Public Assessment Report

Decentralised Procedure

Pantoprazole 40 mg gastro-resistant tablets

UK/H/3355/002/DC
UK licence number: PL 34771/0005

Macleods Pharma UK Limited
LAY SUMMARY

On 22 December 2011, the MHRA granted Macleods Pharma UK Limited a Marketing Authorisation (licence) for the medicinal product, Pantoprazole 40 mg gastro-resistant tablets. This is a prescription-only medicine (POM).

The active ingredient, pantoprazole, belongs to a group of medicines called proton pump inhibitors. It blocks the ‘pump’ that produces stomach acid. Hence it reduces the amount of acid in your stomach.

Pantoprazole 40 mg gastro-resistant tablets are used for treating acid-related diseases of the stomach and intestine, including:

- moderate to severe forms of reflux oesophagitis (an inflammation of your oesophagus accompanied by the regurgitation of stomach acid)
- 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
- duodenal ulcers
- 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. It was judged that the benefits of Pantoprazole 40 mg gastro-resistant tablets outweigh the risks; hence a Marketing Authorisation has been granted.
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# Module 1

## Information about Initial Procedure

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<thead>
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<th>Product Name</th>
<th>Pantoprazole 40 mg gastro-resistant tablets</th>
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<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
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<td>Active Substance</td>
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<tr>
<td>Form</td>
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<tr>
<td>Strength</td>
<td>40 mg</td>
</tr>
<tr>
<td>MA Holder</td>
<td>Macleods Pharma UK Limited</td>
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<td>Golden Gate Lodge,</td>
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<td>Crewe Hall</td>
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<td>Timetable</td>
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Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Pantoprazole 40 mg gastro-resistant tablets (PL 34771/0005) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Pantoprazole 40 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each gastro-resistant tablet contains
45.1 mg of pantoprazole sodium sesquihydrate equivalent to 40 mg of pantoprazole

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant tablet
Yellow oval, biconvex enteric coated tablets imprinted ‘CL25’ on one side and plain on other side.

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
Pantoprazole 40 mg gastro-resistant tablets should not be chewed or crushed, and should be swallowed whole with liquid before a meal.

Recommended dosage:
Adults and adolescents 12 years of age and above:
Mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing)
The recommended oral dosage is one gastro-resistant tablet Pantoprazole 20 mg per day. 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 gastro-resistant tablet Pantoprazole 20 mg per day is recommended, increasing to 40 mg pantoprazole per day if a relapse occurs. Pantoprazole 40 mg is available for this case. After healing of the relapse the dosage can be reduced again to 20 mg pantoprazole.

Adults:
Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment
The recommended oral dosage is one gastro-resistant tablet Pantoprazole 20 mg per day.

Children below 12 years of age:
Pantoprazole is not recommended for use in children below 12 years of age due to limited data in this age group (see section 5.2).
Special populations:
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment. No dose adjustment is necessary in elderly patients or in those with impaired renal function.

4.3 Contraindications
Hypersensitivity to the active substance, or to any of the excipients of Pantoprazole.
Pantoprazole, like other PPIs, should not be co-administered with atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

Special warnings
None

Special precautions for use
In patients with severe liver impairment the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise of the liver enzymes the treatment should be discontinued.
The use of Pantoprazole 20 mg 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. 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.

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

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.

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

4.5 Interaction with other medicinal products and other forms of interaction
Pantoprazole 20 mg may reduce the absorption of medicinal products whose bioavailability is pH-dependent (e.g. ketoconazole).

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore PPIs, including pantoprazole, should not be co-administered with atazanavir (see section 4.3).

Pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system. An interaction of pantoprazole with other drugs or compounds which are metabolized using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and an oral contraceptive.

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in INR have been reported during concomitant treatment in the post-marketing period. Therefore, in patients being treated with coumarin anticoagulants, monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.
There were also no interactions with concomitantly administered antacids.

4.6 Fertility, 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 5.3). The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary.

Lactation
It is unknown whether pantoprazole is excreted in human breast milk. Animal studies have shown excretion of pantoprazole in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Pantoprazole should be made taking into account the benefit of breast-feeding to the child and the benefit of Pantoprazole therapy to the woman.

