Public Assessment Report

Decentralised Procedure

Pantoprazole 40mg Gastro-resistant Tablets

UK/H/2769/002DC

UK licence no: PL 25298/0028

Applicant: Brown & Burk UK Ltd
LAY SUMMARY

The MHRA granted Brown & Burk UK Limited a Marketing Authorisation (licence) for the medicinal product Pantoprazole 40mg Gastro-resistant Tablets on 16th May 2011. This is a prescription-only medicine.

Pantoprazole is a gastric proton pump inhibitor. Proton pump inhibitors reduce the amount of stomach acid produced. Pantoprazole is used for treating adults and adolescents 12 years of age and above:

- treatment and prevention of reflux oesophagitis (inflammation of the oesophagus) which is accompanied by the regurgitation of stomach acid

In adults:

- treatment of infections caused by the bacteria *Helicobacter pylori* when given in combination with antibiotic therapy in patients with duodenal ulcers and stomach ulcers
- duodenal and stomach ulcers
- Zollinger-Ellison syndrome and other conditions producing too much acid in the stomach

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Pantoprazole 40mg Gastro-resistant Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
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## Module 1

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<th>Pantoprazole 40mg Gastro-resistant Tablets</th>
</tr>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Pantoprazole sodium sesquihydrate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>40mg</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Brown &amp; Burk UK Ltd</td>
</tr>
<tr>
<td></td>
<td>5 Marryat Close, Hounslow West, Middlesex, TW4 5DQ United Kingdom</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
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</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Germany</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/2769/002/DC</td>
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<tr>
<td><strong>Timetable</strong></td>
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</table>
Module 2
Summary of Product Characteristics

The UK Summary of Product Characteristics (SPC) for Pantoprazole 40mg Gastro-resistant Tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Pantoprazole 40mg Gastro-resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One gastro-resistant tablet contains:
40mg Pantoprazole (as pantoprazole sodium sesquihydrate).

For excipients see 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant coated tablet.
A yellow, oval, biconvex, enteric-coated tablet imprinted with “PT40” in brown ink on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Adults and adolescents 12 years of age and above
• Reflux oesophagitis.

Adults
• Eradication of Helicobacter pylori (H. pylori) in combination with appropriate antibiotic therapy in patients with H. pylori associated ulcers.
• Gastric and duodenal ulcer.
• Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.

4.2 Posology and method of administration
Tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

Recommended dosage:
Adults and adolescents 12 years of age and above:
Reflux oesophagitis
One tablet of Pantoprazole sodium 40mg per day. In individual cases the daily dose can be doubled to two tablets (increase to 2 tablets Pantoprazole sodium 40mg daily), especially when there has been no response to other treatment. A 4 week period is usually required for the treatment of reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Adults:
Eradication of H. pylori in combination with two appropriate antibiotics
In H. pylori positive patients with gastric and duodenal ulcers, eradication of the germ by a combination therapy should be achieved. Considerations should be given to official local guidance (e.g. national recommendations) regarding bacterial resistance and the appropriate use and prescription of antibacterial agents. Depending upon the resistance pattern, the following combinations can be recommended for the eradication of H. pylori:

The following combinations have been shown to be effective:

(a) Pantoprazole sodium 40 mg twice daily,  
plus 1000 mg amoxycillin twice daily  
and 500 mg clarithromycin twice daily
(b) Pantoprazole sodium 40 mg twice daily, plus 400-500 mg metronidazole twice daily (or 500 mg tinidazole) and 250-500 mg clarithromycin twice daily

(c) Pantoprazole sodium 40 mg twice daily, plus 1000 mg amoxicillin twice-daily and 400-500 mg metronidazole twice-daily (or 500 mg tinidazole)

In combination therapy for eradication of *H. pylori* infection, the second Pantoprazole sodium tablet should be taken 1 hour before the evening meal. The combination therapy is implemented for 7 days in general and can be prolonged for a further 7 days to a total duration of up to two weeks. If, to ensure healing of the ulcers, further treatment with pantoprazole is indicated, the dose recommendations for duodenal and gastric ulcers should be considered.

