

Public Assessment Report

Decentralised Procedure

Pantoprazole 20mg Gastro-Resistant Tablets
Pantoprazole 40mg Gastro-Resistant Tablets

UK/H/0946/001-2/DC
UK licence no: PL 01656/0022-23

KRKA D.D.

LAY SUMMARY

The MHRA today granted KRKA d.d Marketing Authorisations (licences) for the medicinal products Pantoprazole 20mg Gastro-Resistant Tablets (PL 01656/0022) and Pantoprazole 40mg Gastro-Resistant Tablets (PL 01656/0023). These are prescription only medicines (POM) that are prescribed to patients with conditions caused by stomach acid.

Pantoprazole 20mg Gastro-Resistant Tablets are used:

- in the treatment of mild gastrooesophageal reflux disease (a condition in which gastric content may rise up to the oesophagus and which can be associated with oesophagitis) caused by acid secretion, and the associated symptoms, such as heartburn, acidic belches and pains on swallowing
- in the long-term treatment and in the prevention of relapse in reflux oesophagitis (a condition in which backwash of gastric content in oesophagus lead to inflammation and pain)
- in the prevention of gastric and duodenal ulcers caused by anti-inflammatory drugs in high-risk patients needing continuous treatment with anti-inflammatory drugs.

Pantoprazole 40mg Gastro-Resistant Tablets are used in the short-term treatment and to relieve the symptoms of:

- duodenal ulcer
- gastric ulcer
- oesophagitis (inflammation of oesophagus) caused by acid secretion.

Additionally, the 40mg preparation is used:

- in combination with antibiotics in patients whose ulceration is related to *Helicobacter pylori* bacteria
- in the long-term treatment of conditions where gastric acid is constantly being secreted too much (e.g. Zollinger-Ellison syndrome).

Pantoprazole belongs to a group of medicines called proton pump inhibitors. Proton pump inhibitors reduce the amount of acid that your stomach makes.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Pantoprazole 20mg and 40mg Gastro-Resistant Tablets outweigh the risks; hence Marketing Authorisations have been granted.

TABLE OF CONTENTS

Module 1: Information about initial procedure	Page 3
Module 2: Summary of Product Characteristics	Page 4
Module 3: Product Information Leaflets	Page 22
Module 4: Labelling	Page 24
Module 5: Scientific Discussion	Page 28
1 Introduction	
2 Quality aspects	
3 Non-clinical aspects	
4 Clinical aspects	
5 Overall conclusions	
Module 6	Steps taken after initial procedure

Module 1

Product Name	Pantoprazole 20mg and 40mg Gastro-Resistant Tablets
Type of Application	Generic, Article 10.1
Active Substance	Pantoprazole
Form	Gastro-Resistant Tablets
Strength	20mg and 40mg
MA Holder	Krka, d.d., Novo mesto, Smarjeska cesta 6, 8501 Novo mesto, Slovenia
RMS	United Kingdom
CMS	Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Malta, The Netherlands, Norway, Sweden, Spain, Portugal
Procedure Number	UK/H/0946/001-2/DC
Timetable	Day 210 – 25 th May 2007

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pantoprazole 20 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient:

Each Pantoprazole 20 mg gastro-resistant tablet contains 18 mg sorbitol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

A light brownish yellow, oval, slightly biconvex 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 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

Method of administration

Pantoprazole 20 mg tablets should not be chewed or crushed, and should be swallowed whole with water before a meal.

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

The recommended dosage is 20 mg pantoprazole daily (1 Pantoprazole 20 mg gastro-resistant tablet). 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 20 mg pantoprazole daily (1 Pantoprazole 20 mg gastro-resistant tablet) is recommended. If a relapse occurs, the dosage is increased to 40 mg pantoprazole per day. Pantoprazole 40 mg gastro-resistant tablets are available for this case. After healing of the relapse the dosage can be reduced again to 20 mg pantoprazole.

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 dosage is 20 mg pantoprazole daily (1 Pantoprazole 20 mg gastro-resistant tablet).

Elderly and patients with renal impairment

A daily dose of 40 mg pantoprazole should not be exceeded in these patient groups.

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). In these patients, hepatic enzyme levels should be monitored during the treatment. If hepatic enzyme levels become elevated, treatment with pantoprazole should be discontinued.

Children

There is no information on the use of pantoprazole in children. Therefore pantoprazole tablets should not be used in children.

4.3 Contraindications

Hypersensitivity to pantoprazole or to any of the excipients.

Pantoprazole like other proton pump inhibitors should not be administered with atazanavir (see section 4.5).

4.4 Special warnings and 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, the treatment should be discontinued (see section 4.2).

The use of Pantoprazole 20 mg gastro-resistant 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.

Decreased gastric acidity due to any means – including proton pump inhibitors – increases gastric counts 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.

Pantoprazole, as all acid-blocking medicinal products, 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 in long-term treatment.

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

Prior to treatment a malignant disease of the oesophagus or stomach should be excluded as the treatment with pantoprazole may alleviate the symptoms of malignant diseases and can thus delay diagnosis.

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

There is no experience with the use of pantoprazole in children.

Pantoprazole contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pantoprazole may reduce the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole, itraconazole, atazanavir).

Studies with other proton pump inhibitors have shown a marked reduction in atazanavir exposure during concomitant proton pump inhibitor treatment. Use of proton pump inhibitors is contraindicated during atazanavir treatment.

Pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system. interactions 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 with a number of such medicinal products or compounds, such as carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and oral contraceptives.

Even though no interactions with pantoprazole and phenprocoumon or warfarin have been observed in clinical pharmacokinetics studies, a few isolated post-marketing cases of INR value changes in concomitant treatment with these substances have been reported. If the patient is using coumarin-type anticoagulants, measurements of prothrombin time / INR values are recommended after the initiation and discontinuation of pantoprazole and in 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. During pregnancy and breast feeding, pantoprazole tablets should only be used when the benefit to the mother is considered greater than the potential risk to the foetus or child.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive and use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). Under these conditions the ability to react may be decreased.

4.8 Undesirable effects

Common ≥ 1/100 to < 1/10

Uncommon ≥ 1/1000 to < 1/100

Rare ≥ 1/10 000 to < 1/1000

Very rare < 1/10 000, including isolated reports

Frequency	Common	Uncommon	Rare	Very rare
Organ system				
Blood and the lymphatic system				Leucopenia, thrombocytopenia
Immune system disorders				Anaphylactic reactions including anaphylactic shock
Psychiatric disorders				Depression
Nervous system disorders	Headache	Dizziness, disturbances in vision (blurred vision)		
Gastrointestinal disorders	Upper abdominal pain, 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 such as Stevens Johnson syndrome, erythema multi-forme, Lyell's syndrome, photosensitivity
Musculoskeletal, connective tissue disorders			Arthralgia	Myalgia
Renal and urinary disorders				Interstitial nephritis
General disorders and administration site conditions				Peripheral edema subsiding after termination of therapy
Investigations				Increased liver enzymes (transaminases, γ -glutamyltransferase), elevated triglycerides, increased body temperature

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. As pantoprazole is extensively protein bound, it is not readily dialyzable.