4.7 Effects on ability to drive and use machines

Pantoprazole has no known 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

The following undesirable effects have been observed in clinical studies with pantoprazole.

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

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>System Organ Class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Blood and lymphatic system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thrombocytopenia; Leukopenia</td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Headache; Dizziness</td>
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<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
<td>Disturbances in vision / blurred vision</td>
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<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td>Diarrhoea; Nausea / vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash / exanthema / eruption; Pruritus</td>
<td></td>
<td></td>
<td></td>
<td>Urticaria; Angioedema</td>
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<tr>
<td>Musculoskeletal, connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td>Arthralgia; Myalgia</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td>Hyperlipidaemias and lipid increases; Weight changes</td>
<td></td>
<td></td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia, fatigue and malaise</td>
<td></td>
<td>Body temperature increased; Oedema peripheral</td>
<td></td>
<td></td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity (incl. anaphylactic reactions and anaphylactic shock)</td>
<td></td>
</tr>
</tbody>
</table>
Hepatobiliary disorders  Liver enzymes increased (transaminases, γ-GT)  Bilirubin increased
Psychiatric disorders  Sleep disorders  Depression (and all aggravations)  Disorientation (and all aggravations)

The following additional undesirable effects have been reported post-marketing:

**Hepatobiliary disorders**: Hepatocellular injury, Jaundice, Hepatocellular failure

**Psychiatric disorders**: Hallucination, Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)

**Renal and urinary disorders**: Interstitial nephritis

**Skin and subcutaneous tissue disorders**: Stevens-Johnson syndrome, Lyell syndrome; Erythema multiforme, Photosensitivity

4.9 Overdose

There are no known symptoms of overdose in man. Doses up to 240 mg intravenous were administered over 2 minutes and were well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable. In the case of overdose with clinical signs of intoxication, the usual rules of intoxication therapy apply.

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 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 within 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, 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

**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 are 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 are dialyzed. Although the main metabolite has a moderately delayed half-life (2 -3h), 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-lifetime values increased to between 3 and 6 h and the AUC values increased by a factor of 3-5, the maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

A slight increase in AUC and Cmax in elderly volunteers compared with younger counterparts is also not clinically relevant.

**Children**
Following administration of single oral doses of 20 or 40 mg pantoprazole to children aged 5–16 years AUC and Cmax 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 a 2-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 the two-year rodent studies an increased number of liver tumors 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.

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 (E421)
Crospovidone type A (E1202)
Sodium carbonate anhydrous
Calcium stearate

Tablet coating:
Hydroxy propyl methyl cellulose 5cP (E464)
Povidone K - 25 (E1201)
Propylene glycol (E1520)
Titanium dioxide (E171)
Iron oxide yellow (E172)
Methacrylic acid copolymer dispersion
Triethyl citrate (E1505)
Opacode Black:
Shellac (E904)
Iron oxide black (E172)
Propylene glycol (E1520)
Ammonium hydroxide 28% (E527)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
Do not store above 25º C.

6.5 Nature and contents of container
Blistar pack: OPA (Oriented polyamide)/ Aluminium/ PVC and Aluminium foil in a carton box.
Pack size: 28 Tablets.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Macleods Pharma UK Limited
Golden Gate Lodge,
Crewe Hall
Crewe, Cheshire
CW1 6UL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 34771/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/12/2011

10 DATE OF REVISION OF THE TEXT
22/12/2011
Module 3

Patient Information Leaflet

2. BEFORE YOU TAKE PANTOPRAZOLE 40 MG TABLETS

Do not take Pantoprazole 40 mg tablets:
- if you are allergic (hypersensitive) to Pantoprazole or to any of the other ingredients of this medicine (See section 6 for a list of these).
- in combination with antibiotics, if you have moderate to severe liver or kidney problems.
- if you are taking a medicine containing atazanavir (for the treatment of HIV-infection) at the same time.

Take special care with Pantoprazole 40 mg tablets:
- if you have severe liver problems. Please tell your doctor if you have ever had problems with your liver. Your doctor may check your liver enzymes more frequently. The dose may be reduced or the treatment may 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.

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 look pale and feel weak (anaemia)
- 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.