If combination therapy is not an option, e.g. if the patient has tested negative for *H. pylori*, the following dose guidelines apply for Pantoprazole sodium monotherapy:

**Treatment of gastric ulcer**
One tablet of Pantoprazole sodium 40mg per day. In individual cases the dose may be doubled (increase to 2 tablets Pantoprazole sodium daily) especially when there has been no response to other treatment. A 4-week period is usually required for the treatment of gastric ulcers. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

**Treatment of duodenal ulcer**
One tablet of Pantoprazole sodium 40mg per day. In individual cases the dose may be doubled (increase to 2 tablets Pantoprazole sodium daily) especially when there has been no response to other treatment. A duodenal ulcer generally heals within 2 weeks. If a 2-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

**Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions**
For the long-term management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions patients should start their treatment with a daily dose of 80mg (2 tablets of Pantoprazole sodium 40mg). Thereafter, the dose can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage above 160mg pantoprazole per day 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.

**Special populations**

**Elderly:**
No dose adjustment is necessary in elderly patients.

**Children below twelve years of age:**
Pantoprazole sodium 40 mg is not recommended for use in children below twelve years of age due to limited data on safety and efficacy in this age group.

**Renal Impairment**
No dose adjustment is necessary in patients with impaired renal function. Pantoprazole sodium 40mg must not be used in combination treatment for eradication of *H. pylori* in patients with impaired renal function since currently no data are available on the efficacy and safety of Pantoprazole sodium 40mg in combination treatment for these patients.

**Hepatic Impairment**
A daily dose of 20 mg pantoprazole (1 tablet of 20 mg pantoprazole) should not be exceeded in patients with severe liver impairment. Pantoprazole sodium 40mg must not be used in combination treatment for eradication of *H. pylori* in patients with moderate to severe hepatic dysfunction since currently no data are available on the efficacy and safety of Pantoprazole sodium 40mg in combination treatment of these patients (see section 4.4).
4.3 Contraindications
Hypersensitivity to the active substance, substituted benzimidazoles or to any of the other excipients or of the combination partners.

4.4 Special warnings and precautions for use

Hepatic Impairment
In patients with severe liver impairment, the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise in liver enzymes, Pantoprazole therapy should be discontinued (see section 4.2).

Combination therapy
In the case of combination therapy, the summaries of product characteristics of the respective medicinal products should be observed.

In presence of alarm symptoms
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis.

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

Co-administration with atazanavir
Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir. A pantoprazole dose of 20 mg per day should not be exceeded.

Influence on vitamin B12 absorption
In patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

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

Gastrointestinal infections caused by bacteria
Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with Pantoprazole sodium may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as Salmonella and Campylobacter.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of pantoprazole on the absorption of other medicinal products
Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may reduce the absorption of drugs with a gastric pH dependent bioavailability, e.g. some azole antifungals as ketoconazole, itraconazole, posaconazole and other medicine as erlotinib.

HIV medications (atazanavir)
Co-administration of atazanavir and other HIV medications whose absorption is pH-dependent with proton-pump inhibitors might result in a substantial reduction in the bioavailability of these HIV medications and might impact the efficacy of these medicines. Therefore, the co-administration of proton pump inhibitors with atazanavir is not recommended (see section 4.4).

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

**Other interactions studies**
Pantoprazole is extensively metabolised in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.

Interaction studies with drugs also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions.

Results from a range of interaction studies demonstrate that pantoprazole does not effect the metabolism of active substances metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with p-glycoprotein related absorption of digoxin.

There were no interactions with concomitantly administered antacids.

Interaction studies have also been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

### 4.6 Pregnancy and lactation

**Pregnancy**

There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Pantoprazole sodium should not be used during pregnancy unless clearly necessary.

**Lactation**

Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Pantoprazole sodium should be made taking into account the benefit of breast-feeding to the child and the benefit of Pantoprazole sodium therapy to women.

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

Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.

### 4.8 Undesirable effects

Approximately 5% of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhoea and headache, both occurring in approximately 1% of patients.

The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:

- Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a "not known" frequency.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions with pantoprazole in clinical trials and post-marketing experience
## Frequency

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known</th>
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<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thrombocytopenia, Leukopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Hypersensitivity (including anaphylactic reactions and anaphylactic shock)</td>
<td></td>
<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td>Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes</td>
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<td>Hyponatraemia</td>
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<tr>
<td>Psychiatric disorders</td>
<td>Sleep disorders</td>
<td></td>
<td>Depression (and all aggravations)</td>
<td>Disorientation (and all aggravations)</td>
<td>Hallucination, Confusion, (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Disturbances in vision (blurred vision)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhoea; Nausea/Vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Liver enzymes increased (transaminases, γ-GT)</td>
<td></td>
<td>Bilirubin increased</td>
<td></td>
<td>Hepatocellular injury; Jaundice; Hepatocellular failure</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash/exanthema/eruption; Pruritus</td>
<td></td>
<td>Urticaria; Angioedema</td>
<td></td>
<td>Stevens-Johnson Syndrome, Lyell-Syndrome; Erythema</td>
</tr>
</tbody>
</table>
4.9 Overdose
There are no known symptoms of over dosage in man.
Systemic exposure with up to 240mg administered intravenously over 2 minutes were well tolerated.
As pantoprazole is extensively protein bound, it is not readily dialysable.

