

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pantium 40 mg Gastro-Resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains:

40 mg of pantoprazole (equivalent to 45.1 mg pantoprazole sodium sesquihydrate)
Excipient: 76.85 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

- Combination therapy with two suitable antibiotics for the eradication of *Helicobacter pylori* and for the prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.
- Duodenal ulcers
- Gastric ulcers
- Moderate and severe forms of reflux oesophagitis
- Long-term treatment of Zollinger-Ellison syndrome and other disorders accompanied by pathological gastric acid hypersecretion.

4.2 Posology and method of administration

Recommended dosage:

Adults and adolescents 12 years of age and above:

Moderate and severe reflux oesophagitis

For reflux oesophagitis, the dose is one Pantium 40 mg gastro-resistant tablet daily.

In individual cases, particularly in patients who have so far failed to respond to other forms of medication, the dose can be doubled (i.e. increased to two Pantium 40 mg gastro-resistant tablets daily).

Adults:

Eradication therapy

In *Helicobacter pylori*-positive patients with gastric and duodenal ulcers, prescribers should seek to eradicate infection by means of combination therapy. Depending on the pattern of resistance, the following combinations are recommended for the eradication of *Helicobacter pylori*:

- a) One Pantium 40 mg gastro-resistant tablet twice daily
 - + 1000 mg amoxicillin twice daily
 - + 500 mg clarithromycin twice daily

- b) One Pantium 40 mg gastro-resistant tablet twice daily
 - + 400 - 500 mg metronidazole twice daily
 - + 250 - 500 mg clarithromycin twice daily

- c) One Pantium 40 mg gastro-resistant tablet twice daily
 - + 1000 mg amoxicillin twice daily
 - + 400 - 500 mg metronidazole twice daily

For further information on the other components of the eradication therapy, see the individual data sheets.

Official regional guidance documents (e.g. national guidelines) on bacterial resistance, for the duration of treatment, and for the correct prescription of antibiotics should be considered.

Gastric and duodenal ulcers

If patients are ineligible for combination therapy, e.g. the patient has tested negative for *Helicobacter pylori*, the following dosage guidelines apply for Pantium 40 mg monotherapy:

For duodenal/gastric ulcers, the dose is one Pantium 40 mg gastro-resistant tablet daily.

In individual cases, particularly in patients who have so far failed to respond to other forms of medication, the dose can be doubled (i.e. increased to two Pantium 40 mg gastro-resistant tablets daily).

Zollinger-Ellison syndrome

For the long-term treatment of Zollinger-Ellison syndrome and other disorders accompanied by pathological gastric acid hypersecretion, the recommended initial dose is 80 mg (two Pantium 40 mg gastro-resistant tablets) daily. Thereafter, the dose can be individually titrated, depending on gastric acid secretion values. At dosages above 80 mg per day, the daily dosage should be divided into two separate doses per day. Temporary dose increases above 160 mg pantoprazole are possible, but should not be applied for longer than required to achieve adequate management of acid secretion. There are no restrictions on the length of treatment for Zollinger-Ellison syndrome or other disorders accompanied by pathological gastric acid hypersecretion; treatment should be maintained for as long as it is clinically required.

Patients with impaired hepatic function

In patients with severe liver impairment, the dose should be lowered to one tablet (40 mg pantoprazole) every other day.

Patients with impaired renal function

No dosage adjustment is recommended.

Elderly patients

In elderly patients, a daily dose of 40 mg pantoprazole should not be exceeded. One exception to this is combination therapy for the eradication of *Helicobacter pylori*, during which even elderly patients should also receive the usual pantoprazole dose (2 x 40 mg/day) over a 1 week treatment period.

Children below 12 years of age

Pantoprazole 40 mg is not recommended for use in children below 12 years of age due to limited data in this age group.

General instructions

Pantium 40 mg gastro-resistant tablets must not be chewed or crushed. They should be taken whole with some water.

In combination therapy for the eradication of *Helicobacter pylori*, the second Pantium 40 mg tablet should be taken before an evening meal. Combination therapy for the eradication of *Helicobacter pylori* infection is generally administered over a 7-day period and can be extended up to a maximum of 2 weeks. If further pantoprazole treatment seems indicated to ensure healing of the ulcer, dosage recommendations for gastric and duodenal ulcers should be applied.

In most cases, duodenal ulcers generally heal within 2 weeks. If a two-week course of treatment is not sufficient, healing will be achieved in almost all cases within 2 weeks of further treatment.

In most cases, a four-week course of therapy is required for the treatment of gastric ulcers and reflux oesophagitis. If this is not sufficient, healing will normally be achieved within 4 weeks of further treatment.

4.3 Contraindications

Pantium 40 mg may not be used in combination therapy for the eradication of *Helicobacter pylori* in patients with severe hepatic dysfunction, as there is currently no clinical experience on the efficacy and safety of using combination therapy in these patients.

Hypersensitivity to the active substance, to any of the excipients or to any of the combination partners.

Pantium 40 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 Zollinger-Ellison syndrome or other disorders accompanied by pathological gastric acid hypersecretion that require long-term treatment, pantoprazole may - as with all other acid-blocking medicinal products - cause vitamin B₁₂ (cyanocobalamin) malabsorption as a result of hypo- or achlorhydria. This should be taken into consideration if associated clinical symptoms become manifest.

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 beyond 4 weeks despite adequate treatment.

In patients with severe liver impairment, the dose should be adjusted (see section 4.2).

In patients with severe liver impairment, the liver enzymes should be checked regularly during treatment, especially during long-term treatment. In case of an increase of these enzymes, the treatment should be stopped.

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.

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 40 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 40 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 or substances. 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.

In human kinetic interaction studies, pantoprazole was administered together with the appropriate antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were observed.

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 40 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 40 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 ($\geq 1/100$ to <1/10)	Uncommon ($\geq 1/1,000$ to <1/100)	Rare ($\geq 1/10,000$ 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	
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 H₂ 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

Pantoprazole is rapidly absorbed. Even after a single oral dose of 40 mg pantoprazole, maximum concentrations of the active substance are achieved.

On average, peak serum concentrations of 2 - 3 µg/ml approx. are reached within 2.5 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 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

Pack sizes:

7, 14, 15, 28, 30, 56, 60, 100 gastro-resistant tablets (blister packs)

100 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 126/175/2

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