Taking other medicines

Pantoprazole 40 mg tablets may influence the effectiveness of other medicines, so:

Tell your doctor if you are taking any other medicines (e.g. ketoconazole) because Pantoprazole may stop certain other medicines from working properly.

Tell your doctor if you are taking any other medicines especially medicines such as warfarin and phenprocoumon, which affect the thickening, or thinning of the blood. You may need further checks.

Tell your doctor if you are taking a medicine containing atazanavir (used to treat HIV-infection). Atazanavir must not be used together with Pantoprazole 40mg.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Pregnancy and breast-feeding

Clinical experience in pregnant women is limited. There is no information as to whether the active substance passes into human breast milk.

If you are pregnant, or think you may be pregnant, or if you are breast-feeding, you should use this medicine only if your doctor considers the benefit for you greater than the potential risk for your unborn child or baby.

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

Driving and using machines

These tablets have no known effect on the ability to drive and to use machinery. Possible side effects (see section 4) like dizziness and disturbances in vision such as blurred vision may decrease the ability to react.

3. HOW TO TAKE PANTOPRAZOLE 40 MG TABLETS

Always take Pantoprazole 40 mg tablets 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 40 mg tablets?

Take one hour before breakfast without chewing or breaking 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:

For reflux oesophagitis:

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 reflux oesophagitis is usually between 4 and 8 weeks.

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 (eradicaton therapy).

One tablet, two times a day plus two antibiotic tablets: amoxicillin, clarithromycin and metronidazole, each to be taken two times a day with your pantoprazole tablet. Take the first pantoprazole tablet one hour before breakfast and the second pantoprazole tablet before your evening meal. Follow your doctor's instructions and make sure you read the package leaflets for these antibiotics.

The usual combinations are the following:

- Pantoprazole 40 mg + 500 mg clarithromycin +1000 mg amoxicillin

- Pantoprazole 40 mg + 500 mg clarithromycin +500 mg metronidazole

- Pantoprazole 40 mg + 500 mg metronidazole +1000 mg amoxicillin

all taken two times daily. The usual treatment period is one to two weeks.

For stomach and duodenal ulcers:

One tablet daily.

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:

Two tablets a day

(Recommended starting dose)

Take the two tablets before breakfast. Your doctor may later adjust the dosage, depending on the amount of stomach acid you produce. If prescribed more than two tablets a day, take the tablets in two equal doses. If your doctor prescribes a daily dosage 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, you should not take more than one tablet a day.
- If you suffer from severe liver problems, you should take one tablet every other day.
- Children below 12 years. These tablets are not recommended for use in children below 12 years.
- The elderly (65 years or more). The elderly should not take more than one tablet a day, except when treatment combines this medicine with the antibiotics mentioned above, in which the maximum number of tablets is two.

If you take more Pantoprazole 40 mg tablets than you should

Consult your doctor or pharmacist. There are no known symptoms of overdose.

If you forget to take Pantoprazole 40 mg 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 40 mg tablets

Do not stop taking these tablets without first talking to your doctor or pharmacist. If you have any further questions about the use of this product, ask your doctor or pharmacist.
4. POSSIBLE SIDE EFFECTS

Like all medicines, Pantoprazole 40 mg tablets can cause side effects, although not everybody gets them.

If you get any of the following side effects, stop taking these tablets and tell your doctor immediately, or contact the casualty department at your nearest hospital:

**Serious allergic reactions:** swelling of the tongue and/or throat, difficulty in swallowing, hives (nettle rash), difficulties in breathing, allergic facial swelling (Quincke's disease / angioedema), severe dizziness with very fast heartbeat and heavy sweating.

**Serious skin conditions** with blistering of the skin and rapid deterioration of your general condition, erosion (incl. slight bleeding) of eyes, nose, mouth lips or genitals (Stevens-Johnson-Syndrome, Lyell-Syndrome) and sensitivity to light.

**Other serious conditions:** yellowing of the skin or whites of the eyes (severe damage to liver cells, jaundice) or fever, rash, and enlarged kidneys sometimes with painful urination and lower back pain (serious inflammation of the kidneys).