In the case of overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Proton Pump Inhibitors. ATC code: A02BC02.

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

Pantoprazole is converted to its active form in the acidic environment in 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 within 2 weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases 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, it can inhibit 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 upper limit of normal. 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, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments (see section 5.3) 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 according to results in animal studies.

5.2 Pharmacokinetic properties
Absorption
Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40 mg oral dose. On average at about 2.5 h p.a. the maximum serum concentrations of about 2-3 $\mu$g/ml are achieved, and these values remain constant after multiple administration.

Pharmacokinetics do not vary after single or repeated 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.

**Distribution**

Pantoprazole's plasma protein binding is about 98%. Volume of distribution is about 0.15 l/kg

**Elimination**

The substance is almost exclusively metabolised in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathway include oxidation by CYP3A4. Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. 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). Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole; the rest are excreted in the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole, which is conjugated with sulphate. The half-life of the main metabolites (about 1.5 hours) is not much longer than that of pantoprazole.

**Characteristics in patients/special groups of subjects**

Approximately 3% of the European population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of pantoprazole.

No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are 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-time values increased to between 7 and 9 hours and the AUC values increased by a factor of 5 to 7, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.

No dose reduction is required when pantoprazole is administered to patients with impaired 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.

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

**Children**

Following administration of single oral doses of 20 or 40 mg pantoprazole to children aged 5-16 years AUC and $C_{\text{max}}$ were in the range of corresponding values in adults. Following administration of single i.v. doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 - 16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

### 5.3 Preclinical safety data

Preclinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.
In the two-year carcinogenicity studies 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 the two-year rodent studies an increased number of liver tumors was observed in rats 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). 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 harmful effects on the thyroid glands are expected.

In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg. 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

Tablet core:
mannitol
crospovidone
anhydrous sodium carbonate
hydroxypropylcellulose
calcium stearate

Tablet coating:
hypromellose
yellow iron oxide (E172)
methacrylic acid-ethylacrylate -copolymer (1:1)
triethyl citrate.

Printing ink:
shellac
black iron oxide (E172)
red iron oxide (E172)
propylene glycol
yellow iron oxide (E172).

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
No special precautions for storage

6.5 Nature and contents of container
Packs: Cartons containing ALU/ALU blisters and HDPE container with polypropylene cap containing a desiccant insert.

Cartons of 7, 14, 15, 28, 30, 50, 56, 60, 90, 98, 100, 140, 280, 500 & 700 tablets.
HDPE container of 1000 tablets.
6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Brown & Burk UK Ltd
5 Marryat Close
Hounslow West
Middlesex
TW4 5DQ
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 25298/0028

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
16/05/2011

10 DATE OF REVISION OF THE TEXT
16/05/2011
Module 3
Patient Information Leaflet

PAR-Pantoprazole 40mg Gastro-resistant Tablets   UK/H/2769/002/DC

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Pantoprazole Tablets are and what they are used for
2. How to take Pantoprazole Tablets
3. Possible side effects
4. How to store Pantoprazole Tablets
5. Further information

1. WHAT PANTOPRAZOLE TABLETS ARE AND WHAT THEY ARE USED FOR

Pantoprazole is a selective “proton pump inhibitor”, a medicine which reduces the amount of acid produced in your stomach. It is used for treating acid-related diseases of the stomach and intestine.

Pantoprazole is used for treating:
- Adults and adolescents 12 years of age and above:
  - Reflux oesophagitis, an inflammation of your oesophagus (the tube which connects your throat to your stomach) accompanied by the regurgitation of stomach acid.
- Adults:
  - An infection with a bacterium called Helicobacter pylori in patients with duodenal ulcers and stomach ulcers in combination with two antibiotics (Eradication therapy).
The aim is to get rid of the bacteria and so reduce the likelihood of these ulcers returning.
  - Stomach and duodenal ulcers.
  - Zollinger-Ellison Syndrome and other conditions producing too much acid in the stomach.

2. BEFORE YOU TAKE PANTOPRAZOLE TABLETS

Do not take Pantoprazole Tablets:
- If you are allergic (hypersensitive) to pantoprazole, or to any of the other ingredients of Pantoprazole (see section 6).
- If you are allergic to medicines containing other proton pump inhibitors.