Cases of overdosage or poisoning should be treated according to the standard treatment practice of toxic conditions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors

ATC code: A02BC02

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 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 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 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 and the maximal plasma concentration is achieved even after one single oral dose. On average, the maximum serum concentrations are 1–1.5 µg/ml at about 2.0–2.5 hours post-administration, 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. However, the daily dose of 40 mg pantoprazole should not be exceeded in patients with impaired renal function.

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.

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 a two-year carcinogenicity study 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 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 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) 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 DNA binding studies 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

The core of tablet:

Mannitol

Crospovidone (type B)

Sodium carbonate, anhydrous

Sorbitol (E420)

Calcium stearate

The film-coating:

Hypromellose

Povidone (K25)

Titanium dioxide (E171)

Iron oxide, yellow (E172)

Propylene glycol

Methacrylic acid - ethyl acrylate copolymer

Sodium lauryl sulphate
Polysorbate 80
Macrogol 6000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Blister pack: Store in the original package in order to protect from moisture.

Container: Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Perforated blister pack (OPA/Aluminium/PVC film and aluminium foil) in a carton box.

Pack-sizes of 7, 14, 15, 28, 30, 56, 60, 84, 98, 100, 100 x 1, 112 or 140 gastro-resistant tablets.

HDPE containers with a silica gel desiccant in a tamper evident PP screw-cap.

Pack-size of 250 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

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8 MARKETING AUTHORISATION NUMBER(S)

PL 01656/0022

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/09/2007

10 DATE OF REVISION OF THE TEXT

24/10/2007

1 NAME OF THE MEDICINAL PRODUCT

Pantoprazole 40 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient:

Each Pantoprazole 40 mg gastro-resistant tablet contains 36 mg sorbitol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

A light brownish yellow, oval, slightly biconvex tablet.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

For relieving the symptoms and for short-term treatment of gastrointestinal diseases which require a reduction in acid secretion:

- duodenal ulcer
- gastric ulcer
- moderate and severe reflux oesophagitis
- eradication of *Helicobacter pylori* in combination with antibiotic therapy in patients with peptic ulcer
- Zollinger-Ellison syndrome and other hypersecretory conditions.

4.2 Posology and method of administrationMethod of administration

Pantoprazole 40 mg tablets should not be chewed or crushed, and should be swallowed whole with water either before or during breakfast.

Duodenal ulcer

The recommended dosage is 40 mg pantoprazole daily (1 Pantoprazole 40 mg gastro-resistant tablet). Duodenal ulcers generally heal within two weeks. If a two-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further two weeks.

Gastric ulcer and moderate and severe reflux oesophagitis

The recommended dosage is 40 mg pantoprazole daily (1 Pantoprazole 40 mg gastro-resistant tablet). A four-week period is usually required for the treatment of gastric ulcers and reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further four weeks.

Eradication of *Helicobacter pylori* (*H. pylori*)

The recommended dose is 40 mg pantoprazole 2 times daily (1 Pantoprazole 40 mg gastro-resistant tablet 2 times daily) in combination with one of the following three combinations:

- a) amoxicillin 1 g twice daily + clarithromycin 500 mg twice daily
- b) clarithromycin 250–500 mg twice daily + metronidazole 400–500 mg twice daily
- c) amoxicillin 1 g twice daily + metronidazole 400–500 mg twice daily

The second pantoprazole tablet should be taken before the evening meal. Combination therapy should be administered for 7 days in most cases but sometimes up to 14 days.

Consideration should be given to official local guidance (e.g. national recommendations) regarding bacterial resistance and the appropriate use and prescription of antibacterial agents.

Zollinger-Ellison-Syndrome and other hypersecretory conditions

In the treatment of Zollinger-Ellison syndrome and other hypersecretory conditions, the initial dose is 80 mg daily (2 Pantoprazole 40 mg gastro-resistant tablets). Thereafter, the dosage can be increased or decreased 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 dosage 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.

Elderly

A daily dose of 40 mg pantoprazole should not be exceeded except in eradication treatment of H. pylori, where elderly patients should receive the standard pantoprazole dose (2 × 40 mg/day) during one week treatment.

Patients with renal impairment

The daily dose of 40 mg pantoprazole should not be exceeded in patients with impaired renal function. For this reason, H. pylori triple therapy is not appropriate in these patients (see section 4.3).

Patients with hepatic impairment

Patients with severe hepatic impairment should be given 40 mg of pantoprazole every other day (see sections 4.3 and 4.4). In these patients, hepatic enzyme levels should be monitored during the treatment. If hepatic enzyme levels become elevated, treatment with pantoprazole should be discontinued. For this reason, H. pylori triple therapy is not appropriate in these patients.

Children

There is no information on the use of pantoprazole in children. Therefore pantoprazole tablets should not be used in children.

4.3 Contraindications

Hypersensitivity to pantoprazole or to any of the excipients.

Pantoprazole like other proton pump inhibitors should not be administered with atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

There is no data available to make dose adjustment in patients with moderate and severe renal impairment. For patient with severe hepatic impairment, patients should be given 40 mg of pantoprazole every other day. 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 and 4.3).

Pantoprazole 40 mg is not intended for the treatment of mild gastrointestinal complaints, such as functional indigestion.

In combination therapy, the Summaries of Product Characteristics of all respective medicinal products should be observed.

Decreased gastric acidity due to any means – including proton pump inhibitors – increases gastric counts 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.

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.

Prior to treatment a malignant disease of the oesophagus or stomach should be excluded as the treatment with pantoprazole may alleviate the symptoms of malignant diseases and can thus delay diagnosis.

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

There is no experience with the use of pantoprazole in children.

Pantoprazole contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pantoprazole may markedly reduce the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole, itraconazole, atazanavir).

Studies with other proton pump inhibitors have shown a marked reduction in atazanavir exposure during concomitant proton pump inhibitor treatment. Use of proton pump inhibitors is contraindicated during atazanavir treatment.

Pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system. Interactions 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 with a number of such medicinal products or compounds, such as carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and oral contraceptives.

Even though no interactions with pantoprazole and phenprocoumon or warfarin have been observed in clinical pharmacokinetics studies, a few isolated post-marketing cases of INR value changes in concomitant treatment with these substances have been reported. If the patient is using coumarin-type anticoagulants, measurements of prothrombin time / INR values are recommended after the initiation and discontinuation of pantoprazole and in irregular use of pantoprazole.

There were also no interactions with concomitantly administered antacids.

4.6 Pregnancy and lactation**Pregnancy**

Clinical experience in pregnant women is limited. Experience with proton pump inhibitors as a class does not indicate an increased risk for major congenital malformations.

In animal reproduction studies, signs of slight fetotoxicity 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, pantoprazole tablets should only be used when the benefit to the mother is considered greater than the potential risk to the foetus or child.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive and use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). Under these conditions the ability to react may be decreased.