**Other known side effects are:**

- **Uncommon** (fewer than 1 in every 100 patients treated)
  - headache; dizziness; diarrhoea; feeling sick, vomiting;
  - abdominal distension and flatulence; constipation; dry mouth; abdominal pain and discomfort; skin rash; exanthema, eruption; itching; feeling weak, exhausted or generally unwell; sleep disorders.

- **Rare** (fewer than 1 in every 1,000 patients treated)
  - disturbances in vision such as blurred vision; hives; pain in the joints; muscle pains; weight changes; raised body temperature; swelling of the extremities (peripheral oedema); allergic reactions; depression.

- **Very Rare** (fewer than 1 in every 10,000 patients treated)
  - disorientation.

**Other side effects reported in general use:**

Hallucination, confusion.

**Side effects identified through blood tests:**

- **Uncommon** (fewer than 1 in every 100 patients treated)
  - an increase in liver enzymes.

- **Rare** (fewer than 1 in every 1,000 patients treated)
  - increased in bilirubin, increased fats in the blood.

- **Very Rare** (fewer than 1 in every 10,000 patients treated)
  - a reduction in the number of blood platelets, which may cause you to bleed or bruise more than normal; a reduction in the number of white blood cells, which may lead to more frequent infections.

Please remember:

- The expected benefits of your medicine will usually be greater than the risks of suffering any harmful side effects.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PANTOPRAZOLE 40 MG TABLETS

Keep out of the reach and sight of children.

Do not use Pantoprazole 40 mg tablets after the expiry date, which is stated on the carton and the container. The expiry date refers to the last day of that month.

Do not store 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 40 mg tablets contain

The active substance is pantoprazole. One tablet contains 40 mg of pantoprazole (as sodium sesquihydrate).

The other ingredients are:

- Core: Mannitol (E421), Crospovidone type A (E1202), Sodium carbonate anhydrous, Calcium stearate.
- Coating: Hydroxy propyl methyl cellulose 5 cP (E464), Povidone K–25 (E1201), Propylene glycol(E1520), Titanium dioxide (E171), Iron oxide yellow (E172), Methacrylic acid copolymer dispersion, Triethyl citrate (E1505), Opacode Black [Shellac (E904), Iron oxide black (E172), Propylene glycol (E1520), Ammoniumhydroxide 28% (E527)]

What Pantoprazole 40 mg tablets look like and contents of the pack

Yellow oval, biconvex, enteric coated tablets imprinted with ‘CL25’ on one side and plain on other side.

Pantoprazole 40 mg tablets are available in the following pack sizes:

Blisters pack having 28 gastro-resistant tablets.

Marketing Authorization Holder
Macleods Pharma UK Limited
Golden Gate Lodge, Crewe Hall
Crewe, Cheshire CW1 6UL, United Kingdom

Manufacturer
Peckforton Pharmaceuticals Ltd.
UK Crew Hall, Crew, Cheshire CW16UL, United Kingdom

PL 34771/0005

This leaflet was last approved in 12/2011
Module 4

Labelling

Blister carton
Braille translation

Pantoprazole 40 mg gastro-resistant tablets

Blister foil
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Macleods Pharma UK Limited a Marketing Authorisation (MA) for the medicinal product, Pantoprazole 40 mg gastro-resistant tablets (PL 34771/0005; UK/H/3355/002/DC) on 22 December 2011. The product is a prescription-only medicine.

This is a generic application for Pantoprazole 40 mg gastro-resistant tablets, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The originator products are Pantozol 20 mg & 40 mg gastro-resistant tablets, first registered by Nycomed GmbH, Germany in August 1994; Protium 20 mg and 40 mg tablets are the registered names of these products in the UK and are considered to be of the same global MA. The UK reference product, Pantoprazole 40 mg gastro-resistant tablets (PL 31752/0020), was authorised to Nycomed GmbH, Germany on 13th August 2009, through an incoming Decentralised procedure [DE/H/1363/002/DC] where Germany was the Reference Member State (RMS). As the UK reference product is considered to be of the same global MA, first authorised in August 1994, the period of data exclusivity has expired.

With the UK as the Reference Member State (RMS) in this Decentralised procedure, Macleods Pharma UK Limited applied for a Marketing Authorisation for Pantoprazole 40 mg gastro-resistant tablets in Germany, Hungary, Italy, Poland, Romania and Spain.

