

Public Assessment Report
Decentralised Procedure

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

UK/H/1163-4/01-02/DC
UK licence nos: PL 04569/0848-51

Generics (UK) Limited

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted Generics UK Marketing Authorisations (licences) for the medicinal products Pantoprazole 20mg and 40mg Gastro-Resistant Tablets and their duplicate licences. These are prescription-only medicines that are prescribed to patients with conditions caused by stomach acid.

Pantoprazole 20mg Gastro-Resistant Tablets are used:

- 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).

Pantoprazole 40mg Gastro-Resistant Tablets are used for the symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:

- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux oesophagitis
- Zollinger-Ellison-Syndrome and other hypersecretory conditions
- Eradication of *Helicobacter pylori*, in combination with antibiotic therapy in patients with peptic ulcer.

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

Data supporting the quality, safety and efficacy of this product was assessed by the MHRA and it was judged that the benefits of using Pantoprazole 20mg and 40mg Gastro-Resistant Tablets outweigh the risk; hence, Marketing Authorisations (MAs) have been granted.

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Module 1

Product Name	Pantoprazole 20mg & 40mg Gastro-Resistant Tablets
Type of Application	Generic, Article 10.1
Active Substance	Pantoprazole
Form	Tablets
Strength	20mg and 40mg
MA Holder	Generics (UK) Limited
RMS	UK
CMS	<p>UK/H/1163/01/DC: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Sweden, Slovenia, and Slovakia.</p> <p>UK/H/1163/02/DC: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Sweden, Slovenia, and Slovakia.</p> <p>UK/H/1164/01-02/DC: Belgium and France</p>
Procedure Number	UK/H/1163-4/01-02/DC
End of Procedure	26 th September 2008

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 22.55 mg of pantoprazole sodium sesquihydrate, equivalent to 20 mg of pantoprazole.

Excipients:

Lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

Yellow to ochre elongated coated 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 gastro-resistant tablet 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 one Pantoprazole 20 mg gastro-resistant tablet daily. Symptom relief is generally accomplished within 2-4 weeks, and a 4-week treatment period is usually required for healing of associated oesophagitis. If this is not sufficient, healing will normally be achieved within a further 4 weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment.

Long-term management and prevention of relapse in reflux oesophagitis.

For long-term management, a maintenance dose of one Pantoprazole 20 mg gastro-resistant tablet per day 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 oral dosage is one Pantoprazole 20 mg gastro-resistant tablet per day.

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 the active substance 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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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).

In cirrhotic patients, the half-life is 7 to 9 hours longer, the AUC is 6 to 8 times greater but the maximal plasma concentrations are increased nearly 1.5 times in comparison to those in healthy patients. Then pantoprazole should only be administered every two days.

The use of Pantoprazole 20 mg gastro-resistant tablet 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 on 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.

4.5 Interaction with other medicinal products and other forms of interaction

Pantoprazole 20 mg gastro-resistant tablet may reduce the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole, itraconazole, atazanavir).

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.

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.

Pharmacokinetic interaction studies have been performed with clarithromycin, metronidazole and amoxicillin. No clinically relevant interactions were found.

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 fetus/baby.

4.7 **Effects on ability to drive and use machines**

Pantoprazole gastro-resistant tablets have no influence 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 $\geq 1/100$ 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

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and the lymphatic system disorders

Very rare $< 1/10\ 000$, including isolated reports

Leukopenia thrombocytopenia

Immune system disorders

Very rare $< 1/10\ 000$, including isolated reports,

Anaphylactic reactions including anaphylactic shock

Psychiatric disorders

Very rare $< 1/10\ 000$, including isolated reports,

Mental depression, hallucination, depression, disorientation and confusion especially in pre-disposed patients, aggravation of these symptoms in cases of pre-existence

Nervous system disorders

Common $\geq 1/100$ to $< 1/10$ Headache

Uncommon $\geq 1/1000$ to $< 1/100$

Dizziness, disturbances in vision (blurred vision)

Gastrointestinal disorders

Common $\geq 1/100$ to $< 1/10$

Upper abdominal pain, diarrhoea, constipation, flatulence

Uncommon $\geq 1/1000$ to $< 1/100$

Nausea, vomiting

Rare $\geq 1/10\ 000$ to $< 1/1000$

Dry mouth

Hepato-biliary disorders

Very rare $< 1/10\ 000$, including isolated reports

Severe hepatocellular damage leading to jaundice with or without hepatic failure

Skin and subcutaneous tissue disorders

Uncommon $\geq 1/1000$ to $< 1/100$

Allergic reactions such as pruritus and skin rash

Very rare $< 1/10\ 000$, including isolated reports

Urticaria, angioedema, severe skin reactions such as Stevens- Johnson Syndrome, Erythema multi-forme, Lyell-Syndrome, photosensitivity

Musculoskeletal, connective tissue and bone disorders

Rare ($\geq 1/10,000$ to $< 1/1000$)

Arthralgia

Very rare ($< 1/10\ 000$)

Myalgia

Renal and urinary disorders

Very rare ($< 1/10,000$)

Interstitial nephritis

Reproductive system and breast disorders

Common $\geq 1/100$ to $< 1/10$

gynaecomastia

General disorders and administration site conditions

Very rare ($< 1/10,000$)

Peripheral oedema

Investigations

Very rare ($< 1/10,000$),

Increased liver enzymes (transaminases, γ -GT); 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: AO2BC02

Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic canaliculi of the parietal cells where it inhibits the H⁺, K⁺-ATPase enzyme, i. e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved in 2 weeks. As with other proton pump inhibitors and 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 given orally or intravenously.

The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the normal upper limit. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far (see Section 5.3), the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids have not been observed in humans.

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid 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 20 mg oral dose. On average at about 2.0 h - 2.5 h p.a. the maximum serum concentrations of about 1-1.5 µg/ml are achieved, and these values remain constant after multiple administration. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg.

Terminal half-life is about 1 h. There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole to the proton pumps of the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

Pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

Pantoprazole's serum protein binding is about 98%. The substance is almost exclusively metabolized in the liver. Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole, the rest is excreted with the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 h) is not much longer than that of pantoprazole.