Take special care with Pantoprazole Tablets:
- If you have severe liver problems. Please tell your doctor if you ever had problems with your liver in the past.
- He will check your liver enzymes more frequently, especially when you are taking Pantoprazole as a long-term treatment. (In the case of a rise in liver enzyme the treatment should be stopped.
- If you have reduced body stores or risk factors for reduced vitamin B12 and receive pantoprazole long-term treatment. As with all acid reducing agents, pantoprazole may lead to a reduced absorption of vitamin B12.
- If you are taking a medicine containing aluminium (for the treatment of HIV-infection) at the same time as pantoprazole, ask your doctor for specific advice.

Tell your doctor immediately if you notice any of the following symptoms:
- an unintentional loss of weight
- repeated vomiting
- difficulty in swallowing
- vomiting blood
- you feel sick and feel weak (anemia)
- you notice blood in your stools
- severe and/or persistent diarrhoea, as Pantoprazole has been associated with a small increase in infectious diarrhoea.

Your doctor may decide that you need some tests to rule out malignant disease because pantoprazole also alleviates the symptoms of cancer and could cause delay in diagnosing it if your symptoms continue in spite of your treatment, further investigations will be considered.

If you take Pantoprazole Tablets 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.

3. HOW TO TAKE PANTOPRAZOLE TABLETS

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

When and how should you take Pantoprazole Tablets?

Take the tablets 1 hour before a meal without chewing or breaking them and swallow them whole with some water.

Unless told otherwise by your doctor, the usual dose is:
- Adults and adolescents 12 years of age and above:
  - To treat reflux oesophagitis: This should last for a year. Your doctor may tell you to increase to 2 tablets daily. The treatment period for reflux oesophagitis is usually between 4 and 8 weeks. Your doctor will tell you how long to take your medicine.
- Adults:
  - For the treatment of an infection with a bacterium called Helicobacter pylori in patients with duodenal ulcers and stomach ulcers in combination with two antibiotics (Eradication therapy).
  - One tablet, two times a day plus two antibiotic tablets of either amoxicillin, clarithromycin and metronidazole (or trimetrexate), each to be taken two times a day with your pantoprazole tablet. Take the first pantoprazole tablet 1 hour before breakfast and the second pantoprazole tablet 1 hour before your evening meal. Follow your doctor’s instructions and make sure you read the package leaflets for these antibiotics. The usual treatment period is one to two weeks.

Pregnancy and breastfeeding
There are no adequate data from the use of pantoprazole in pregnant women. Excretion into human milk has been reported if you are pregnant, or think you may be pregnant, or if you are breastfeeding, you should use this medicine only if your doctor considers the benefit to you greater than the potential risk for your unborn child/baby.

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

Driving and using machines
If you experience side effects like dizziness or disturbance of vision, you should not drive or operate machines.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescription.

- 14 -
For the treatment of stomach and duodenal ulcers. The usual dose is one tablet a day. After consultation with your doctor, the dose may be doubled.

Your doctor will tell you how long to take your medicine. The treatment period for stomach ulcers is usually between 4 and 8 weeks. The treatment period for duodenal ulcers is usually between 2 and 4 weeks.

For the long-term treatment of Zollinger-Ellison Syndrome and of other conditions in which too much stomach acid is produced. The recommended starting dose is usually two tablets a day.

Take the two tablets 1 hour before a meal. Your doctor may later adjust the dose, depending on the amount of stomach acid you produce. If prescribed more than two tablets a day, the tablets should be taken twice daily.

If your doctor prescribes a daily dose of more than four tablets a day, you will be told exactly when to stop taking the medicine.

Special patient groups:
- If you have kidney problems, moderate or severe liver problems, you should not take Pantoprazole for eradication of Helicobacter pylori.
- If you suffer from severe liver problems, you should not take more than one tablet 20 mg pantoprazole a day (for this purpose tablets containing 20 mg pantoprazole are available).
- Children below 12 years. These tablets are not recommended for use in children below 12 years.

If you take more Pantoprazole Tablets than you should
Consult your doctor or pharmacist. There are no known symptoms of overdose.

If you forget to take Pantoprazole Tablets
Do not take a double dose to make up for the forgotten dose. Take your next, normal dose at the usual time.

If you stop taking Pantoprazole Tablets
Do not stop taking these tablets without first taking your doctor or pharmacist.

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

6. POSSIBLE SIDE EFFECTS

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

The frequency of possible side effects listed below is defined using the following convention: very common (affects more than 1 in 10 people who take this medicine); common (affects 1 to 10 people in 100 people); uncommon (affects 1 to 10 people in 1,000 people); rare (affects 1 in 10,000 people).