4.8 Undesirable effectsCommon $\geq 1/100$ to $< 1/10$ Uncommon $\geq 1/1000$ to $< 1/100$ Rare $\geq 1/10\ 000$ to $< 1/1000$ Very rare $< 1/10\ 000$, including isolated reports

Frequency	Common	Uncommon	Rare	Very rare
Organ system				
Blood and the lymphatic system				Leucopenia, thrombocytopenia
Immune system disorders				Anaphylactic reactions including anaphylactic shock
Psychiatric disorders				Depression
Nervous system disorders	Headache	Dizziness, disturbances in vision (blurred vision)		
Gastrointestinal disorders	Upper abdominal pain, 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 such as Stevens Johnson syndrome, erythema multi-forme, Lyell's syndrome, photosensitivity
Musculoskeletal, connective tissue disorders			Arthralgia	Myalgia
Renal and urinary disorders				Interstitial nephritis
General disorders and administration site conditions				Peripheral edema subsiding after termination of therapy
Investigations				Increased liver enzymes (transaminases, γ -glutamyltransferase), elevated triglycerides, increased body temperature

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. As pantoprazole is extensively protein bound, it is not readily dialyzable.

Cases of overdosage or poisoning should be treated according to the standard treatment practice of toxic conditions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors

ATC code: A02BC02

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 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 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 administered orally or intravenously.

5.2 Pharmacokinetic properties

General pharmacokinetics

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single oral dose. On average, the maximum serum concentrations are 2–3 µg /ml after 2.5 hours post-administration 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. However, the daily dose of 40 mg pantoprazole should not be exceeded in patients with impaired renal function.

Although for patients with liver cirrhosis (classes A and B according to Child) the half-time values increased to between 7 and 9 hours and the AUC values increased by a factor of 5 to 7, the maximum plasma 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.

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 a two-year carcinogenicity study 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 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 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) 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 DNA binding studies 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

The core of tablet:

Mannitol
Crospovidone (type B)
Sodium carbonate, anhydrous
Sorbitol (E420)
Calcium stearate

The film-coating:

Hypromellose
Povidone (K25)
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Propylene glycol
Methacrylic acid - ethyl acrylate copolymer
Sodium lauryl sulphate
Polysorbate 80
Macrogol 6000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Blister pack: Store in the original package in order to protect from moisture.

Container: Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Perforated blister pack (OPA/Aluminium/PVC film and aluminium foil) in a carton box.

Pack-sizes of 7, 14, 15, 28, 30, 56, 60, 84, 98, 100, 100 x 1, 112 or 140 gastro-resistant tablets.

HDPE containers with a silica gel desiccant in a tamper evident PP screw-cap.

Pack-size of 250 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

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8 MARKETING AUTHORISATION NUMBER(S)

PL 01656/0023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/09/2007

10 DATE OF REVISION OF THE TEXT

24/10/2007

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pantoprazole 20 mg gastro-resistant tablets

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 Pantoprazole is and what it is used for
2. Before you take Pantoprazole
3. How to take Pantoprazole
4. Possible side effects
5. How to store Pantoprazole
6. Further information

1. What Pantoprazole is and what it is used for

Pantoprazole belongs to a group of medicines called proton pump inhibitors. Proton pump inhibitors reduce the amount of acid that your stomach makes.

You have been given Pantoprazole tablets because you have a condition caused by stomach acid.

Pantoprazole 20 mg gastro-resistant tablets are used:

- in the treatment of mild gastroesophageal reflux disease (a condition in which gastric content may rise up to the esophagus and which can be associated with esophagitis) caused by acid secretion, and the associated symptoms, such as heartburn, acidic belches and pains on swallowing
- in the long-term treatment and in the prevention of relapse in reflux esophagitis (a condition in which backwash of gastric content in esophagus lead to inflammation and pain)
- in the prevention of gastric and duodenal ulcers caused by anti-inflammatory drugs in high-risk patients needing continuous treatment with anti-inflammatory drugs.

2. Before you take Pantoprazole

Do not take Pantoprazole

- if you are allergic (hypersensitive) to pantoprazole or any of the other ingredients of Pantoprazole
- if you are taking atazanavir (which is used for the treatment of HIV infection).

Take special care with Pantoprazole

Please tell the doctor who prescribed this medicine:

- if you have severe liver impairment. In case of severe hepatic disorder your doctor should monitor your liver function while you use Pantoprazole
- if you have been diagnosed with vitamin B12 malabsorption
- if your doctor has given you Pantoprazole together with anti-inflammatory medicines to treat your pain or rheumatic disease: please also read the package leaflets of these medicines carefully
- if you take Pantoprazole 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.

Please tell your doctor if you suffer or have recently suffered from any of the following symptoms: unintentional weight loss, recurrent vomiting or vomiting of blood, or dark stool. Your doctor may perform or have performed an additional investigation called an endoscopy in order to diagnose your condition and/or exclude malignant disease.

Pantoprazole tablets are not recommended for children.

Taking other medicines

Other concomitant medication may affect the efficacy and safety of this medicine. Pantoprazole may also affect the efficacy and safety of other medications. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Remember to tell your doctor about your treatment with Pantoprazole if you are prescribed another medicine while the treatment is still ongoing.

It is especially important to tell your doctor:

- if you are using atazanavir which is used for the treatment of HIV infection
- if you are using ketoconazole or itraconazole which are used for the treatment of fungal infections, since pantoprazole may affect their concentrations in your body
- if you are using anticoagulant medicines, e.g. warfarin, since it may be necessary to monitor your blood coagulation tests more often.

Taking Pantoprazole with food and drink

Take Pantoprazole tablets with water before a meal.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Experience with use of Pantoprazole in pregnant women is limited. There is no information on the excretion of pantoprazole into human breast milk. If you are pregnant or if you are breast-feeding, you should use this medicine only if your treating physician considers the benefit for you greater than the potential risk for your unborn child or baby.

Driving and using machines

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

Adverse drug reactions such as dizziness and visual disturbances may occur and which may decrease the ability to react.

Important information about some of the ingredients of Pantoprazole

Intolerance to sugars: If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product. This because Pantoprazole contains sorbitol.



3. How to take Pantoprazole

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

Method of administration

Do not chew or crush Pantoprazole tablets but swallow them whole with liquid before a meal.

Dosage

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

Treatment of mild reflux disease and the associated symptoms (e.g. heartburn, acidic belches and pain in swallowing):

The recommended dose is 1 tablet (20 mg) daily.

Long-term treatment and the prevention of relapse in reflux esophagitis:

For long term treatment the recommended dose is 1 tablet (20 mg) daily, if relapse occurs, the dosage is increased to 40 mg daily (2 x 20 mg tablets or 1 x 40 mg tablet).

Prevention of gastric and duodenal ulcers caused by anti-inflammatory drugs:

The recommended dose is 1 tablet (20 mg) daily.

Elderly and patients with renal impairment:

Daily dose of 40 mg should not be exceeded.

Patients with hepatic impairment:

Daily dose of 20 mg should not be exceeded.

Children:

Pantoprazole 20 mg gastro-resistant tablets should not be used in children.