Bioavailability

Pantoprazole is completely absorbed after oral administration. The absolute bioavailability from the tablet was found to be about 77%. Concomitant intake of food had no influence on AUC, maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

Characteristics in patients/special groups of subjects

No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole can be dialyzed. Although the main metabolite has a moderately delayed half-life (2-3 h), excretion is still rapid and thus accumulation does not occur.

Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 3 and 6 h and the AUC values increased by a factor of 3 - 5, the maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

A slight increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is also not clinically relevant.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

In a two-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 high-dose treatment.

In the two-year rodent studies, an increased number of liver tumours were observed in rats (in one rat study only) and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg) in one two-year study. The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no side effects on the thyroid glands are expected.

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

Investigations revealed no evidence of impaired fertility or teratogenic effects.

Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, the concentration of pantoprazole in the foetus is increased shortly before birth.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Lactose monohydrate
Croscarmellose sodium
Silica, colloidal anhydrous
Magnesium stearate

Colour coating (OPADRY II 85F32097 Yellow)

Polyvinyl alcohol
Macrogol 3350
Titanium dioxide (E171)
Talc
Iron oxide yellow (E-172)
Quinoline aluminium yellow lake (E104)

Gastro-resistant coating

Sodium lauryl sulphate
Polysorbate 80
Methacrylic acid-ethyl acrylate copolymer
Triethylcitrate
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

White HDPE bottle with screw cap containing a dessicant capsule (LDPE)
Pack sizes: 7, 14, 15, 28, 30, 50, 56, 60, 100, 250 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd., Station Close, Potters Bar, Hertfordshire, EN6 1TL, U.K.

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/0848
PL 04569/0850

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/11/2008

10 DATE OF REVISION OF THE TEXT

10/11/2008

1 NAME OF THE MEDICINAL PRODUCT

Pantoprazole 40 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 45.10 mg of pantoprazole sodium sesquihydrate, equivalent to 40 mg of pantoprazole.

Excipients:

Lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

Pale yellow to ocher elongated coated tablet.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

For symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:

- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux oesophagitis
- Zollinger-Ellison-Syndrome and other hypersecretory conditions
- Eradication of *Helicobacter pylori*, in combination with antibiotic therapy in patients with peptic ulcer.

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 Generics 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.

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

Gastric ulcer and moderate and severe reflux oesophagitis

The recommended dosage is 40 mg pantoprazole daily (1 Pantoprazole Generics 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 Generics 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.

Eradication therapy in patients with peptic ulcer:

In *Helicobacter pylori* positive patients with ulcer duodeni or ulcer ventriculi, the eradication of the bacteria should be pursued with a combination therapy. Dependent on the resistance pattern, the following combination can be recommended for the eradication of *Helicobacter pylori*:

two times daily an enteric coated tablet of Pantoprazole 40 mg

+ two times daily 1000 mg of amoxicillin

+ two times daily 500 mg of clarithromycin

two times daily an enteric coated tablet of Pantoprazole Generics 40 mg

+ two times daily 500 mg of metronidazol or 500 mg of tinidazole at least (considering the intermediate susceptibility of *H. pylori* strain dose/treatment duration can be increased).

+ two times daily 500 mg of clarithromycin

two times daily an enteric coated tablet of Pantoprazole 40 mg

+ two times daily 1000 mg of amoxicillin

+ two times daily 500 mg of metronidazol or 500 mg of tinidazole at least (considering the intermediate susceptibility of *H. pylori* strain dose/treatment duration can be increased).

If combination therapy is not an option, which means when no *Helicobacter pylori* can be documented, the following doses of Pantoprazole Generics 40 mg mono-therapy are recommended:

One gastro-resistant tablet of Pantoprazole Generics 40 mg per day for ulcer duodeni or ulcer ventriculi and for moderate to severe reflux oesophagitis. In individual cases the dose may be doubled (increasing to two enteric coated tablets of Pantoprazole Generics 40 mg per day) particularly if there is no response to other treatments.

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 Generics 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.

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 if respective clinical symptoms are observed.

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 the active substance or to any of the excipients.

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

There is no data available to make dose adjustment in patients with moderate and severe renal impairment. In patients with severe hepatic impairment, the dose regimen should be reduced to 40 mg of pantoprazole every other day. In particular H. pylori triple therapy is not appropriate in these patients.

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). In cirrhotic patients, the half-life is 7 to 9 hours longer, the AUC is 6 to 8 times greater but the maximal plasma concentrations are increased nearly 1.5 times in comparison to those in healthy patients. Then pantoprazole should only be administered every two days.

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 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption 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.

Pharmacokinetic interaction studies have been performed with clarithromycin, metronidazole and amoxicillin. No clinically relevant interactions were found.

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

Pantoprazole gastro-resistant tablets have no influence 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 $\geq 1/100$ 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

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and the lymphatic system disorders

Very rare $< 1/10\ 000$, including isolated reports

Leukopenia thrombocytopenia

Immune system disorders

Very rare $< 1/10\ 000$, including isolated reports,

Anaphylactic reactions including anaphylactic shock

Psychiatric disorders

Very rare $< 1/10\ 000$, including isolated reports,

Mental depression, hallucination, depression, disorientation and confusion especially in pre-disposed patients, aggravation of these symptoms in cases of pre-existence

Nervous system disorders

Common $\geq 1/100$ to $< 1/10$ Headache

Uncommon $\geq 1/1000$ to $< 1/100$

Dizziness, disturbances in vision (blurred vision)

Gastrointestinal disorders

Common $\geq 1/100$ to $< 1/10$

Upper abdominal pain, diarrhoea, constipation, flatulence

Uncommon $\geq 1/1000$ to $< 1/100$

Nausea, vomiting

Rare $\geq 1/10\ 000$ to $< 1/1000$

Dry mouth

Hepato-biliary disorders

Very rare $< 1/10\ 000$, including isolated reports

Severe hepatocellular damage leading to jaundice with or without hepatic failure

Skin and subcutaneous tissue disorders

Uncommon $\geq 1/1000$ to $< 1/100$

Allergic reactions such as pruritus and skin rash

Very rare $< 1/10\ 000$, including isolated reports

Urticaria, angioedema, severe skin reactions such as Stevens- Johnson Syndrome, Erythema multi-forme, Lyell-Syndrome, photosensitivity

Musculoskeletal, connective tissue and bone disorders

Rare ($\geq 1/10,000$ to $\leq < 1/1000$)

Arthralgia

Very rare ($< 1/10\ 000$)

Myalgia

Renal and urinary disorders
Very rare (<1/10,000)
Interstitial nephritis

Reproductive system and breast disorders
Common $\geq 1/100$ to $< 1/10$
gynaecomastia

General disorders and administration site conditions
Very rare (<1/10,000)
Peripheral oedema

Investigations
Very rare (<1/10,000),
Increased liver enzymes (transaminases, γ -GT); 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 dialysable.