Side effects which may be serious:
- Nausea (affects less than 1 in 10 people who take this medicine).
- Diarrhoea (affects less than 1 in 10 people who take this medicine).
- Headache (affects less than 1 in 10 people who take this medicine).
- Rash (affects less than 1 in 10 people who take this medicine).
- Dizziness (affects less than 1 in 10 people who take this medicine).
- Fatigue (affects less than 1 in 10 people who take this medicine).
- Muscle weakness (affects less than 1 in 10 people who take this medicine).
- Inflammation of the mouth and throat (affects less than 1 in 10 people who take this medicine).
- Mouth ulcers (affects less than 1 in 10 people who take this medicine).
- Severe skin rash (affects less than 1 in 10 people who take this medicine).

Other side effects:
- Nausea (affects less than 1 in 10 people who take this medicine).
- Diarrhoea (affects less than 1 in 10 people who take this medicine).
- Headache (affects less than 1 in 10 people who take this medicine).
- Dizziness (affects less than 1 in 10 people who take this medicine).
- Fatigue (affects less than 1 in 10 people who take this medicine).
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- Mouth ulcers (affects less than 1 in 10 people who take this medicine).
- Severe skin rash (affects less than 1 in 10 people who take this medicine).

Possible side effects include:
- Nausea (affects less than 1 in 10 people who take this medicine).
- Diarrhoea (affects less than 1 in 10 people who take this medicine).
- Headache (affects less than 1 in 10 people who take this medicine).
- Dizziness (affects less than 1 in 10 people who take this medicine).
- Fatigue (affects less than 1 in 10 people who take this medicine).
- Muscle weakness (affects less than 1 in 10 people who take this medicine).
- Inflammation of the mouth and throat (affects less than 1 in 10 people who take this medicine).
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- Mouth ulcers (affects less than 1 in 10 people who take this medicine).
- Severe skin rash (affects less than 1 in 10 people who take this medicine).

6. FURTHER INFORMATION

What Pantoprazole Tablets contain
- The active substance is pantoprazole. Each tablet contains 40 mg of pantoprazole (as sodium sesquicarbonate).
- The other ingredients are mannitol, croscarmellose sodium, magnesium carbonate, hydroxypropyl cellulose, calcium stearate, hydroxypropyl methylcellulose, yellow iron oxide (E172), black iron oxide (E172), methacrylic acid-methacrylate copolymer (1:1), triethyl citrate, shellac and propylene glycol.

What Pantoprazole Tablets look like and contents of the pack

A yellow, oval, biconvex enterico-coated tablet imprinted with “P405” on one side in brown ink.

Packets: Cartons containing aluminium blisters and HDPE container with polystyrene cap containing a desiccant insert.

Pantoprazole 40 mg tablets are available in the following pack-sizes:
- Cartons of T 14, 25, 50, 50, 60, 90, 90, 100, 100, 140, 280, 509 and 759 tablets.
- HDPE container of 1000 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
- Brown & Bush UK Ltd
- 5 Merrywell Close, Mountview West
- Middlesex, TW5 9DO, UK

This leaflet was last approved on 19/04/2011
Module 4
Labelling

Pantoprazole 40mg Film-Coated Tablets
Carton

Blister Foil
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
On 11th April 2011, Germany and the UK agreed to grant a Marketing Authorisation (MA) to Brown and Burk UK Limited for the medicinal product Pantoprazole 40mg Gastro-resistant Tablets. The MA was granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (RMS UK/H/2769/002/DC). After the national phase, an MA was granted in the UK on 16th May 2011 (PL 25298/0028). This product is a prescription-only medicine.

This is an abridged application for Pantoprazole 40mg Gastro-resistant Tablets submitted under Article 10.1 of 2001/83 EC, as amended. This application refers to the UK reference medicinal product Protium® 40mg Gastro-resistant Tablets first authorised in the UK to Altana Pharma AG (PL 20141/0002) on 4th June 1996. The licence underwent a Change of Ownership (CoA) procedure on 16th January 2008 and is currently authorised to Nycomed GmbH. The reference product has been registered in the EEA for more than 10 years, hence the period of data exclusivity has expired.