If you take more Pantoprazole than you should

If you or someone you know accidentally takes a lot more than the stated dose (an overdose) you should contact a doctor immediately.

If you forget to take Pantoprazole

If you forget to take a dose, take it as soon as you remember, unless it is almost time for your next dose. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Pantoprazole

Do not change the dosage or stop the medication without discussing it with your doctor first.

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

4. Possible side effects

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

The frequencies are defined as

common	less than 1 in 10, but more than 1 in 100 people
uncommon	less than 1 in 100, but more than 1 in 1000 people
rare	less than 1 in 1000, but more than 1 in 10,000 people
very rare	less than 1 in 10,000 people

Common:

Upper abdominal pain, diarrhea, constipation, flatulence and headache.

Uncommon:

Nausea, vomiting, dizziness, blurred vision and allergic reactions such as itching and rash.

Rare:

Dry mouth, joint pain.

Very rare:

White blood cell deficiency (leucopenia), platelet deficiency (thrombocytopenia), swelling of hands and feet, severe liver cell damage and associated jaundice with potential liver failure, severe allergic reaction manifested as acute general symptoms with potential acute and substantial drop in blood pressure, elevated liver enzyme and triglyceride levels, elevated body temperature, muscle pain, depression, kidney inflammation, hives, hypersensitivity/attacks of local skin and mucous membrane swelling in the face, limbs, lips, tongue, larynx and/or vocal cords (angioedema, see special warning below), photosensitivity reactions and severe skin reactions such as Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis (Lyell's syndrome).

You should stop taking Pantoprazole and see your doctor immediately if you experience symptoms of angioedema, such as

- swollen face, tongue or throat
- difficulty to swallow
- hives and difficulties to breath

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 Pantoprazole

Keep out of the reach and sight of children.

Blister pack: Store in the original package in order to protect from moisture.

Container: Keep the container tightly closed in order to protect from moisture.

Expiry date

Do not use Pantoprazole after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

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 Pantoprazole contains

- Each gastro-resistant tablet contains 20 mg pantoprazole (as pantoprazole sodium sesquihydrate).
- The other ingredients are mannitol, crospovidone (type B), anhydrous sodium carbonate, sorbitol (E420), calcium stearate in the tablet core and hypromellose, povidone (K25), titanium dioxide (E171), yellow iron oxide (E172), propylene glycol, methacrylic acid - ethyl acrylate copolymer, sodium lauryl sulphate, polysorbate 80, macrogol 6000 and talc in the film-coating.

What Pantoprazole looks like and contents of the pack

The 20 mg gastro-resistant tablets are light brownish yellow, oval, slightly biconvex tablets.

Pack sizes:

Boxes of 7, 14, 15, 28, 30, 56, 60, 84, 98, 100, 100 x 1, 112 and 140 gastro-resistant tablets in blister packs.

A plastic container of 250 gastro-resistant tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

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

- AT PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- BE PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- DK PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- FI PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- FR PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- DE PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- EL PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- IE PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- IT PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- UK PANTOPRAZOLE 20 mg gastro-resistant tablets
- NL PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- NO PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- SE PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- ES PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- MT PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- PT PANTOPRAZOLE KRKA 20 mg gastro-resistant tablets
- PL NOLPAZA 20 mg gastro-resistant tablets
- SK NOLPAZA 20 mg gastro-resistant tablets
- LV NOLPAZA 20 mg gastro-resistant tablets
- EE NOLPAZA 20 mg
- LT NOLPAZA 20 mg gastro-resistant tablets
- CZ NOLPAZA 20 mg gastro-resistant tablets



This leaflet was last approved in October 2007.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pantoprazole 40 mg gastro-resistant tablets

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 Pantoprazole is and what it is used for
2. Before you take Pantoprazole
3. How to take Pantoprazole
4. Possible side effects
5. How to store Pantoprazole
6. Further information

1. What Pantoprazole is and what it is used for

Pantoprazole belongs to a group of medicines called proton pump inhibitors. Proton pump inhibitors reduce the amount of acid that your stomach makes.

You have been given Pantoprazole tablets because you have a condition caused by stomach acid.

Pantoprazole 40 mg gastro-resistant tablets are used in the short-term treatment and to relieve the symptoms of:

- duodenal ulcer
- gastric ulcer
- esophagitis (inflammation of esophagus) caused by acid secretion.

Additionally, the preparation is used:

- in combination with antibiotics in patients whose ulceration is related to *Helicobacter pylori* bacteria
- in the long-term treatment of conditions where gastric acid is constantly being secreted too much (e.g. Zollinger-Ellison syndrome).

2. Before you take Pantoprazole**Do not take Pantoprazole**

- if you are allergic (hypersensitive) to pantoprazole or any of the other ingredients of Pantoprazole
- if you are taking atazanavir (which is used for the treatment of HIV infection)
- if you have any relevant impairment of liver or kidney function and the product has been prescribed for you for the eradication of *Helicobacter pylori*.

Take special care with Pantoprazole

Please tell the doctor who prescribed this medicine:

- if you have severe liver impairment. In case of severe hepatic disorder your doctor should monitor your liver function while you use Pantoprazole
- if you have been diagnosed with vitamin B12 malabsorption
- if your doctor has given you Pantoprazole in addition to other medicines intended for the treatment of *Helicobacter pylori* infection (antibiotics): please also read the package leaflets of these medicinal products carefully.

Please tell your doctor if you suffer or have recently suffered from any of the following symptoms: unintentional weight loss, recurrent vomiting or vomiting of blood, or dark stool. Your doctor may perform or have performed an additional investigation called an endoscopy in order to diagnose your condition and/or exclude malignant disease.

Pantoprazole tablets are not recommended for children.

Taking other medicines

Other concomitant medication may affect the efficacy and safety of this medicine. Pantoprazole may also affect the efficacy and safety of other medications. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Remember to tell your doctor about your treatment with Pantoprazole if you are prescribed another medicine while the treatment is still ongoing.

It is especially important to tell your doctor:

- if you are using atazanavir which is used for the treatment of HIV infection
- if you are using ketoconazole or itraconazole which are used for the treatment of fungal infections, since pantoprazole may affect their concentrations in your body
- if you are using anticoagulant medicines, e.g. warfarin, since it may be necessary to monitor your blood coagulation tests more often.

Taking Pantoprazole with food and drink

Take Pantoprazole tablets with water either before or during breakfast.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Experience with use of Pantoprazole in pregnant women is limited. There is no information on the excretion of pantoprazole into human breast milk. If you are pregnant or if you are breast-feeding, you should use this medicine only if your treating physician considers the benefit for you greater than the potential risk for your unborn child or baby.

Driving and using machines

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

Adverse drug reactions such as dizziness and visual disturbances may occur and which may decrease the ability to react.

Important information about some of the ingredients of Pantoprazole

Intolerance to sugars: If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product. This because Pantoprazole contains sorbitol.

3 How to take Pantoprazole

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

Method of administration

Do not chew or crush Pantoprazole tablets but swallow them whole with liquid before a meal.