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 40 mg oral dose. On average, the maximum serum concentrations are approximately 2-3 μ g/ml about 2.5 hours post-administration and these values remain constant after multiple administration. Terminal half-life is about 1 hour. 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 activation within the parietal cell, the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

Pharmacokinetics does not vary after single or repeated administration. In the dose range of 10 mg to 80 mg, the plasma kinetics of pantoprazole is 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 of the tablet is about 77%. Concomitant intake of food or antacids had no influence on AUC, maximum serum concentrations and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

Characteristics in patients/special groups of subjects

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.

No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialysed. Although the main metabolite has a moderately delayed half-life (2-3 hours), 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.

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 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

Cellulose, microcrystalline
Lactose monohydrate
Croscarmellose sodium
Silica, colloidal anhydrous
Magnesium stearate

Colour coating (OPADRY II 85F32097 Yellow)

Polyvinyl alcohol
Macrogol 3350
Titanium dioxide (E171)
Talc
Iron oxide yellow (E172)
FD&C yellow #5/tartrazine aluminium lake (E102)

Gastro-resistant coating
Sodium lauryl sulphate
Polysorbate 80
Methacrylic acid-ethyl acrylate copolymer
Triethylcitrate
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White HDPE bottle with screw cap containing a dessicant capsule (LDPE)
Pack sizes: 7, 14, 15, 28, 30, 50, 56, 60, 100, 250 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd., Station Close, Potters Bar, Hertfordshire, EN6 1TL, U.K.

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/0849
PL 04569/0851

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/11/2008

10 DATE OF REVISION OF THE TEXT

10/11/2008

Module 3

PATIENT INFORMATION LEAFLET

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 side effect 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 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 pain 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 is 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.

Taking Pantoprazole with food and drink - Swallow these 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 - Pantoprazole contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

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:

- Swallow the tablets whole with water before a meal
- Do not chew or crush the tablets.

Dosage:

Treatment of mild reflux disease and the associated symptoms (eg. 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).

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 - Do not give Pantoprazole to children.

If you take more Pantoprazole than you should - If you or someone you know accidentally takes a 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 of Pantoprazole, 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.

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 breathe.

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 1,000 people.
Rare less than 1 in 1,000, but more than 1 in 10,000 people.
Very rare less than 1 in 10,000 people.

Common: headache, upper abdominal pain, diarrhoea, constipation, wind, swelling of breasts (males).

Uncommon: dizziness, nausea, vomiting, 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).

If any side effect gets serious, or if you notice any side effects not mentioned in the leaflet, please tell your pharmacist or doctor.

5. HOW TO STORE PANTOPRAZOLE

Keep out of the reach and sight of children. 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. Do not store this medicine above 25°C. 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 22.55 mg of pantoprazole sodium sesquihydrate, equivalent to 20 mg of pantoprazole. The other ingredients are cellulose, microcrystalline lactose monohydrate, croscarmellose sodium, silica colloidal anhydrous and magnesium stearate. The coating contains sodium lauryl sulphate, polyborate 80, methacrylic acid-ethyl acrylate copolymer, triethylcitrate, polyvinyl alcohol, macrogol 3350, titanium dioxide (E171), talc, iron oxide (E172) and quinoline aluminium yellow lake (E104).

What Pantoprazole looks like and contents of the pack - The tablets are yellow and oblong. Pantoprazole is available in plastic bottles of 7, 14, 15, 28, 30, 50, 56, 60, 100 and 250 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder: Generics [UK] Ltd., Station Close, Potters Bar, Hertfordshire, EN6 1TL, UK.

Manufacturer: McDermott Laboratories t/o Gerard Laboratories, 35/36 Baldryke Industrial Estate, Grange Road, Dublin 13, Ireland.

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

Austria - Pantoprazol Arzono 20 mg magensaftresistente Tabletten

Belgium - Pantoprazole Mylan 20 mg

Czech Republic, Denmark, Finland, Norway, Slovakia,

Sweden - Pantoprazol Mylan 20 mg

France - PANTOPRAZOLE MYLAN 20 mg, comprimé gastro-résistant

Germany - Pantoprazol dura 20 mg magensaftresistente Tabletten

Ireland - Protlezo 20 mg

Italy - Pantoprazolo Mylan Generics 40 mg

The Netherlands - Pantoprazol Mylan 20 mg, magensaftresistente tabletten

Poland - Pantogee 20 mg

Portugal - PANTOPRAZOL MYLAN GENÉRICOS 20mg

Slovenia - Pantoprazol Mylan 20 mg gastrorezistentne tablete.

Date of leaflet preparation: October 2008

10001098

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 side effect 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.

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 (eg. 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 if you have severe liver problems:

- 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.

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 - Pantoprazole contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

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:

- Swallow the tablets whole with water before a meal
- Do not chew or crush the tablets.

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 (eg. 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 - Do not give Pantoprazole to 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 of Pantoprazole, 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.

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 breathe.

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 1,000 people.

Rare less than 1 in 1,000, but more than 1 in 10,000 people.

Very rare less than 1 in 10,000 people.

Common: headache, upper abdominal pain, diarrhoea, constipation, wind, swelling of breasts (mole).

Uncommon: dizziness, nausea, vomiting, 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).

If any side effect gets serious, or if you notice any side effects not mentioned in the leaflet, please tell your pharmacist or doctor.

5. HOW TO STORE PANTOPRAZOLE

Keep out of the reach and sight of children. 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 45.10 mg of pantoprazole sodium sesquihydrate, equivalent to 40 mg of pantoprazole. The other ingredients are cellulose, microcrystalline lactose monohydrate, croscarmellose sodium, silica colloidal anhydrous and magnesium stearate. The coating contains sodium lauryl sulphate, polyorbate 80, methacrylic acid-ethyl acrylate copolymer, triethylcitrate, polyvinyl alcohol, macrogol 3350, titanium dioxide (E171), talc, iron oxide yellow (E172) and tartrazine aluminium lake (E102).