Pantoprazole a substituted benzimidazole derivative, is an irreversible proton pump (H⁺/K⁺-ATPase) inhibitor (PPI) that decreases acid secretion from gastric parietal cells. PPIs are substituted benzimidazoles that accumulate in the highly acidic environment of the parietal-cell canalicular lumen and are activated by conversion to cyclic sulfenamides. PPIs reduce stomach acid by blocking the enzyme system responsible for active transport of acid into the gastrointestinal lumen of the gastric parietal cell, also known as the ‘proton pump’. Inactivation of proton pumps is accomplished by covalent binding of sulfenamides to the proton pumps’ cysteine residues.

It is used for the treatment of acid related disease like upper gastrointestinal ulceration and oesophageal reflux disease and – in conjunction with antibiotics – for the eradication of Helicobacter pylori.

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that the application is based on essential similarity to products that have been licensed for over 10 years.

The application is supported by two bioequivalence studies under fed and fasting conditions comparing the pharmacokinetic profile of the test product, Pantoprazole 40mg Gastro-resistant Tablets, to that of the reference product, Protium® 40mg Gastro-resistant Tablets (Nycomed GmbH). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or 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 considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. The excipients used in the product formulation are commonly used pharmaceutical compounds. There are no environmental concerns associated with the method of manufacture or formulation of the product.

II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Pantoprazole 40mg Gastro-resistant Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Pantoprazole sodium sesquihydrate</td>
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<tr>
<td>Pharmacotherapeutic classification</td>
<td>Proton Pump Inhibitor (A02BC02)</td>
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<td>(ATC code)</td>
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<td>Pharmaceutical form and strength(s)</td>
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<td>UK/H/2769/002/DC</td>
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<td>Procedure</td>
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<td>Reference Member State</td>
<td>United Kingdom</td>
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<tr>
<td>Member States concerned</td>
<td>Germany</td>
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<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 25298/0028</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Brown &amp; Burk UK Ltd</td>
</tr>
<tr>
<td></td>
<td>5 Marryat Close, Hounslow West, Middlesex,</td>
</tr>
<tr>
<td></td>
<td>TW4 5DQ</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

Nomenclature
INN name: Pantoprazole Sodium Sesquihydrate

Chemical name:
Sodium 5-Difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sesquihydrate

III.1.2 Structure

Molecular formula: C₁₆H₁₄F₂N₃NaO₄S·1.5H₂O
Molecular Weight: 432.4

III.1.3 General properties

Physical form: White or almost white, crystalline powder.
Solubility: Freely soluble in water and ethanol (96 per cent), practically insoluble in water.

The active substance, pantoprazole sodium sesquihydrate, is the subject of a European Pharmacopoeia (EP) monograph.

All aspects of the manufacture and control of the active substance pantoprazole sodium sesquihydrate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

The active substance is stored in appropriate packaging. Satisfactory specifications have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph.Eur. requirements and complies with Directive 2002/72/EC (as amended) and is suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support the 48 months re-test period that has been applied.
**DRUG PRODUCT**

**Description and Composition**

Pantoprazole 40mg Gastro-resistant Tablets are presented as yellow, oval, biconvex, enteric-coated tablets imprinted with “PT40” in brown ink on one side. Each gastro-resistant tablet contains 40mg of the active ingredient pantoprazole, as pantoprazole sodium sesquihydrate.

Other ingredients consist of pharmaceutical excipients namely mannitol, crospovidone, anhydrous sodium carbonate, hydroxypropylecellulose, calcium stearate making up the tablet core; hypromellose, yellow iron oxide (E172), methacrylic acid-ethylacrylate-copolymer (1:1) and triethyl citrate making up the tablet coating and shellac, balsek iron oxide (E172), red iron oxide (E172), propylene glycol, yellow iron oxide (E172) making up the printing ink.

All excipients used comply with their respective European Pharmacopoeial monograph with the exception of the iron oxide which is controlled to US Pharmacopoeia (USP). Satisfactory Certificates of Analysis have been provided for all excipients. Appropriate justification for the inclusion of each excipient has been provided.

The MAH has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the product.

**Pharmaceutical development**

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The objective was to develop a robust, stable, generic formulation, bioequivalent to the innovator product, Protium® 40mg Gastro-resistant Tablets, Nycomed GmbH, UK (PL 31752/0002).

Comparative dissolution and impurity profiles were provided for the test and reference products and were found to be similar.

**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. Process validation studies have been conducted and are accepted. The validation data demonstrated consistency of the manufacturing process.

**Finished Product Specification**

Finished product specifications are provided for both release and shelf-life, and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.
Container-Closure System
The finished product is licensed for marketing in either high density polyethylene (HDPE) bottles with polypropylene caps containing a desiccant insert or blister packs composed of aluminium. Both presentations are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons; the blister packs are licensed in pack sizes of 7, 14, 15, 28, 30, 50, 56, 60, 90, 98, 100, 140, 280, 500 & 700 tablets and the HDPE container in pack size of 1000 tablets only. Specifications and Certificates of Analysis have been provided.

