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).

Excipients with known effect
Each gastro-resistant tablet contains 38.425 mg maltitol, 0.345 mg lecithin (derived from soya oil) and 1.84 mg sodium (see section 4.4).

For the 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 mildreflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing).
- For long-term treatment 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

Posology

Adults and adolescents 12 years of age and above

Symptomatic gastro-oesophageal reflux disease
The recommended oral dose is one Pantium 20 mg tablet 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, taking one tablet 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 Pantium 20 mg tablet per day is recommended, increasing to 40 mg pantoprazole per day if a relapse occurs. Pantium 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 Pantium 20 mg tablet per day.

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

Patients with renal impairment
No dose adjustment is necessary in patients with impaired renal function (see section 5.2).

Elderly patients
No dose adjustment is necessary in elderly patients (see section 5.2).

Paediatric population
Pantoprazole 20 mg is not recommended for use in children below 12 years of age because of limited data on safety and efficacy in this age group (see section 5.2).

Method of administration

Oral use
The tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients listed in section 6.1.

Pantium 20 mg contains soya lecithin and must not be used in patients who are hypersensitive to peanut or soya.

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 20 mg pantoprazole 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.

Gastric malignancy
Symptomatic response to pantoprazole may mask the symptoms of gastric malignancy and may delay diagnosis. 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.

Further investigation is to be considered if symptoms persist despite adequate treatment.

Co-administration with HIV protease inhibitors
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, due to significant reduction in their bioavailability (see section 4.5).

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

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 medicinal products that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Bone fractures
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.

Subacute cutaneous lupus erythematosus (SCLE)
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping pantoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, lansoprazole treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

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

This medicinal product contains less than 1 mmol sodium (23 mg) per gastro-resistant tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Medicinal products with pH-dependent absorption pharmacokinetics
Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with the absorption of other medicinal products where gastric pH is an important determinant of oral availability, e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other medicines such as erlotinib.

HIV protease inhibitors
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir due to significant reduction in their bioavailability (see section 4.4).

If the combination of HIV protease inhibitors with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitor may need to be adjusted.

Coumarin anticoagulants (phenprocoumon or warfarin)
Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and

even death. Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

Methotrexate
Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors has been reported to increase methotrexate levels in some patients. Therefore in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

Other interactions studies
Pantoprazole is extensively metabolised 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 medicinal products also metabolised with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol, did not reveal clinically significant interactions.

An interaction of pantoprazole with other medicinal products or compounds, which are metabolised using the same enzyme system, cannot be excluded.

Results from a range of interaction studies demonstrate that pantoprazole does not affect 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 by concomitantly administering pantoprazole with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

Medicinal products that inhibit or induce CYP2C19:

Inhibitors of CYP2C19 such as fluvoxamine could increase the systemic exposure of pantoprazole. A dose reduction may be considered for patients treated long-term with high doses of pantoprazole, or those with hepatic impairment.

Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John´s wort (*Hypericum perforatum*) may reduce the plasma concentrations of PPIs that are metabolised through these enzyme systems.

4.6 Fertility, pregnancy and lactation

Pregnancy
A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformative or foeto/ neonatal toxicity of pantoprazole.
Animal studies have shown reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of pantoprazole during pregnancy.

Breastfeeding
Animal studies have shown excretion of pantoprazole in breast milk. There is insufficient information on the excretion of pantoprazole in human milk but excretion into human milk has been reported. A risk to the newborns/infants cannot be excluded.. Therefore, a decision on whether to discontinue breastfeeding or to discontinue/abstain from pantoprazole therapy should take into account the benefit of breastfeeding to the child, and the benefit of pantoprazole therapy for the woman.

Fertility
There was no evidence of impaired fertility following the administration of pantoprazole in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Pantoprazole has no or negligible influence on the 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			Agranulocytosis	Leukopenia, Thrombocytopenia, Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemias and lipid increases (triglycerides, cholesterol), Weight changes		Hyponatraemia, Hypomagnesaemia (see section 4.4), Hypocalcaemia [(1)], Hypokalaemia
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination, Confusion (especially in predisposed patients, as well as the aggravation of these symptoms in case of pre-existence)
Nervous system disorders		Headache, Dizziness	Taste disorders		Paraesthesia
Eye disorders			Disturbances in vision / blurred vision		
Gastrointestinal disorders	Fundic gland polyps (benign)	Diarrhoea, Nausea / vomiting, Abdominal distension and bloating, Constipation,			Microscopic colitis

		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, Subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal, connective tissue disorders		Fracture of the hip, wrist or spine (see section 4.4)	Arthralgia, Myalgia		Muscle spasm [2]
Renal and urinary disorders					Interstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions		Asthenia, fatigue and malaise	Body temperature increased, Oedema peripheral		

[1] Hypocalcaemia in association with hypomagnesaemia
[2] Muscle spasm as a consequence of electrolyte disturbance

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 an 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: 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 an 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.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

5.2 Pharmacokinetic properties

General pharmacokinetics
Pantoprazole is rapidlyabsorbed. 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 u 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.

Paediatric population
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 IV 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

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

In the 2-year carcinogenicity study in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the fore-stomach of rats in one study. 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 rodent studies an increased number of liver tumours was observed in rats (in one rat study only) and in female mice and was interpreted as being due to the high metabolic rate in the liver.

A slight increase in neoplastic changes of the thyroid was observed in the group rats receiving the highest dose (200 mg/kg) in one 2-year study. The 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.

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

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

For Alu-Alu blisters: 5 years.
For HDPE bottles: 5 years.

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

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Alu-Alu blisters
HDPE bottles with PP closure and desiccant

Pack sizes:
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
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/175/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd October 2008

Date of last renwal: 20th December 2012

10 DATE OF REVISION OF THE TEXT

November 2019