What Pantoprazole looks like and contents of the pack - The tablets are pale yellow and oblong. Pantoprazole is available in plastic bottles of 7, 14, 15, 28, 30, 50, 56, 60, 100 and 250 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder: Generics [UK] Ltd., Station Close, Potters Bar, Hertfordshire, EN6 1TL, UK.

Manufacturer: McDermott Laboratories t/a Gerard Laboratories, 35/36 Baldyle Industrial Estate, Grange Road, Dublin 13, Ireland.

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

Austria - Pantoprazol Arcano 40 mg mogensoftresistente Tabletten
Belgium - Pantoprazole Mylan 40 mg
Czech Republic, Denmark, Finland, Norway, Slovakia,

Sweden - Pantoprazol Mylan 40 mg

France - PANTOPRAZOLE MYLAN 40 mg, comprimé gastro-résistant

Germany - Pantoprazol duro 40 mg mogensoftresistente Tabletten
Greece - Pantoprazol/Generics 40 mg

Ireland - Protazole 40 mg

Italy - Pantoprazolo Mylan Generics 40 mg

The Netherlands - Pantoprazol Mylan 40 mg, maagsopresistente tabletten

Poland - PantoGen 40 mg

Portugal - PANTOPRAZOL MYLAN GENÉRICOS 40 mg

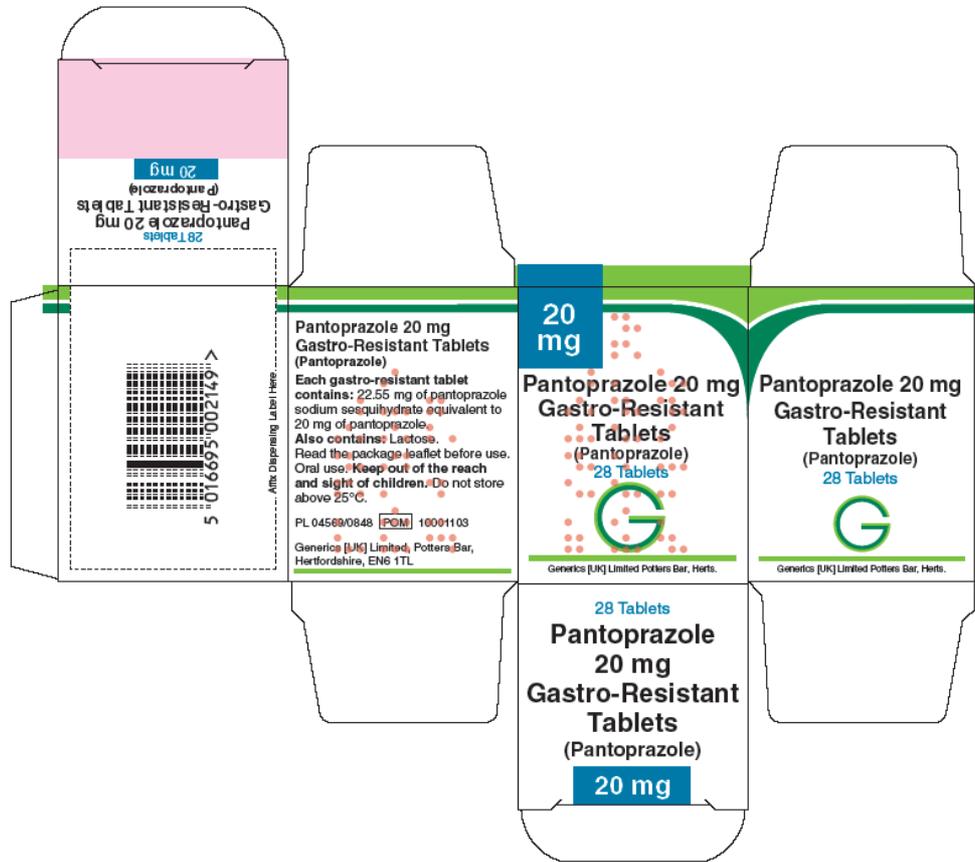
Slovenia - Pantoprazol Mylan 40 mg gastrozestresitene tablete.

Date of leaflet preparation: October 2008

10001097

Module 4 Labelling

Carton - 20mg Tablets



Carton - 40mg Capsules



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Pantoprazole 20mg and 40mg Gastro-Resistant Tablets, or the treatment of duodenal ulcers, benign gastric ulcers, reflux oesophagitis and associated conditions is approvable.

This application is made under Article 10.1 of 2001/83 EC, as amended, Pantoprazole 20mg and 40mg Gastro-Resistant Tablets, have been shown to be generic products of the EU reference products Pantoloc 20mg and 40mg Tablets authorised to Altana Pharma AG, Germany on 6th May 1994 in Sweden.

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.

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.

No new preclinical or clinical studies were conducted with the exception of an additional HRPT locus study and an Ames test at the request of the assessor which is satisfactory for applications of this type. These applications are for generic products and refer to Pantoloc 20mg and 40mg Tablets first authorised to Altana Pharma AG Germany, which have been licensed within the EEA for over 10 years.

During the DC procedure the application for the 20mg strength only was referred to CMD(h) on the 24th September 2008 on the grounds of potential serious risk to public health. The CMS's considered that there was a clear difference in the dissolution profiles between 40mg and 20mg strengths and that dissolution and therefore possible absorption and/or possible degradation if still in acidic environment; occurs at an earlier stage and at a faster rate for the 20 mg tablets than for those containing 40 mg.

Following the discussion at the CMD(h), the RMS positively concluded the procedure with the following conditions:

1. The applicant has committed to perform a biostudy for the 20mg strength and will withdraw the product from the market should the biostudy fail.