The MA Holder (MAH) has not provided mock-ups for all pack sizes to be marketed however, the MAH has committed to submitting the proposed packaging/labelling for any pack size before it is marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 24 months has been set which is satisfactory. There are no specific storage conditions for this medicinal product which is satisfactory.

Bioequivalence Study
Two bioequivalence studies were presented under fasting and fed conditions comparing the test product, Pantoprazole 40mg Gastro-resistant Tablets, to the reference product; Protium® 40mg Gastro-resistant Tablets, Nycomed GmbH, UK (PL 31752/0002).

An evaluation of the bioequivalence studies can be found in the Clinical Aspects section of this report.

Expert Report
A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are pharmaceutically acceptable. Text versions of the PIL and labels have been provided and are satisfactory. In accordance with the medicines legislation, the product shall not be marketed in the UK until prior approval of the product labelling and leaflet mock-ups has been obtained.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.
Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

III.2 NON-CLINICAL ASPECTS
The pharmacological, 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 provided none. An overview based on a literature review is thus appropriate. An adequate overview has been written by as suitably qualified person.

There are no objections to the approval of pantoprazole from a non-clinical point of view.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of this application, the marketing authorisation holder has submitted the following two bioequivalence studies under fasting and fed conditions. The reference product used for the bioequivalence studies is Protium® 40mg Gastro-resistant Tablets (Altana Pharma AG, Germany) and is considered to be equivalent to the UK reference product Protium 40mg Gastro-resistant Tablets, Nycomed GmbH, UK (PL 31752/0002).

Study 1
This is an open label, randomised, balanced, two-treatment, two-period, two-sequence, crossover, single-dose comparative oral bioavailability study of Pantoprazole 40mg Gastro-resistant Tablets (test product) and Protium 40mg Gastro-resistant Tablets (Altana Pharma AG, Germany) in healthy adults under fasting conditions.

The study was conducted in compliance with Good Clinical Practice (ICH-GCP) and Good Laboratory Practice.

Study design
A single dose of the investigational products (1 tablet of 40mg) was administered orally to each subject in each period with 240 ml of water after an overnight fast of at least 10 hours.

Serial blood sampling before dosing and up to 24 hours after drug administration was carried out.

A washout period of 8 days was maintained between the two dosing periods in each group which is sufficient time for pantoprazole to be eliminated from the body.

A validated LC-MS/MS analytical methodology was used for quantification of pantoprazole from the human plasma samples. Primary variables analysed were: \( C_{\text{max}} \), \( \text{AUC}_{0,\text{t}} \) and \( \text{AUC}_{0,\infty} \) and additional pharmacokinetic parameters were \( t_{\text{max}}, t_{1/2}, K_{\text{el}} \) and AUC% Extrapol.

Statistical methods
Mean, standard deviations and coefficients of variation were calculated for the demographic variables at each individual time point as well as for the
pharmacokinetic parameters for Pantoprazole and in addition the geometric means, ratios of means and 90% Confidence Intervals for $C_{\text{max}}$, AUC$_{0-\infty}$ and AUC$_{0-t}$, were also calculated.

The untransformed and ln-transformed pharmacokinetic parameters ($C_{\text{max}}$, AUC$_{0-\infty}$ and AUC$_{0-t}$) were statistically analysed. ANOVA was performed on log transformed pharmacokinetic parameters $C_{\text{max}}$, AUC$_{\infty}$ and AUC$_{0-t}$.

Results

ANOVA 90% CI (Log transformed) and CV% for primary and secondary parameters of pantoprazole (test vs. reference).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio (T/R%)</th>
<th>90% Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ratio test/reference)</td>
<td>4356.639</td>
<td>4554.775</td>
<td>95.65</td>
<td>90.29 – 101.33</td>
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<tr>
<td>AUC$_{0.5}$ (ratio test/reference)</td>
<td>155897.129</td>
<td>16752.427</td>
<td>94.89</td>
<td>91.26 – 98.67</td>
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<tr>
<td>AUC$_{0-\infty}$ (ratio test/reference)</td>
<td>16810.519</td>
<td>17750.281</td>
<td>94.71</td>
<td>91.09 – 98.46</td>
</tr>
</tbody>
</table>

Conclusion

The 90% Confidence Intervals for the geometric ratios from Ln-transformed data of $C_{\text{max}}$, AUC$_{0-\infty}$ and AUC$_{0-t}$ of Pantoprazole, were within the bioequivalence acceptance range (80-125%). Based on these results, Pantoprazole 40mg gastro-resistant tablets (Test) is bioequivalent with that of Protium® 40mg gastro-resistant tablets (Reference) of Altana Phanna AG, Germany, under fasting conditions.