Dosage

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

Duodenal ulcer:

The recommended dose is 1 tablet (40 mg) daily.

Gastric ulcer and esophagitis (inflammation of esophagus) caused by acid secretion:

The recommended dose is 1 tablet (40 mg) daily.

In combination with antibiotics in patients whose ulceration is related to *Helicobacter pylori* bacteria:

The recommended dose is 1 tablet (40 mg) two times daily in combination with antibiotics. The second pantoprazole tablet should be taken before the evening meal.

Long-term treatment of conditions where gastric acid is constantly being secreted too much (e.g. Zollinger-Ellison syndrome):

Initial dose is 2 tablets (2 x 40 mg) daily. With doses above 80 mg daily, the dose should be divided and given twice daily.

Elderly and patients with renal impairment:

Daily dose of 40 mg should not be exceeded, except in elderly whose ulceration is related to *Helicobacter pylori* bacteria.

Patients with hepatic impairment:

Dose of 1 tablet (40 mg) should be given every second day.

Children:

Pantoprazole 20 mg gastro-resistant tablets should not be used in children.

If you take more Pantoprazole than you should

If you or someone you know accidentally takes a lot more than the stated dose (an overdose) you should contact a doctor immediately.

If you forget to take Pantoprazole

If you forget to take a dose, take it as soon as you remember, unless it is almost time for your next dose. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Pantoprazole

Do not change the dosage or stop the medication without discussing it with your doctor first, especially if you are taking Pantoprazole together with antibiotics in order to eradicate *Helicobacter pylori*, as this may increase the resistance of the germ to certain antibiotics.

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

4. Possible side effects

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

The frequencies are defined as

common	less than 1 in 10, but more than 1 in 100 people
uncommon	less than 1 in 100, but more than 1 in 1000 people
rare	less than 1 in 1000, but more than 1 in 10,000 people
very rare	less than 1 in 10,000 people

Common:

Upper abdominal pain, diarrhea, constipation, flatulence and headache.

Uncommon:

Nausea, vomiting, dizziness, blurred vision and allergic reactions such as itching and rash.

Rare:

Dry mouth, joint pain.

Very rare:

White blood cell deficiency (leucopenia), platelet deficiency (thrombocytopenia), swelling of hands and feet, severe liver cell damage and associated jaundice with potential liver failure, severe allergic reaction manifested as acute general symptoms with potential acute and substantial drop in blood pressure, elevated liver enzyme and triglyceride levels, elevated body temperature, muscle pain, depression, kidney inflammation, hives, hypersensitivity/attacks of local skin and mucous membrane swelling in the face, limbs, lips, tongue, larynx and/or vocal cords (angioedema, see special warning below), photosensitivity reactions and severe skin reactions such as Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis (Lyell's syndrome).

You should stop taking Pantoprazole and see your doctor immediately if you experience symptoms of angioedema, such as

- swollen face, tongue or throat

- difficulty to swallow
- hives and difficulties to breath

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 Pantoprazole

Keep out of the reach and sight of children.

Blister pack: Store in the original package in order to protect from moisture.

Container: Keep the container tightly closed in order to protect from moisture.

Expiry date

Do not use Pantoprazole after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

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 Pantoprazole contains

- Each gastro-resistant tablet contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate).
- The other ingredients are mannitol, crospovidone (type B), anhydrous sodium carbonate, sorbitol (E420), calcium stearate in the tablet core and hypromellose, povidone (K25), titanium dioxide (E171), yellow iron oxide (E172), propylene glycol, methacrylic acid - ethyl acrylate copolymer, sodium lauryl sulphate, polysorbate 80, macrogol 6000 and talc in the film-coating.

What Pantoprazole looks like and contents of the pack

The 40 mg gastro-resistant tablets are light brownish yellow, oval, slightly biconvex tablets.

Pack sizes:

Boxes of 7, 14, 15, 28, 30, 56, 60, 84, 98, 100, 100 x 1, 112 and 140 gastro-resistant tablets in blister packs.

A plastic container of 250 gastro-resistant tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

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

AT PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 BE PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 DK PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 FI PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 FR PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 DE PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 EL PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 IE PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 IT PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 UK PANTOPRAZOLE 40 mg gastro-resistant tablets
 NL PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 NO PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 SE PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 ES PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 MT PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 PT PANTOPRAZOLE KRKA 40 mg gastro-resistant tablets
 PL NOLPAZA 40 mg gastro-resistant tablets
 SK NOLPAZA 40 mg gastro-resistant tablets
 LV NOLPAZA 40 mg gastro-resistant tablets
 EE NOLPAZA 40 mg
 LT NOLPAZA 40 mg gastro-resistant tablets
 CZ NOLPAZA 40 mg gastro-resistant tablets

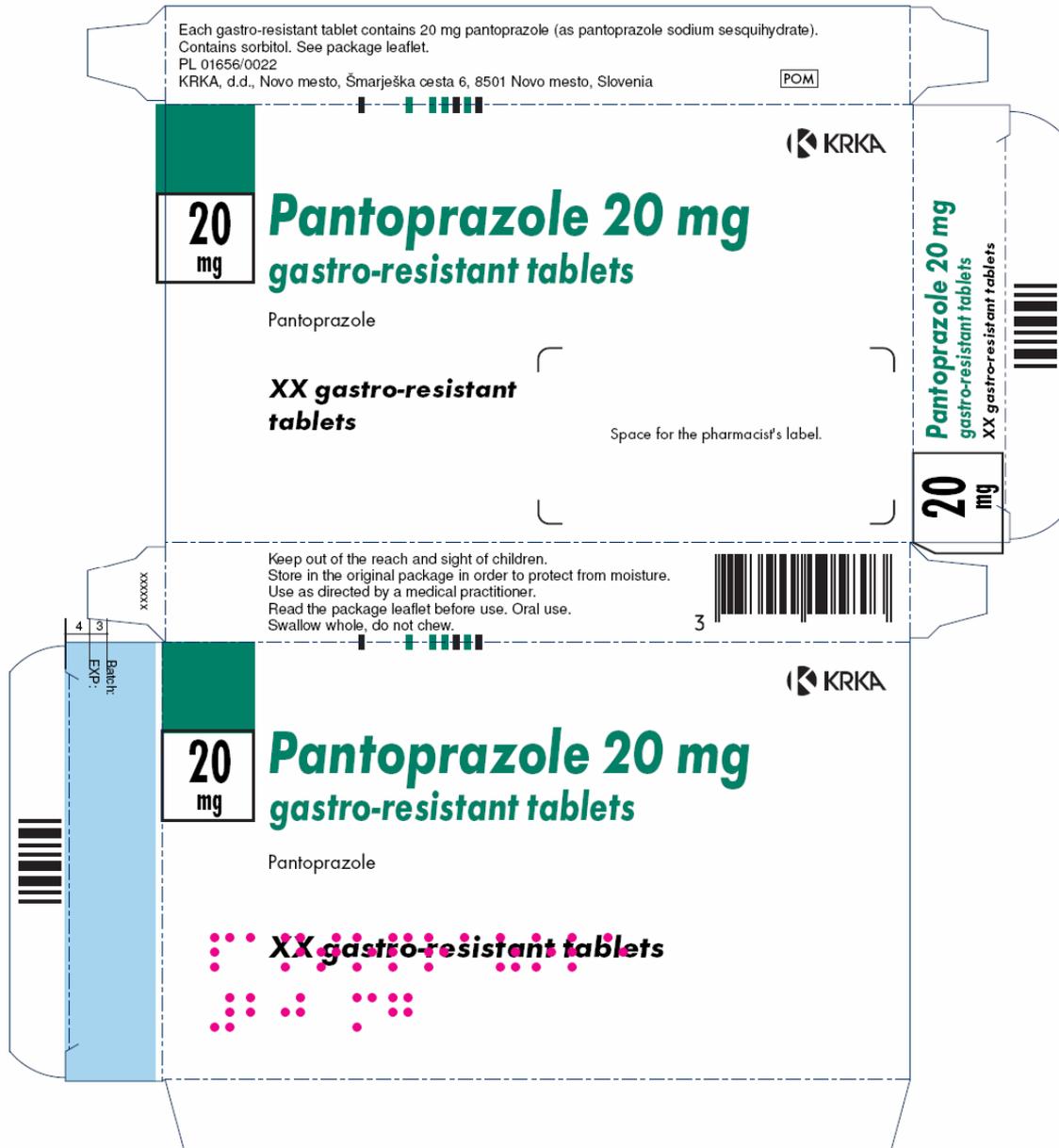
This leaflet was last approved in October 2007.