2. A request for general advice from Quality Working Party (QWP) on the justification required for statistical methods employed to prove the similarity of dissolution studies.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, batch release and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS has been reassured that the submitted studies have been carried out in accordance with GCP, and agreed ethical principles.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet 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.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Pantoprazole 20mg & 40mg Gastro-Resistant Tablets
Name(s) of the active substance(s) (INN)	Pantoprazole
Pharmacotherapeutic classification (ATC code)	A02 BC02 Proton Pump Inhibitor
Pharmaceutical form and strength(s)	Tablets, 20mg and 40mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1163-4/01-02/DC
Reference Member State	United Kingdom
Member States concerned	UK/H/1163/01/DC: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Sweden, Slovenia, and Slovakia. UK/H/1163/02/DC: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Sweden, Slovenia, and Slovakia. UK/H/1164/01-02/DC: Belgium and France
Marketing Authorisation Number(s)	PL04569/0848-51

Name and address of the authorisation holder	Generics (UK) Ltd Station Close, Potters Bar, Hertfordshire EN6 1TL United Kingdom
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III SCIENTIFIC OVERVIEW AND DISCUSSION QUALITY ASPECTS

S. Active substance

General Information

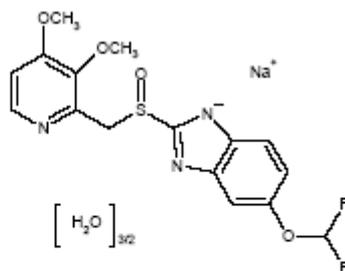
S.1.1 Nomenclature

INN: Pantoprazole sodium Sesquihydrate

Chemical name(s):

5-(difluoromethoxy)-2-(((3,4-dimethoxy-2-pyridinyl)methyl) sulfinyl)-1H-benzimidazole sodium salt sesquihydrate

S.1.2 Structure



MOLECULAR FORMULA: C₁₆H₁₄F₂N₃NaO_{4.5}. 3/2 H₂O

MOLECULAR WEIGHT: 432.39

S.1.3 General Properties Physico-chemical characterisation

The drug substance is a white to beige solid.

Freely soluble in water, soluble in methanol, ethanol and sparingly soluble in isopropyl alcohol, slightly soluble in ethyl acetate and practically insoluble in toluene, hexane and ether.

Pantoprazole is the subject of a European Pharmacopoeia monograph.

Manufacture

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance pantoprazole. The active substance specification provided is acceptable.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active pantoprazole is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data have been provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. Satisfactory re-test periods have been stated based on the stability data provided.

P Medicinal Product

Other ingredients consist of pharmaceutical excipients cellulose microcrystalline, lactose monohydrate, croscarmellose sodium, silica, colloidal anhydrous, magnesium stearate. All ingredients within the body of the tablet comply with relevant Ph Eur monographs

The colour coating contains: polyvinyl alcohol, macrogol 3350, titanium dioxide (E171), talc, iron oxide yellow (E-172), quinoline aluminium yellow lake (E104)-20mg strength only and FD&C yellow #5/tartrazine aluminium lake (E102) 40mg strength only. All the ingredients used for the colour coating comply with their relevant Ph Eur monographs with the exception of iron oxide yellow (E-172) in the absence of Ph Eur monograph is controlled to the National Formulary (NF) and both quinoline aluminium yellow lake (E104) and FD&C yellow #5/tartrazine aluminium lake (E102) comply with in-house specifications.

The gastro-resistant coating contains sodium lauryl sulphate, polysorbate 80, methacrylic acid-ethyl acrylate copolymer, triethylcitrate and talc. All the ingredients used for the gastro-resistant coating comply with their relevant Ph Eur monographs

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.

The development of the product has been described, the choice of excipients is justified and their functions explained.

Dissolution and impurity profiles

Dissolution and impurity profiles for both strengths of drug product were found to be similar to those for the reference products. Dissolution tests comparing the applicant's 40 mg and 20 mg strengths showed differences and these are discussed fully in the clinical section.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Validations of the analytical methods have been presented. Preliminary validation studies have been carried out on three pilot-scale batches and were found to be satisfactory. The batch analysis results show that the finished products meet the specifications proposed. Certificates of analysis have been provided for any working standards used.

Container Closure System

The product is packaged in white high density polyethylene (HDPE) bottles with a screw cap, made of low density polyethylene (LDPE) containing a desiccant capsule. The product is

packaged in sizes of 17, 14, 15, 28, 30, 50, 56, 60, 100, 250 tablets. The MA Holder has stated that not all the pack sizes may be marketed.

Specifications and certificates of analysis for the packaging types used have been provided. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf life of 24 months has been set for the product when stored below 25°C, which is satisfactory.

Bioequivalence

See Clinical Assessment

ADMINISTRATIVE

Expert Report

A pharmaceutical expert has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)

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

Labelling

These are satisfactory.

Patient Information Leaflet

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. The proposed products have met the requirements of a generic medicinal product with respect to qualitative and quantitative content of the active substance used in the proposed and reference products.

III.2 Non Clinical aspects

PHARMACODYNAMICS

Pantoprazole is an irreversible proton pump inhibitor (PPI) that has been developed for the treatment of acid-related gastrointestinal disorders. In common with other drugs of its class, pantoprazole reduces gastric acid secretion through inhibition of the proton pump on the gastric parietal cell.

The benzimidazole sulphoxide of all PPIs is chemically transformed in an acidic environment into a cyclic sulfenamide which then reacts covalently with a cysteine thiol group of the H⁺, K⁺-ATPase. Pantoprazole is the only proton pump inhibitor that binds to cysteine 822, which is buried in the transport domain of the proton pump, and appears inaccessible to glutathione or dithiothreitol (which could reverse the inhibition). In rats, the H⁺, K⁺-ATPase could be reactivated by dithiothreitol and glutathione (SH-reducing agents) after treatment with omeprazole, lansoprazole and rabeprazole, but it could not be reactivated following pantoprazole administration. Therefore, it seems that pantoprazole's effect is more irreversible than the effect of other PPIs, having a longer duration of action. These findings

have also been confirmed at clinical level: in humans, the half-life of the inhibitory effects on gastric secretion was 46 h for pantoprazole and 28 h for omeprazole.

In vivo, pantoprazole has been shown to be very selective in its gastric acid antisecretory and gastric protective actions. In all the studies reviewed, pantoprazole exhibited higher potency in both healing and preventing mucosal ulcers when administered by different routes (intraduodenal, intravenous and oral) compared with other PPIs.

Antibacterial activity against *Helicobacter pylori* has also been detected.

Safety Pharmacology

No references to safety pharmacology studies were found. Because of the selectivity of pantoprazole for its target, non-specific interactions at different cells other than parietal cells are not expected. The extensive clinical use of pantoprazole indicates that there are no safety concerns in respect of hypergastrinaemia.

