**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

**MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007**

**(S.I. No.540 of 2007)**

**PPA1328/001/002**
Case No: 2061361

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

**B & S Healthcare**

**Unit 4, Bradfield Road**, **Ruislip**, **Middlesex**, **HA4 0NU**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

**Protium 20mg Gastro-resistant Tablets**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **15/05/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

# Part II

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Protium 20 mg Gastro-resistant Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 20mg pantoprazole (as sodium sesquihydrate).
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

*Product imported from the UK:*
A yellow, oval biconvex film-coated tablet imprinted with ‘P20’ in brown ink on one side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

For the treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing).
For long-term management and prevention of relapse in reflux oesophagitis.
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

**Recommended dosage:**

**Adults and adolescents 12 years of age and above:**

Mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing)

The recommended oral dosage is one gastro-resistant tablet Protium 20 mg per day. Symptom relief is generally accomplished within 2-4 weeks, and a 4-week treatment period is usually required for healing of associated oesophagitis. If this is not sufficient, healing 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 dosage 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 dosage is one gastro-resistant tablet Protium 20 mg per day.

***Children below 12 years of age:***

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

**Note:**

A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment.
No dose adjustment is necessary in elderly patients or in those with impaired renal function.

**General instructions:**

Protium 20 mg gastro resistant tablets should not be chewed or crushed, and should be swallowed whole with liquid before a meal.

## 4.3 Contraindications

Protium 20 mg should not be used in cases of known hypersensitivity to one of the constituents of Protium 20 mg.
Pantoprazole, like other PPIs, should not be co-administered with atazanavir (see Section 4.5).

## 4.4 Special warnings and precautions for use

Special warnings None.

***Special precautions for use***

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 Protium 20 mg should be discontinued.

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.

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.

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

Note:
Prior to treatment the possibility of malignancy of gastric ulcer or a malignant disease of the oesophagus should be excluded as the treatment with pantoprazole may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Patients who do not respond after 4 weeks should be investigated.

## 4.5 Interaction with other medicinal products and other forms of interaction

Protium 20 mg may reduce or increase the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole).
It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore PPIs, including pantoprazole, should not be co-administered with atazanavir (see Section 4.3).

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

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in INR have been reported during concomitant treatment in the post-marketing period. Therefore, in patients being treated with coumarin anticoagulants, monitoring of prothrombin time/INR is recommended after initiation, termination or during irregular use of pantoprazole.
There were also no interactions with concomitantly administered antacids.

## 4.6 Pregnancy and lactation

Clinical experience in pregnant women is limited. In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg. There is no information on the excretion of pantoprazole into human breast milk. Pantoprazole tablets should only be used when the benefit to the mother is considered greater than the potential risk to the foetus/baby.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

| Frequency Organ system | Common (>1/100, <1/10) | Uncommon (>1/1,000, <1/100) | Rare (<1/1,000, >1/10,000) | Very rare (<1/10,000, incl. Isolated reports) |
|---|---|---|---|---|
| Blood and lymphatic system | | | | Leukopenia; Thrombocytopenia |
| Gastrointestinal Disorders | Upper abdominal pain; Diarrhoea; Constipation; Flatulence | Nausea / Vomiting | Dry mouth | |
| General disorders and administration site conditions | | | | Peripheral oedema |
| Hepatobiliary disorders | | | | Severe hepatocellular damage leading to jaundice with or without hepatic failure |

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|---|---|---|---|---|
| Immune system disorders | | | | Anaphylactic reactions including anaphylactic shock |
| Investigations | | | | Increased liver enzymes (transaminases, γ -GT); Elevated triglycerides; Increased body temperature |
| Musculoskeletal, connective tissue disorders | | | Arthralgia | Myalgia |
| Nervous system disorders | Headache | Dizziness;<br><br>Disturbances in vision (blurred vision) | | |
| Psychiatric disorders | | | Depression, Hallucination, Disorientation and Confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence | |
| Renal and urinary disorders | | | | Interstitial nephritis |
| Skin and sub-cutaneous tissue disorders | | Allergic reactions such as pruritus and skin rash | | Urticaria; Angioedema; Severe skin reactions such as Stevens- Johnson Syndrome, Erythema multi-forme, Lyell-Syndrome; Photosensitivity |

## 4.9 Overdose

There are no known symptoms of over-dosage in man. Doses up to 240 mg i.v. were administered over 2 minutes and were well tolerated.
In the case of over-dosage with clinical signs of intoxication, the usual rules of intoxication therapy apply.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Proton pump inhibitors
ATC Code: AO2BC02
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic canaliculi of 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 in 2 weeks. As with other proton pump inhibitors and $H_2$ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in 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, the substance can affect 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 normal upper limit. 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**

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. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg.
Terminal half-life is about 1 h. 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).
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.
Pantoprazole's serum protein binding is about 98%. The substance is almost exclusively metabolized in the liver. 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 h) is not much longer than that of pantoprazole.

**Bioavailability**

Pantoprazole is completely absorbed after oral 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.

**Characteristics in patients/special groups of subjects**

No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short.

Only very small amounts of pantoprazole can be 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 Cmax 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 Cmax were in the range of corresponding values in adults.
Following administration of single i.v. doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 – 16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

## 5.3 Preclinical safety data

Pre-clinical 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 (corresponding to lifetime treatment) in rates, neuroendocrine neoplasms were found, In addition, squamous cell papillomas were found in the forestomach of rats in one study. The mechanism leading to the formation of gastric carcinoids by substituted bensimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to teh 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 were observed in rats (in one rat study only) 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 obsered in the group of rats receiving the highest dose (200mg/kg) in one 2 year study. 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 side effects on the thyroid glands are expected.

From mutagenicity studies, cell transformation tests and a DNA binding study it is concluded that pantoprazole has no genotoxic potential.

Investigations revealed no evidence of impaired fertility or teratogenic effects.
Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium carbonate
Mannitol
Crospovidone
Povidone K90
Calcium stearate
Hypromellose
Povidone K25
Methacrylic acid-ethylacrylate-copolymer (1:1)
Propylene glycol
Polysorbate 80

Sodium laurilsulfate
Triethyl citrate
Titanium dioxide (E 171)
Yellow ferric oxide (E 172)
Printing ink (shellac, red, black and yellow ferric oxide E172, soya lecithin, titanium dioxide E171, antifoam DC 1510)

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf Life

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

## 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

## 6.5 Nature and contents of container

Aluminium blisters in a cardboard carton containing 28 tablets.

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

No special requirements.

## 7 Parallel Product Authorisation Holder

B&S Healthcare
Unit 4, Bradfield Road
Ruislip
Middlesex
HA4 0NU
UK

## 8 Parallel Product Authorisation Number

PPA1328/1/2

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th May 2009

## 10 DATE OF REVISION OF THE TEXT