Module 4 Labelling Pantoprazole 20mg Gastro-Resistant Tablets (PL 01656/0022)

<p>20 mg Pantoprazole 20 mg gastro-resistant tablets Pantoprazole </p>	<p>20 mg Pantoprazole 20 mg gastro-resistant tablets Pantoprazole </p>
---	--

<p>20 mg</p>	<p>Pantoprazole 20 mg <i>gastro-resistant tablets</i> </p> <p>Pantoprazole</p> <p>250 gastro-resistant tablets</p> <p>Each gastro-resistant tablet contains 20 mg pantoprazole (as pantoprazole sodium sesquihydrate). Contains sorbitol. See package leaflet. Keep out of the reach and sight of children. Keep the container tightly closed in order to protect from moisture. Swallow whole, do not chew. Use as directed by a medical practitioner. Read the package leaflet before use. Oral use. KRKA, d.d., Novo mesto Šmarješka cesta 6, 8501 Novo mesto, Slovenia PL 01656/0022</p>	<p>xxxxxx</p> <p>Batch: _____</p> <p>EXP: _____</p>
---------------------	--	---



Pantoprazole 40mg Gastro-Resistant Tablets (PL 01656/0023)

40 mg	Pantoprazole 40 mg gastro-resistant tablets Pantoprazole	
40 mg	Pantoprazole 40 mg gastro-resistant tablets Pantoprazole	
40 mg	Pantoprazole 40 mg gastro-resistant tablets Pantoprazole	
40 mg	Pantoprazole 40 mg gastro-resistant tablets Pantoprazole	
40 mg	Pantoprazole 40 mg gastro-resistant tablets Pantoprazole	
40 mg	Pantoprazole 40 mg gastro-resistant tablets Pantoprazole	

40 mg	Pantoprazole 40 mg gastro-resistant tablets	
	Pantoprazole	
250 gastro-resistant tablets	Each gastro-resistant tablet contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate). Contains sorbitol. See package leaflet. Keep out of the reach and sight of children. Keep the container tightly closed in order to protect from moisture. Swallow whole, do not chew. Use as directed by a medical practitioner. Read the package leaflet before use. Oral use. KRKA, d.d., Novo mesto Šmarješka cesta 6, 8501 Novo mesto, Slovenia. PL 01656/0023	
	xxxxxx	Batch: _____ EXP: _____



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Pantoprazole 20mg and 40mg Gastro-Resistant Tablets (and duplicates) to KRKA d.d (PL 01656/0022-23) on 21st September 2007. The products are prescription-only medicines.

The applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC, claiming to be generic products to the original products Somac 20mg and 40mg Gastro-Resistant Tablets (Altana Pharma AG, Finland), which have been authorised in the EEA for over 10 years.

The products contain the active ingredient pantoprazole. Indications for the 20mg strength consist of:

the treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing).

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).

Indications for the 40mg strength consist of relieving the symptoms and for short-term treatment of gastrointestinal diseases which require a reduction in acid secretion:

- duodenal ulcer
- gastric ulcer
- moderate and severe reflux oesophagitis
- eradication of *Helicobacter pylori* in combination with antibiotic therapy in patients with peptic ulcer
- Zollinger-Ellison syndrome and other hypersecretory conditions.

Pantoprazole is one of the proton pump inhibitors. It inhibits gastric acid by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (the 'proton pump') of the gastric parietal cell. Proton pump inhibitors are used for the treatment of peptic ulceration and the associated disease conditions.

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Pantoprazole 20mg and 40mg Gastro-Resistant Tablets
Name(s) of the active substance(s) (INN)	Pantoprazole
Pharmacotherapeutic classification (ATC code)	Proton Pump Inhibitors (A02B C02)
Pharmaceutical form and strength(s)	20mg and 40mg Gastro-Resistant Tablets
Reference numbers for the Decentralised Procedure	UK/H/0946/01-02/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Malta, The Netherlands, Norway, Sweden, Spain, Portugal
Marketing Authorisation Number(s)	PL 01656/0022-23
Name and address of the authorisation holder	Krka, d.d., Novo mesto, Smarjeska cesta 6, 8501 Novo mesto, Slovenia

III SCIENTIFIC OVERVIEW AND DISCUSSION**III.1 QUALITY ASPECTS****S. Active substance**

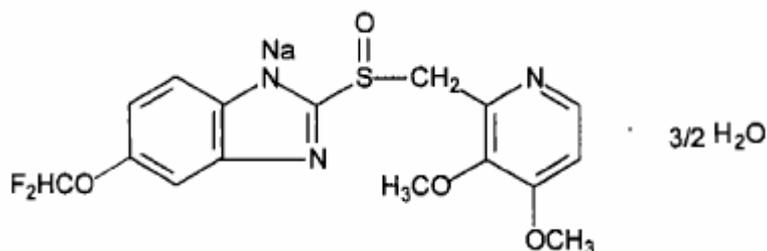
INN: Pantoprazole sodium sesquihydrate

Chemical Name: 5-(difluoromethoxy)- 2-[(3,4-dimethoxy-pyridin-2-yl) methylsulfinyl]- 3H-benzimidazole

CAS Registry No: 164579-32-2

Molecular Formula: $C_{16}H_{14}F_2N_3NaO_4S \cdot 3/2H_2O$

Structure:



Molecular Weight: 432.4

Appearance: White to cream, odourless crystalline powder

Solubility: Freely soluble in water, soluble in methanol, practically insoluble in methylene chloride and hexane.