The risk of thyroid hyperplasia caused by the induction of the UDP-glucuronyl transferase induced by pantoprazole was assessed in rats, showing that pantoprazole had a less pronounced effect on this enzyme than other proton pump inhibitors, such as omeprazole and lansoprazole.

Pharmacokinetics

Pantoprazole is acid-labile and has, therefore, been formulated as encapsulated enteric-coated granules to prevent gastric decomposition and improve systemic bioavailability. Therefore, absorption of pantoprazole begins only after the tablet leaves the stomach.

Absorption studies in animals have not been found in the scientific literature. In clinical studies, it has been shown that the drug is subject to low first-pass hepatic extraction, as reflected in an estimated absolute oral bioavailability of 77%. After oral administration as an enteric-coated tablet in humans, maximum concentrations occurred within 3.0 hours.

Pantoprazole is highly protein bound, has a low volume of distribution and has a short elimination half-life. It was found to cross the placenta in rats. It is extensively metabolised by cytochrome P450, and has a lower capacity to inhibit P450s or induce CYP1A than other PPIs.

In rats and monkeys, the principal route of elimination is renal. Similar results were obtained in normal metaboliser volunteers, in whom approximately 71% of the dose was excreted in the urine and 18% was excreted in the faeces through biliary excretion.

Toxicology

The maximum non-lethal doses obtained in mice, rats and dogs by the i.v. route ranged between 150 and 400 mg/kg while by the oral route these values ranged between 300 and 750 mg/kg.

The repeated-dose toxicity studies revealed that administration of pantoprazole for a 4-week period resulted in lower no-effect doses and tolerated doses after intravenous than after oral administration. The oral tolerated dose was about 5 mg/kg/day (10 fold the pharmacological dose) in rats and 15 mg/kg/day in dogs. The intravenous no-effect dose was 30 mg/kg/day in rats and 40 mg/kg/day in dogs after 4 weeks of treatment. Frequent effects were hypergastrinaemia and morphological changes in the gastric mucosa of both species, as well

as an increase in stomach and liver weight. The effects were reversible and attributable to the pharmacodynamic drug action, i.e. suppression of acid secretion.

The target organs after 12 months' dosing were the stomach, thyroid gland, gall bladder, lungs, spleen and kidney.

Enterochromaffin-like (ECL) cell proliferation and benign and malignant gastric neuroendocrine cell tumours occurred dose-dependently in rats treated with doses from 0.5 to 200 mg/kg. Increased incidences of hepatocellular adenomas and carcinomas occurred in female mice treated orally with 150 mg/kg. These pathological findings are common to other proton-pump inhibitors. It is postulated that they are attributable to the pronounced hypergastrinaemia produced as a secondary effect of almost complete inhibition of acid secretion by the large doses used in the toxicity studies.

Clinical studies showed that there were no significant changes in ECL cell numbers after 2 years' treatment with pantoprazole 40-80 mg/day, and ECL-cell density in the gastric oxyntic mucosa was only slightly increased (from 0.3%-0.5%) after 4 years' treatment with oral pantoprazole (mainly 40 mg/day), in patients with peptic ulcer disease. Indices associated with an increased risk of gastric cancer were not increased in 46 patients with peptic ulcer disease receiving pantoprazole 40-120 mg/day for 5 years.

Reproductive toxicology

Studies performed in rats and rabbits at oral doses showed no adverse effects on fertility and reproductive performance of male and female rats or harm to the fetus related to pantoprazole.

Genetic toxicology

Results of short-term mutagenicity tests showed that pantoprazole is not genotoxic in the Ames test, the mammalian cell forward gene mutation assay, the in vitro rat hepatocyte unscheduled DNA synthesis test and the rat bone marrow cell chromosomal aberration test. Conversely, it was positive in the in vitro human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the in vitro Chinese hamster ovarian cell forward mutation assay.

Although some positive results were obtained in three mutagenicity tests, based on the clinical experience gained by the widespread clinical use in man of medicinal products containing pantoprazole, it can be concluded that this drug is devoid of mutagenic potential.

One of the CMSs raised an objection regarding the drug substance and the fact that the starting material could be genotoxic because of its structure. As it is present as an impurity, it should be controlled in accordance with the level permitted in the Note for Guidance on Genotoxic Impurities. The applicant was requested to provide the full reports on an HRPT locus study and an Ames test that had been carried out which would assist in assessing this question.

The applicant has provided the study reports as requested; the studies were conducted on the starting material.

Report RCC – CCR Study Number 767601

In the Ames test, there was a slight increase in the numbers of revertant colonies in strains TA 100 and WP2uvrA (base pair changes). These increases met (or almost met) the criteria of the laboratory for a positive result but were lower than the numbers produced by the

positive control substances. There was no evidence of mutations in strains TA 1535, TA 1537 or TA 98.

Report RCC – CCR Study Number 808300

The HRPT locus report revealed no evidence of genotoxicity.

Assessment of Applicant's Response

The laboratory conducting the Ames test concluded that the starting material; was genotoxic under the conditions of the tests. Since the increases in the numbers of revertant colonies were not of the same order as those induced by the positive controls, the result is considered not to indicate a severe genotoxic risk; this is supported by the fact that the test in mammalian cells was negative. However, since there is some evidence of genotoxicity, the level of the starting material should be reduced as far as possible, preferably below the threshold of toxic concern of 1.5 µg/person/day.

The applicant has provided reassurances that the level of the starting material will be maintained below the threshold of toxic concern of 1.5 µg/person/day.

Excipients

All the excipients are commonly used in tablet formulations and comply with the European Pharmacopoeia with the exception of the colour, which is controlled by an in-house specification.

Impurities / Residual solvents

The non-clinical overview refers to Module 3 (Quality) for a discussion of the impurities.

The residual solvents in the drug substance are methanol, tert-butyl methyl ether, toluene and isopropyl alcohol.

All the impurities and residual solvents are controlled at acceptable levels.

Environmental risk assessment

The applicant has noted that, since this is an application for a generic product intended to replace an existing product, it is not expected to increase the amount of material reaching the environment. However, a Phase I Environmental Risk Assessment has been conducted. The predicted environmental concentration (PEC) in surface water was 0.20 µg/l, based on the assumption that no metabolism takes place. A PEC of this value would normally trigger a Phase II assessment; however, the applicant has argued that since the metabolism of pantoprazole is nearly complete, only inactive metabolites will be excreted. Since pantoprazole is of a low order of toxicity, it is not anticipated that there will be any risk to the environment should any of the parent compound be excreted.

