SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pantium 20 mg Gastro-Resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains:

20 mg of pantoprazole (equivalent to 22.6 mg pantoprazole sodiumsesquihydrate)
Excipient: 38.425 mg Maltitol (see section 4.4)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet

Yellow, oval tablet.

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 treatment 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

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 Pantium 20 mg gastro-resistant tablet per day. Relief from symptoms is generally achieved within 2-4 weeks, and a 4-week course of treatment is usually required for the healing of associated oesophagitis. If this is not sufficient, healing will normally be achieved within a further 4 weeks.

Once relief from symptoms has been achieved, recurrent symptoms can be controlled using an on-demand regimen of 20 mg pantoprazole once daily, if required. If adequate symptom control cannot be maintained with on-demand treatment, a switch to continuous therapy should be considered.

Long-term treatment and prevention of relapse in reflux oesophagitis
For long-term treatment, a maintenance dose of one Pantium 20 mg gastro-resistant tablet per day is recommended, which can be increased to 40 mg pantoprazole per day in the event of a relapse. Pantium 40 mg is available for such cases. Upon recovery from the recurrent episode, the dosage can again be reduced to 20 mg pantoprazole.

In long-term therapy, length of treatment should only exceed one year in cases where a careful analysis of the risk/benefit ratio has been performed, as drug safety over several years is not sufficiently established.

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 Pantium 20 mg gastro-resistant tablet per day.

Patients with impaired liver function
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment.

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

Elderly patients
No dose adjustment is necessary in elderly patients.

Children below 12 years of age
Pantoprazole 20 mg is not recommended for use in children below 12 years of age due to limited data in this age group.

General instructions
Pantoprazole 20 mg gastro-resistant tablets must not be chewed or crushed. They should be taken whole with some water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Pantoprazole 20 mg, like other PPIs, should not be co-administered with atazanavir (see chapter 4.5, interactions).

4.4 Special warnings and precautions for use

In patients with severe liver impairment, liver enzyme values should be monitored regularly during treatment with pantoprazole, particularly during long-term therapy. In the event of a rise in liver enzymes, Pantium 20 mg should be discontinued.

Use of Pantium 20 mg in the prevention of gastroduodenal ulcers induced by non-selective, non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and who are at increased risk of developing gastrointestinal complications. Increased risk should be assessed on the basis of individual risk factors, e.g. advanced age (>65 years), history of gastroduodenal ulcers or upper gastrointestinal bleeding.

As with all acid-blocking medicinal products, pantoprazole may cause vitamin B_{12} (cyanocobalamin) malabsorption as a result of hypo- or achlorhydria. This should be taken into consideration particularly during long-term therapy in patients with reduced vitamin B_{12} reserves or with particular risk factors for vitamin B_{12} malabsorption.

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.

Decreased gastric acidity due to any means – including proton pump inhibitors – increases gastric count of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to a slightly increased risk of gastrointestinal infections, such as Salmonella and Campylobacter.

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

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

To date, there has been no experience with the treatment of children below the age of 12.

This medicinal product contains maltitol.
Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

Risk of hip, wrist and spine fracture
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with PPIs like pantoprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Pantium 20 mg may reduce the absorption of medicinal products whose bioavailability is pH-dependent (e.g. ketoconazole or itraconazole).

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).

The active substance of Pantium 20 mg is metabolised in the liver via the cytochrome P450 enzyme system. Interactions with other medicinal products or substances which are metabolised via this same enzyme system cannot be excluded. However, no clinically significant interactions were demonstrated in specific tests on a number of such medicinal products. Tests have been performed on carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and an oral contraceptive.

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

Similarly, there are no interactions with concomitantly administered antacids.

4.6 Fertility, pregnancy and lactation

Pregnancy
Clinical experience in pregnant women is limited. In animal reproduction studies, signs of slight foetotoxicity were observed (see section 5.3).

Caution should be exercised when prescribing to pregnant women.

Breast-feeding
There is no information on the excretion of pantoprazole into human breast milk. During breast feeding, Pantium 20 mg tablets should only be used if the benefit to the mother outweighs the potential risk for the foetus or child.

4.7 Effects on ability to drive and use machines

Pantium 20 mg has no influence on the ability to drive and use machines.
However, the appearance of some side effects like dizziness and blurred vision may affect the patient's ability to react, which in turn might impair the ability to drive and operate machinery.

4.8 Undesirable effects

The following frequency convention is used in the evaluation of undesirable effects:

Frequency / Organ System	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)
Blood and lymphatic system disorders				Leukopenia; thrombocytopenia	
Immune system disorders				Anaphylactic reactions including anaphylactic shock	
Metabolism and nutrition disorders					Hypomagnesaemia (see section 4.4)
Psychiatric disorders			Depression, hallucination, disorientation and confusion, especially in predisposed patients as well as the aggravation of these symptoms in case of pre-existence		
Nervous system disorders	Headache	Dizziness; visual disturbances (blurred vision)			
Gastrointestinal disorders	Upper abdominal complaints; diarrhoea; constipation; flatulence	Nausea/vomiting	Dry mouth		
Hepatobiliary disorders				Severe hepatocellular damage leading to jaundice with or without hepatic failure	
Skin and sub-cutaneous tissue disorders		Allergic reactions such as pruritus and skin rash		Urticaria; angioedema; severe skin reactions e.g. Stevens Johnson syndrome; erythema multiforme; Lyell's syndrome; photosensitivity reaction	
Musculoskeletal, connective tissue disorders		Fracture of the hip, wrist or spine (see section 4.4)	Arthralgia	Myalgia	
Renal and urinary disorders				Interstitial nephritis	
Reproductive system and breast disorders				Gynaecomastia	

Frequency / Organ System	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)
General disorders and administration site conditions				Peripheral oedema	
Investigations				Increased liver enzymes (transaminases, gamma GT); elevated triglycerides; increased body temperature; hypernatraemia in the elderly	

4.9 Overdose

There are no known symptoms of overdose in humans.