Study 2

This is an open label, randomised, two-treatment, two-sequence, crossover, single dose comparative oral bioavailability study of Pantoprazole 40mg Gastro-resistant Tablets (test product) and Protium® 40mg Gastro-resistant Tablets (Altana Pharma AG, Germany) in healthy adults under fed conditions.

The study was conducted in compliance with Good Clinical Practice (ICH-GCP) and Good Laboratory Practice.

Study design

A single dose of the investigational products (1 tablet of 40mg) was administered orally to each subject in each period after an overnight fast of at least 10 hours and 30 minutes after receiving a high fat and high calorie breakfast. The tablets were taken with 240ml of water.

Serial blood sampling before dosing and up to 48 hours after drug administration was carried out in each group.

A washout period of 8 days was maintained between the two dosing periods in each group which is sufficient time for lansoprazole to be eliminated from the body.

A validated LC-MS/MS analytical methodology was used for quantification of pantoprazole from the human plasma samples. Primary variables analysed were: $C_{\text{max}}$, AUC$_{0.5}$ and AUC$_{0-\infty}$ and additional pharmacokinetic parameters were $t_{\text{max}}$, $t_{1/2}$, $K_{\text{el}}$ and AUC% Extrapolated.
Statistical methods
Mean, standard deviations and coefficients of variation were calculated for the demographic variables at each individual time point as well as for the pharmacokinetic parameters for Pantoprazole and in addition the geometric means, ratios of means and 90% Confidence Intervals for $C_{\text{max}}$, $AUC_{0-\infty}$ and $AUC_{0-t}$, were also calculated.

The untransformed and ln-transformed pharmacokinetic parameters ($C_{\text{max}}$, $AUC_{0-\infty}$ and $AUC_{0-t}$) were statistically analysed. ANOVA was performed on log transformed pharmacokinetic parameters $C_{\text{max}}$, $AUC_{\infty}$ and $AUC_{0-t}$.

Results
ANOVA 90% CI (Log transformed) and CV% for primary and secondary parameters of pantoprazole (test vs. reference).

<table>
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<tr>
<th>Variable</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio (T/R%)</th>
<th>90% Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ratio test/reference)</td>
<td>3032.422</td>
<td>3436.105</td>
<td>88.25</td>
<td>83.34 – 93.46</td>
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<td>$AUC_{0-t}$ (ratio test/reference)</td>
<td>10510.140</td>
<td>10714.267</td>
<td>98.09</td>
<td>93.76 – 102.63</td>
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<tr>
<td>$AUC_{0-\infty}$ (ratio test/reference)</td>
<td>10628.854</td>
<td>10835.116</td>
<td>98.10</td>
<td>93.75 – 102.64</td>
</tr>
</tbody>
</table>

Conclusion
The 90% Confidence Intervals for the geometric ratios from ln-transformed data of $C_{\text{max}}$, $AUC_{0-\infty}$ and $AUC_{0-t}$ of Pantoprazole, were within the bioequivalence acceptance range (80-125%). Based on these results, Pantoprazole 40mg gastro-resistant tablets (Test) is bioequivalent with that of Protium® 40mg gastro-resistant tablets (Reference) of Altana Phanna AG, Germany under fed conditions.

Pharmacodynamics
No new pharmacodynamic data have been submitted and none is required for this application.

Clinical efficacy
No new efficacy data have been submitted and none is required for this application.

Clinical safety
No new safety data have been submitted and none are required for this application.

BENEFIT RISK ASSESSMENT
The benefit-risk ratio is considered favourable.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
Summary of Product Characteristics (SmPC)
The approved SmPC is consistent with those for the reference product and are acceptable.
Product Information Leaflet (PIL)
The final wording for the PIL is in line with the approved SmPC and is satisfactory.

Labelling
The labelling is satisfactory.

Expert Report
A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

CONCLUSIONS
There are no objections to the approval of this product from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Pantoprazole 40mg Gastro-resistant Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Pantoprazole 40mg Gastro-resistant Tablets and the reference product Protium® 40mg Gastro-resistant Tablets (Altana Pharma AG, Germany) under fasting and fed conditions.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

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

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<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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