The pharmacodynamic, pharmacokinetic and toxicological properties of pantoprazole are well known. As pantoprazole is a widely used, well-known active substance, no further studies are required and the applicant has not provided any. An overview based on a literature review is, thus, appropriate. The report refers to 45 publications up to the year 2004 and dated the 18th of April 2007.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

CLINICAL ASPECTS

Introduction

This assessment report covers the main elements of the clinical information provided by the applicant in the dossier. The applicant has submitted two bioequivalence studies performed under fasting and fed conditions. The two study reports are summarised in this assessment report.

The applicant has also provided a satisfactory clinical overview, which covers clinical pharmacology, efficacy and safety. The overview refers to 106 publications up to year 2005.

A formal *Environmental Risk Assessment* has not been performed as the product is intended for generic substitution. Hence, no increase in environmental risk is to be expected compared to that of the reference product.

No *Risk Management Plan* other than documentation of pharmacovigilance system has been provided. For generics, this is acceptable, since the innovator product is not subject to specific risk management measures.

User Consultation: The applicant has performed round one of user readability testing which appears satisfactory.

CLINICAL ASSESSMENT

No new Pharmacokinetic or Pharmacodynamic studies have been submitted and none are required for an application of this kind.

Clinical study reports

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. No new safety issues have been identified.

Bioequivalence Studies

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

Study No.1 (PNL-P4-243) – Fasting State

The objective of the study was to compare the bioavailability of the test 40 mg pantoprazole enteric-coated tablets and the reference 40 mg Eupantol enteric-coated ® (Altana Pharma, France) administered to 30 healthy volunteers under fasting conditions. This was a single-dose, randomized, two-period, two-sequence cross-over study under fasting conditions with a 1 week washout period between doses. The study was conducted by Algorithm Pharma Inc., Montreal, Quebec, Canada. 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 MS 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 rank transformed T_{max}. The main pharmacokinetic parameters are summarised in tables 1 and 2 below.

Table 1. Summary of the main pharmacokinetic parameters of pantoprazole 40mg tablets under fasted conditions n=30.

Parameter	Test		Reference	
	Mean	CV	Mean	CV
C _{max} (ng/mL)	2920.6	37.7	3118.6	33.8
ln (C _{max}) (ng/mL)	7.8909	5.9	7.9640	5.9
T _{max} (hours)*	2.33	33.1	2.33	38.2
AUC _T (ng.h/mL)	6374.9	58.0	6100.0	60.6
ln (AUC _T) ng.h/mL)	8.6022	6.7	8.5558	6.7
AUC _∞ (ng.h/mL)**	6652.5	55.9	6373.4	58.4
AUCT/∞(%)**	97.52	1.5	97.75	1.3
T _{1/2el} (hours)	1.24	38.8	1.23	39.7

*median is presented

Table 2. The 90% confidence intervals and point estimates for comparison of the main pharmacokinetics of Pantoprazole 40 mg tablets under fasted conditions, n=30.

Parameter	Geometric LS means		Ratio	90% Confidence Limits		Power of the Study (%)
	Test	Reference		Lower	Upper	
C _{max}	2672.9	2875.5	92.95	86.06	100.39	>99
AUC _T	5443.7	5196.7	104.75	99.82	109.93	100
AUC _∞ **	5789.0	5551.1	104.29	99.43	109.38	100

**n=29

Thirteen (13) of the thirty-six (36) subjects experienced a total of twenty-one (21) adverse events during the study. Fourteen adverse events (13 different types) were reported after the single dose administration of the Test (A) product and twelve adverse events (10 different types) were reported after the single dose administration of the Reference (B) product.

The events palpitations, abdominal pain, abdominal pain upper, diarrhoea, flatulence, nausea, pain, pain in extremity, headache (2 episodes out of 3), and somnolence were assessed to be possibly related to the study drugs. The other events venipuncture site

swelling, scratch, blood pressure diastolic decreased, dizziness and headache (1 episode out of 3) were assessed to be unlikely or not related to the study drugs.

The results presented herein show that the criteria used to estimate bioequivalence between the two formulations were all fulfilled. The 90% confidence interval of the relative geometric mean of the Test to the Reference formulation for C_{max} , AUC_T and AUC_{∞} was within the acceptance range of 80-125% (that of C_{max} was also within the pre-determined acceptance range of 75-133.33%).

The Test formulation (Pantoprazole 40mg Enteric-Coated tablets, Laboratories Dr Esteve S.A., Spain) is judged to be bioequivalent under fasting conditions to the Reference formulation (Eupantol® 40 mg Enteric-coated tablets, Altana Pharma, France) on the basis of C_{max} and AUC parameters

Study No. 2 (PNL - P4 - 224) – Fed State

The objective of the study was to evaluate post-prandial bioavailability of the test 40 mg pantoprazole tables in comparison with the reference 40 mg Eupantol (®) tablets (Altana Pharma, France) administered to 30 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. The study was conducted by Algorithm Pharma Inc., Montreal, Quebec, Canada. All subjects received the study at the same dosage, i.e. a single dose (40 mg) 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 MS 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 $AUC-t$ 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 rank T_{max} . The main pharmacokinetic parameters are summarised in tables 3 and 4 below.

Table 3. Summary of the main pharmacokinetic parameters of pantoprazole 40mg tablets under fed conditions, n=30.

Parameter	Test		Reference	
	Mean	CV	Mean	CV
C_{max} (ng/mL)	2480.9	30.6	2619.9	26.9
$\ln(C_{max})$ (ng/mL)	7.7599	4.7	7.8362	3.4
T_{max} (hours)*	6.75	50.3	6.00	55.5
AUC_T (ng.h/mL)	4384.2	40.6	4580.5	48.8
$\ln(AUC_T)$ (ng.h/mL)	8.3023	5.1	8.3223	5.7
AUC_{∞} (ng.h/mL)**	4632.0	38.8	4781.5	48.1
AUC_T/∞ (%)**	8.3641	4.9	8.3655	5.7
$T_{1/2el}$ (hours) **	1.20	32.9	1.28	45.2

*median is presented

Table 4. The 90% confidence intervals and point estimates for comparison of the main pharmacokinetics of Pantoprazole 40 mg tablets under fed conditions, n=30.

