials (160 mg) a day. If your stomach acid level needs to be controlled rapidly, a starting dose of 160 mg (four vials) should be enough to lower the amount of stomach acid sufficiently.

Special patient groups:
- If you suffer from severe liver problems, the daily injection should be only 20 mg (half a vial).

- Children (under 18 years). These injections are not recommended for use in children.

If you use more Protium than you should
These doses are carefully checked by your nurse or your doctor so an overdose is extremely unlikely. There are no known symptoms of overdose.

If you have any further questions about the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Protium can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

If you get any of the following side effects, tell your doctor immediately, **or contact the casualty department at your nearest hospital:**

- **Serious allergic reactions (frequency rare):** swelling of the tongue and/or throat, difficulty in swallowing, hives (nettle rash), difficulties in breathing, allergic facial swelling (Quincke's oedema / angioedema), severe dizziness with very fast heartbeat and heavy sweating.

- **Serious skin conditions (frequency not known):** blistering of the skin and rapid deterioration of your general condition, erosion (including slight bleeding) of eyes, nose, mouth/lips or genitals (Stevens-Johnson-Syndrome, Lyell-Syndrome, Erythema multiforme) and sensitivity to light.

- **Other serious conditions (frequency not known):** yellowing of the skin or whites of the eyes (severe damage to liver cells, jaundice) or fever, rash, and enlarged kidneys sometimes with painful urination and lower back pain (serious inflammation of the kidneys).

Other side effects are:
- **Common** (affects 1 to 10 users in 100)
  inflammation of the wall of the vein and blood clotting (thrombophlebitis) where the medicine is injected.
- **Uncommon** (affects 1 to 10 users in 1,000)

headache; dizziness; diarrhoea; feeling sick, vomiting; bloating and flatulence (wind); constipation; dry mouth; abdominal pain and discomfort; skin rash, exanthema, eruption; itching; feeling weak, exhausted or generally unwell; sleep disorders.

- **Rare** (affects 1 to 10 users in 10,000)
  disturbances in vision such as blurred vision; hives; pain in the joints; muscle pains; weight changes; raised body temperature; swelling of the extremities (peripheral oedema); allergic reactions; depression; breast enlargement in males.
- **Very Rare** (affects less than 1 user in 10,000)
  disorientation.
- **Not known** (frequency cannot be estimated from the available data)
  Hallucination, confusion (especially in patients with a history of these symptoms); decreased sodium level in blood.

Side effects identified through blood tests:

- **Uncommon** (affects 1 to 10 users in 1,000)
  an increase in liver enzymes.
- **Rare** (affect 1 to 10 users in 10,000)
  an increase in bilirubin; increased fats in the blood.
- **Very Rare** (affects less than 1 user in 10,000)
  a reduction in the number of blood platelets, which may cause you to bleed or bruise more than normal; a reduction in the number of white blood cells, which may lead to more frequent infections.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PROTIUM

Keep out of the reach and sight of children.

Do not use Protium after the expiry date, which is stated on the carton and the vial after EXP.
The expiry date refers to the last day of that month.

Do not store above 25 °C.
Keep the vial in the outer carton in order to protect it from light.

Use the reconstituted solution within 12 hours.
Use the reconstituted and diluted solution within 12 hours.

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 12 hours at not more than 25 °C.

Do not use Protium if you notice that the visual appearance has changed (e.g. if cloudiness or precipitation is observed).

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Protium contains

- The active substance is pantoprazole. Each vial contains 40 mg of pantoprazole (as sodium sequihydrate).

- The other ingredients are: disodium edetate and sodium hydroxide (for pH adjustment).

What Protium looks like and contents of the pack

Protium is a white to off-white powder for solution for injection. It comes in a 10 ml clear glass vialclosed with an aluminium cap and grey rubber stopper containing 40 mg powder for solution for injection.

Protium is available in the following pack sizes:

Pack with 1 vial.
Pack with 5 (5x1) vials.
Hospital pack with 1 vial.
Hospital pack with 5 (5x1) vials.
Hospital pack with 10 (10x1) vials.
Hospital pack with 20 (20x1) vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

[See Annex I - To be completed nationally]
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

Manufacturer

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicine is authorised in the Member States of the EEA under the following names:

Name of Member State	**Name of the medicine**
Austria	Pantoloc 40 mg Trockenstechampulle, Zurcal 40 mg Trockenstechampulle
Belgium	Pantozol IV, Zurcale IV
Cyprus	Controloc i.v.
Czech Republic	Controloc i.v.
Denmark	Pantoloc
Finland	Somac 40 mg powder for solution for injection
France	Eupantol 40 mg poudre pour solution injectable IV, Inipomp 40 mg
Germany	Pantozol i.v., Pantoloc i.v., Pantoprazol-Byk i.v.
Greece	Controloc i.v., Zurcazol i.v.
Hungary	Controloc i.v.
Ireland	Protium i.v.
Italy	Pantorc

Name of Member State	Name of the medicine
Luxembourg	Pantozol-IV, Panto-Byk-IV
Netherlands	Pantozol i.v.
Norway	Somac
Poland	Controloc 40 mg
Portugal	Pantoc IV
Romania	Controloc i.v.
Slovakia	Controloc i.v.
Slovenia	Controloc 40 mg prašek za raztopino za injiciranje
Spain	Anagastra 40 mg polvo para solución inyectable I.V.
Sweden	Pantoloc
United Kingdom	Protium i.v.

[See Annex I - To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicinal product is available on the website of the Heads of Medicines Agencies (HMA) http://www.hma.eu

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The following information is intended for medical or healthcare professionals only:

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. This solution may either be administered directly or after mixing it with 100 ml sodium chloride 9 mg/ml (0.9 %) solution for injection or glucose 55 mg/ml (5 %) solution for injection. Glass or plastic containers should be used for dilution.

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

After preparation, the solution must be used within 12 hours. 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 12 hours, at no more than 25 °C.

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

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