Chirality: Pantoprazole, sulfoxide with different substituents attached to the sulphur, is a chiral compound due to its tetrahedral configuration. Substance occurs as a racemate.

Polymorphism: Pantoprazole sodium was found to exist in the sesquihydrate polymorphic form. Infrared spectroscopy and X-ray powder diffraction were used in its characterisation.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance pantoprazole sodium. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

The specifications for the container-closure for active pantoprazole sodium have been provided and are satisfactory. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been provided to support a retest period of 24 months when stored in the proposed packaging. Suitable post approval stability commitments for the active substance have been provided.

P Medicinal Product

Other Ingredients

Other ingredients consists of the pharmaceutical excipients macrogol 6000, purified water, sorbitol, calcium stearate, methacrylic acid-ethyl acrylate copolymer, hypromellose, propylene glycol, talc, titanium dioxide, crospovidone, povidone, mannitol, anhydrous sodium carbonate, yellow iron oxide E172, sodium lauryl sulphate and polysorbate 80.

All excipients used comply with respective Ph. Eur monographs, with the exception of yellow iron oxide, which is controlled to a suitable in-house specification. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin.

Pharmaceutical Development

The applicant has provided a suitable product development rationale and data.

Gastro-resistance was found to be comparable between the proposed and reference products, with no drug released from either formulation when placed in medium at acidic pH.

Similar impurity profiles have been provided for the proposed versus reference products and the bioequivalence studies performed have shown that the products are bioequivalent.

Manufacture

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the product.

The manufacturing process has been validated and has shown satisfactory results.

Control of Drug Product

The finished product specifications proposed are acceptable and provide an assurance of the quality of the finished product. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specifications.

Satisfactory data on the characterisation of impurities have been provided.

Reference Standards or Materials

Certificates of analysis for all reference standards used have been provided and are satisfactory.

Container Closure System

Both tablet strengths are packaged in:

- Blister pack (OPA/aluminium/PVC film and aluminium foil) in a carton box in pack sizes of 7, 14, 15, 28, 30, 56, 60, 84, 100, 100 x 1, 112 or 140 gastro-resistant tablets.
- HDPE containers with a silica gel desiccant in a tamper evident PP screw-cap in pack sizes of 250 gastro-resistant tablets.

Stability of the Drug Product

Stability data provided support a shelf-life of 24 months for both strengths, with the storage conditions 'Store in the original package. Protect from moisture' for the blister packs and 'Protect from moisture. Keep container tightly closed' for the HDPE containers.

Bioequivalence/bioavailability

Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated.

SPC, PIL, Labels

The SPC, PIL and labels are pharmaceutically acceptable.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

CONCLUSION

It is recommended that marketing authorisations are granted for these applications.

III.2 PRE-CLINICAL ASPECTS

In these applications, the products are claiming to be generic products of Somac 20mg and 40mg Gastro-Resistant Tablets (Altana Pharma AG, Finland), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.

**III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY****Pharmacodynamics**

No new pharmacodynamic data have been provided and none are required for applications of this type.

Pharmacokinetics

With the exception of the bioequivalence studies, no new pharmacokinetic data have been provided and none are required for applications of this type.

Bioequivalence

The applicant has submitted three bioequivalence studies two performed under fasting and one under fed conditions. All studies were conducted in compliance with GCP. The two studies are summarised below.

Fasted State Study 20mg

The objective of the study was to compare the bioavailability of the test 20mg pantoprazole tablets and the reference 20mg pantoprazole tablets (Pantozol®) administered to healthy volunteers under fasting conditions. This was a single-dose, randomized, two-period, two-sequence crossover study under fasting conditions with a 1-week washout period between doses. All subjects received the study drug at the same dosage, i.e. a single dose (20mg) pantoprazole in the form of the test product followed by the form of the reference product or vice versa.

Following drug administration serial blood samples were collected at frequent intervals up to 16 hours post dose. Plasma samples were analysed for pantoprazole by a validated HPLC method with UV detection.

Analysis of variance (ANOVA) followed by the calculation of 90% confidence intervals for the test/reference ratio was performed for AUC, AUC_{0-t}, C_{max}, C_{max}/AUC parameters of pantoprazole. The data was ln-transformed prior to analysis. Bioequivalence was concluded if the corresponding 90% confidence intervals for the ratio of the means of AUC and AUC_{0-t} were included between 0.80 and 1.25 and C_{max} between 0.75 and 1.33. A non-parametric test was used for the untransformed t_{max} parameter. The main pharmacokinetic parameters are summarised in tables 1 and 2 below.

Table 1. Summary of the main pharmacokinetic parameters of pantoprazole following administration of Pantoprazole 20 mg tablets (Formulation A) and Pantozol® 20 mg tablets (Formulation B) to healthy volunteers under fasting conditions

		AUC (ng/mL*h)	AUC _{0-t} (ng/mL*h)	C _{max} (ng/mL)	t _{max} (h)	C _{max} /AUC (1/h)	MRT (h)	t _{1/2} (h)
Formulation								
A	Mean	3389.3	3195.8	1561.4	2.64	0.566	4.08	1.38
	std	2749.3	2282.9	502.0	0.70	0.172	1.70	1.12
B	Mean	3320.2	3171.8	1480.9	2.66	0.547	4.11	1.33
	std	2665.7	2349.9	470.1	0.87	0.164	1.46	0.99

Table 2. The 90% confidence intervals and point estimates for comparison of pantoprazole pharmacokinetic parameters between Pantoprazole 20 mg tablets (Formulation a) and Pantozol® 20 mg tablets (Formulation B) to healthy volunteers under fasting conditions

	90% confidence interval		Point estimate
	Lower limit	Upper limit	
AUC	98.44%	107.12%	(102.69 %)
AUC_{0-t}	97.96%	106.79%	(102.28%)
C_{max}	100.67%	111.07%	(105.74%)

Three adverse events (mild headache, nausea and vomiting) were reported by three volunteers and were assessed as not related to the study drugs.

Based on the results of the study, it can be concluded that the test Pantoprazole 20 mg tablets and the reference Pantozol® 20 mg tablets are bioequivalent when given under fasting conditions

Fasted State Study 40 mg

The objective of the study was to compare the bioavailability of the test 40mg pantoprazole tablets and the reference 40mg pantoprazole tablets (Pantozol®) in healthy volunteers under fasting conditions. This was a single-dose, randomized, two-period, two-sequence crossover study under fasting conditions with a 1-week washout period between doses. All subjects received the study drug at the same dosage, i.e. a single dose (40mg) pantoprazole in the form of the test product followed by the form of the reference product or vice versa.

Following drug administration serial blood samples were collected at frequent intervals up to 24 hours post dose. Plasma samples were analysed for pantoprazole by a validated HPLC method with UV detection.