Parameter	Geometric LS means		Ratio	90% Confidence Limits		Power of the Study (%)
	Test	Reference		Lower	Upper	
C _{max}	2344.7	2530.7	92.65	82.61	103.92	>99
AUC _T	4033.1	4114.5	98.02	92.40	103.98	>99
AUC _∞ **	4290.3	4296.1	99.86	94.43	105.61	>99

**n= 28

Twenty (20) of the thirty-six (36) subjects experienced a total of thirty (30) adverse events during the study. Twenty adverse events (15 different types) were reported after the single dose administration of the Test (A) product and twenty-one adverse events (15 different types) were reported after the single dose administration of the Reference (B) product.

The abdominal pain upper, dizziness, gastrointestinal pain, headache (1 episode out of 2), loose stools, nausea, muscle spasms and urethral discharge were assessed to be possibly related to the drugs. The event nasal congestion was assessed to be unlikely related to the study drugs. The events haematoma, headache (1 episode out of 2), scratch, syncope vasovagal, and venipuncture site swelling were assessed to be not related to the study drugs.

The results presented herein show that the criteria used to estimate bioequivalence between the two formulations were all fulfilled. The 90% confidence interval of the relative geometric mean of the Test to the Reference formulation for C_{max}, AUC_T and AUC_∞ was within the acceptance range of 80-125% (that of C_{max} was also within the pre-determined acceptance range of 75-133.33%).

The Test formulation (Pantoprazole 40mg enteric-coated tablets, Laboratories Dr Esteve S.A., Spain) is judged to be bioequivalent under fed conditions to the Reference formulation (Eupantol® 40 mg enteric-coated tablets, Altana Pharma, France) on the basis of C_{max} and AUC parameters.

Assessor's Comments

The pharmacokinetics of pantoprazole are 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 are considered sufficient for the demonstration of essential similarity between the generic 40mg product and the reference 40mg product.

Certain Member States involved in this DC procedure raised a potential serious risk to public health regarding the applicant's 20mg strength tablet.

Rationale

Dissolution testing comparing the 40 mg biobatch with 3 different batches of the 20 mg strength clearly shows differences in the dissolution profiles at pH 5.5. and especially at 6.8. These differences concern the most relevant time-points (at pH 6.8) between 15 and 30 minutes. Whereas the 20 mg strength batches show a relatively fast dissolution (approx. 95% dissolved after 20 minutes), the dissolution of the 40 mg strength is delayed, with a >95% dissolution achieved at 45 minutes only.

Although the f_2 similarity factor could not be calculated due to high variability in dissolution within the batches, it is obvious that for the time-points 15 minutes, 20 minutes, and 25 minutes the differences in the mean rates are clearly $>10\%$, indicating dissimilarity.

Additional dissolution testing (graphs only) were presented with the Day 205 ARD for a “scaled formulation” (where the amount of coating material was related to the surface area of the substrate) which largely showed similar dissolution profiles for the two strengths, thus indicating that a conclusion on dissimilar dissolution of the formulations applied for is justified.

Moreover, the argumentation that a different dissolution would only affect C_{max} but not AUC values and would therefore not affect clinical performance of the drug, as this is considered to be dependent on AUC only cannot be accepted in this context of the concept of bioequivalence which includes similarity of extent and rate of absorption.

The “Mahalanobis method” which has been applied instead of the calculation of the f_2 similarity factor, allegedly revealed similarity (or rather: excluded differences) regarding dissolution of the products. However, this method has to be regarded as an unvalidated method regarding the possible clinical implications of conclusions on similarity regarding two strengths of one product.

Considering the “first sight” visual differences of the dissolution profiles and the numeric differences as displayed above, the “Mahalanobis method” is may not be able to detect differences regarding dissolution profiles.

The dissolution profiles have clearly shown that the dissolution and therefore possible absorption (and/or possible degradation if still in acidic environment; see differences of dissolution at pH 5.5.) occurs at an earlier stage and at a faster rate for the 20 mg tablets than for those containing 40 mg.

It remains therefore largely unknown whether this will have implications on the pharmacokinetic profile and the speed and total amount of absorption, and hence, bioequivalence.

Therefore, it is concluded that in the case where the requirements of the bioequivalence guideline cannot be fulfilled (an f_2 similarity factor of >50 could not be shown for the comparison of the two strengths because it could not be calculated), and differences in the dissolution profiles are most obvious, the company is requested to perform a separate bioequivalence study for the lower strength.

The biowaiver for the 20 mg tablet strength is not considered acceptable.

The 20mg strength was referred to CMD(h) on the 24th September 2008 on the grounds of potential serious risk to public health. These CMS's considered that there was clear difference in the dissolution profiles between 40mg and 20mg strengths and that dissolution and therefore possible absorption and/or possible degradation if still in acidic environment, occurs at an earlier stage and at a faster rate for the 20 mg tablets than for those containing 40 mg.

Following the discussion at the CMD(h), the RMS positively concluded the procedure with the following conditions:

1. The applicant has committed to perform a biostudy for the 20mg strength and will withdraw the product from the market should the biostudy fail.

2. A request for general advice from Quality Working Party (QWP) on the justification required for statistical methods employed to prove the similarity of dissolution studies.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

Conclusion

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

Based on the discussions during the procedure and the referral to CMD(h) for the 20mg strength only, the UK and CMSs consider the product approvable and have agreed to the amendments made to the SPC and PIL as acceptable.

Approval is therefore recommended on medical grounds.

Benefit-Risk assessment

The application contains an adequate review of published clinical data. Approval is recommended from the clinical point of view.

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 with the exception of an HRPT locus study and an Ames test conducted on the starting material as there were concerns that it caused genotoxicity. The level of the starting material has been reduced as far as possible, below the threshold of toxic concern of 1.5 µg/person/day.

EFFICACY

Bioequivalence data has been demonstrated between the applicant's Pantoprazole Gastro-Resistant Tablets and 40 mg Eupantol enteric-coated ® (Altana Pharma, France). The applicant has committed to perform a biostudy for the 20mg strength and will withdraw the product from the market should the biostudy fail. The SPC, PIL and labelling are satisfactory and consistent with that for the innovator products.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. 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