Doses of up to 240 mg intravenous over 2 minutes have been administered and well tolerated.
In the event of overdose with clinical signs of intoxication, general rules for the treatment of intoxication apply.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: proton pump inhibitors

ATC code: A02B C02

Pantoprazole is a substituted benzimidazole which inhibits gastric acid secretion by specifically reacting with the proton pumps of parietal cells.

Pantoprazole is converted to its active form in the acidic channel 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 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 administered 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 (see section 5.3), the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids can be ruled out for humans.

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid and liver enzymes according to results in animal studies.

5.2 Pharmacokinetic properties

General pharmacokinetics
Pantoprazole is rapidly absorbed. Even after a single oral dose of 20 mg pantoprazole, maximum concentrations of the active substance are achieved. On average, peak serum concentrations of 1 – 1.5 µg/ml approx. are reached within 2 hours post-dose, and remain constant even after multiple dosing. Volume of distribution is 0.15 l/kg approx. and clearance is approximately 0.1 l/h/kg. Its terminal elimination half-life was calculated to be 1 hour approx. A few cases of subjects with delayed elimination have been observed. Due to the specific activity of pantoprazole within the parietal cell, there is no correlation between elimination half-life and the much longer duration of action (inhibition of acid secretion).

There is no variation in pharmacokinetic characteristics after single or repeated dosing. Within the dose range of 10-80 mg, the kinetics of pantoprazole is virtually linear, both after oral and intravenous dosing.

Serum protein binding of pantoprazole is around 98%. Pantoprazole is almost exclusively metabolised by the liver. Most of its metabolites (80% approx.) are renally excreted; the remainder are excreted with the faeces. In both serum and urine, the main metabolite is desmethylpantoprazole which is conjugated with sulphate. Half-life of the main metabolite (about 1.5 hours) is not significantly longer than that of pantoprazole.

Bioavailability
Pantoprazole is completely absorbed after oral dosing. Absolute bioavailability of the tablet was found to be about 77%. Concomitant intake of food or antacids had no influence on AUC, maximum serum concentrations and thus bioavailability. Administration with food may delay its absorption up to 2 h or longer.

Special patient groups
No dose reduction is required when pantoprazole is administered to patients with impaired renal function (including patients on dialysis). As with healthy subjects, the half-life of pantoprazole is short. Only very small amounts of pantoprazole are dialysed. Although the main metabolite has a moderately prolonged half-life (2 – 3 hours), excretion is nevertheless rapid and thus accumulation does not occur.

In patients with liver cirrhosis (classes A and B according to Child), its half-life is prolonged to values ranging from 7 to 9 hours, and AUC values are increased by a factor of 5-7. Compared with healthy subjects, peak serum concentrations increase only slightly by a factor of 1.5.

Similarly, the slight increase in AUC and C_{max} in elderly subjects compared with younger counterparts has no clinical relevance.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In a 2-year carcinogenicity study in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the fore-stomach 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 treatment.
In the two-year studies, an increased number of liver tumours was observed in rats and female mice, which is interpreted as being the result of the high metabolic rate of pantoprazole in the liver.

A slight increase in neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg). Occurrence of these neoplasms is associated with pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic human dose is low, no adverse reactions on the thyroid glands are expected.

Investigations revealed no evidence of impaired fertility or teratogenic effects. Daily doses above 5 mg/kg led to delayed development of the skeleton in rats. The ability of pantoprazole to penetrate the placenta has been investigated in the rat and was found to increase with advanced gestation. As a result, pantoprazole concentrations in the foetus are increased shortly before birth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Maltitol (E965)
Crospovidone type B
Carmellose sodium
Sodium carbonate, anhydrous (E500)
Calcium stearate

Tablet coating

Poly(vinyl alcohol)
Talc (E553b)
Titanium dioxide (E171)
Macrogol 3350
Soya lecithin (E322)
Iron oxide yellow (E172)
Sodium carbonate, anhydrous (E500)
Methacrylic acid-ethyl acrylate copolymer (1:1)
Triethyl citrate (E1505)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

After first opening of the bottle use the medicinal product within three months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu-Alu blisters
HDPE bottles with PP closure and desiccant

28, 126, 154 and 196 gastro-resistant tablets (blister packs)
100, 126, 154 and 196 gastro-resistant tablets (HDPE bottles)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd,
Waterford Road,
Clonmel,
Co. Tipperary.

8. MARKETING AUTHORISATION NUMBER(S)

PA 126/175/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd October 2008

10. DATE OF REVISION OF THE TEXT

November 2012