Analysis of variance (ANOVA) followed by the calculation of 90% confidence intervals for the test/reference ratio was performed for AUC, AUC_{0-t}, C_{max}, C_{max}/AUC parameters of pantoprazole. The data was ln-transformed prior to analysis. Bioequivalence was concluded if the corresponding 90% confidence intervals for the ratio of the means of AUC and AUC_{0-t} were included between 0.80 and 1.25 and C_{max} between 0.75 and 1.33. A non-parametric test was used for the untransformed t_{max} parameter. The main pharmacokinetic parameters are summarised in tables 3 and 4 below.

Table 3. Summary of the main pharmacokinetic parameters of pantoprazole following administration of Pantoprazole 40 mg tablets (Formulation A) and Pantozol® 40 mg tablets (Formulation B) to healthy volunteers under fasting conditions.

		AUC (µg/mL*h)	AUC _{0-t} (µg/mL*h)	C _{max} (µg/mL)	t _{max} (h)	C _{max} /AUC (1/h)	MRT (h)	t _{1/2} (h)
Formulation								
A	Mean	7.102	6.842	3.229	3.08	0.583	4.66	1.55
	std	5.901	5.205	1.075	0.93	0.223	2.04	1.50
B	Mean	7.246	7.023	3.068	2.64	0.553	4.08	1.42
	std	6.264	5.755	0.781	0.94	0.191	1.60	1.28

Table 4. The 90% confidence intervals and point estimates for comparison of pantoprazole pharmacokinetic parameters between Pantoprazole 40 mg tablets (Formulation A) and Pantozol® 40 mg tablets (Formulation B) to healthy volunteers under fasting conditions.

	90% confidence interval		
	Lower limit	Upper limit	Point estimate
<u>AUC</u>	93.70%	106.09%	(99.70 %)
<u>AUC_{0-t}</u>	93.59%	106.21%	(99.70%)
<u>C_{max}</u>	93.47%	113.20%	(102.86%)

Three adverse events (headache, nausea and sweating) were experienced by one volunteer and were assessed as being unlikely to be related to study treatment.

Based on the results of the study it can be concluded that the test Pantoprazole 40 mg tablets and the reference Pantozol® 40 mg tablets are bioequivalent when given under fasted conditions.

Fed State Study 40 mg

The objective of the study was to evaluate post-prandial bioavailability of the test 40mg pantoprazole tablets in comparison with the reference 40mg pantoprazole tablets (Pantozol®) administered to healthy volunteers following a high-fat breakfast. The study was a single-dose, randomized, two period, two sequence cross-over study under fed conditions with a 1 week washout period between doses. All subjects received the study at the same dosage, i.e. a single dose (40mg) of pantoprazole in the form of the test product followed by the form of the reference or vice versa

After drug administration serial blood samples were collected at frequent intervals up to 16 hours post dosing. Plasma samples were analysed for pantoprazole by a validated HPLC method with UV detection.

Analysis of variance (ANOVA) followed by the calculation of 90% confidence intervals for the test/reference ratio was performed for AUC, AUC_{0-t}, C_{max}, C_{max}/AUC parameters of pantoprazole. The data was ln-transformed prior to analysis. Bioequivalence was concluded if the corresponding 90% confidence intervals for the ratio of the means of AUC and AUC_{0-t} were included between 0.80 and 1.25, and C_{max} between 0.75 and 1.33. A non-parametric test was used for the untransformed t_{max} parameter. All statistical analyses pertaining to

parameters C_{max}/AUC , MRT and t_{max} were reported for indicative purposes. The main pharmacokinetic parameters are summarised in tables 5 and 6 below.

Table 5. Summary of the main pharmacokinetic parameters of pantoprazole following administration of Pantoprazole 40 mg tablets (Formulation A) and Pantozol® 40 mg tablets (Formulation B) to healthy volunteers under fed conditions

		AUC ($\mu\text{g/mL}\cdot\text{h}$)	AUC _{0-t} ($\mu\text{g/mL}\cdot\text{h}$)	C_{max} ($\mu\text{g/mL}$)	t_{max} (h)	C_{max}/AUC (1/h)	MRT (h)	$t_{1/2}$ (h)
Formulation								
A	Mean	5.966	5.755	2.918	5.49	0.607	6.79	1.39
	std	5.325	4.735	0.834	2.12	0.190	2.47	1.33
B	Mean	5.870	5.638	2.773	5.72	0.592	6.98	1.38
	std	5.096	4.448	0.791	1.64	0.185	2.17	1.28

Table 6. The 90% confidence intervals and point estimates for comparison of pantoprazole pharmacokinetic parameters between the test Pantoprazole 40 mg tablets (Formulation A) and the reference Pantozol® 40 mg tablets (Formulation B) in healthy volunteers under fed conditions

	90% confidence interval		Point estimate
	Lower limit	Upper limit	
<u>AUC</u>	97.12%	107.76%	(102.30 %)
<u>AUC_{0-t}</u>	97.23%	108.15%	(102.54%)
<u>C_{max}</u>	97.43%	112.30%	(104.60%)

One adverse event, abdominal pain, was reported after administration of the test drug by one volunteer. This was reported as mild and it was possibly related to the study drug.

Based on the results of the study it can be concluded that the test Pantoprazole 40 mg tablets and the reference Pantozol® 40 mg tablets are bioequivalent when given under fed conditions.

Assessor's Comments

The pharmacokinetics of pantoprazole is linear and there is no evidence of drug accumulation following multiple dosing. In which case, a single-dose study under fasted conditions and a single-dose study under fed conditions is considered sufficient for the demonstration that the test product is a generic medicinal product of the reference products.

EFFICACY

No new efficacy data are presented for this application and none are required. However, the applicant has provided a review of clinical trials published in the literature confirming the efficacy and safety of pantoprazole.

SAFETY

No new safety issues have been identified.

EXPERT REPORT

A satisfactory clinical expert report has been submitted, which has been written by an appropriately qualified medical practitioner.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

These are satisfactory and consistent with those for the reference products.

PATIENT INFORMATION LEAFLET (PIL)

This is satisfactory and consistent with the SPC.

LABELLING

These are satisfactory.

DISCUSSION

Proton pump inhibitors, including pantoprazole, have been used for the treatment of peptic ulceration and the associated conditions for more than 10 years within the EU. The use of pantoprazole is well-established. It has recognised efficacy and acceptable safety.

With regards to the current application, sufficient clinical information has been submitted.

When used as indicated, pantoprazole has a favourable benefit-to-risk ratio.

CONCLUSION

Overall, there are no clinical objections to the grant of marketing authorisations for these applications. No new or unexpected safety concerns arise from these applications. The SPC, PIL and packaging are satisfactory and consistent with that for the reference product.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**QUALITY**

The important quality characteristics of Pantoprazole 20mg and 40mg Gastro-Resistant Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Pantoprazole 20mg and 40mg Gastro-Resistant Tablets and Pantozol 20mg and 40mg Gastro-Resistant Tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the reference products.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with pantoprazole is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
15/10/2007	IA	To register the addition of a pack size of 98 tablets, with consequential changes to section 6.5 of the SPC. The PIL is approved on the basis that it has been revised only in respect of the proposed change. Any other changes will require independent assessment.	Granted 25/10/2007