Pantoprazole 40 mg gastro-resistant tablets are indicated for

- the treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing)
- long-term management and prevention of relapse in reflux oesophagitis
- prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment

Pantoprazole is a substituted benzimidazole (ATC code - A02BC02) 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, a cyclic sulphenamide, 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. 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 active substance is given orally or intravenously.

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that the application was for a generic version of a product that has been licensed for over 10 years.
The application is supported by two bioequivalence studies (one under fasted conditions, one under fed conditions) comparing the pharmacokinetic profile of the test product, Pantoprazole 40 mg gastro-resistant tablets, to that of the reference product, Protium 40 mg 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 Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. 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 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 Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) 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 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 risk 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. 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 40 mg gastro-resistant tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Pantoprazole (as pantoprazole sodium sesquihydrate)</td>
</tr>
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<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Proton pump inhibitors (A02BC02)</td>
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<td>Pharmaceutical form and strength(s)</td>
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</tr>
<tr>
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<tr>
<td>Member States concerned</td>
<td>DE, ES, HU, IT, PL, RO</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 34771/0005</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Macleods Pharma UK Limited</td>
</tr>
<tr>
<td></td>
<td>Golden Gate Lodge,</td>
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<tr>
<td></td>
<td>Crewe Hall</td>
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<td></td>
<td>Crewe, Cheshire</td>
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<td></td>
<td>CW1 6UL</td>
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<td>United Kingdom</td>
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</tbody>
</table>
III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Pantoprazole sodium

Nomenclature:
INN: Pantoprazole sodium sesquihydrate
Chemical names: 5-difluoromethoxy-2-\{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl\}-1H-benzimidazole sodium salt sesquihydrate

Structure:

![Structure of Pantoprazole sodium](image)

Molecular formula: C₁₆H₁₄F₂N₃NaO₄S · 3/2 H₂O
Molecular weight: 432.38 g/mol
CAS No: 164579-32-2
Physical form: White to off-white powder
Solubility: Freely soluble in water, methanol and ethanol, practically insoluble in hexane

The active substance, pantoprazole sodium, is the subject of a European Pharmacopeia (Ph. Eur) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis 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 satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and an appropriate retest period has been applied.
MEDICINAL PRODUCT

Description and Composition

Pantoprazole 40 mg gastro-resistant tablets are presented as yellow, oval, biconvex, enteric-coated tablets imprinted ‘CL25’ on one side and plain on other side. Each tablet contains 40 mg of the active ingredient, pantoprazole, as pantoprazole sodium sesquihydrate.

Other ingredients consist of pharmaceutical excipients, namely mannitol (E421), crospovidone type A (E1202), sodium carbonate anhydrous and calcium stearate making up the tablet cores; and hydroxy propyl methyl cellulose 5cP (E464), povidone K - 25 (E1201), propylene glycol (E1520), titanium dioxide (E171), iron oxide yellow (E172), methacrylic acid copolymer dispersion, triethyl citrate (E1505) and ‘Opacode Black’ making up the film coating. Opacode Black contains shellac (E904), iron oxide black (E172), propylene glycol (E1520) and ammonium hydroxide 28% (E527). Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective Ph. Eur monographs, with the exceptions of ‘Opacode Black’, which is controlled to satisfactory in-house specifications, and iron oxide yellow (E172), which complies with the USP and National Formulary (NF). Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant 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 proposed product. None of the excipients are sourced from genetically modified organisms. There were no novel excipients used.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The objective was to develop a stable, gastro-resistant tablet formulation of pantoprazole 40 mg, bioequivalent to the innovator product, Protium 40 mg gastro-resistant tablets (Nycomed GmbH).

Comparative dissolution and impurity data were provided for batches of the test product and appropriate reference product. The dissolution and impurity profiles were satisfactory.

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 were conducted and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process. A commitment has been made by the MAH that full process validation will be conducted on commercial scale batches in accordance with the process validation protocol.

Finished product specification

Finished product specifications are provided for release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been 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

Pantoprazole 40 mg gastro-resistant tablets are licensed for marketing in oriented polyamide (OPA)-polyvinylchloride (PVC)-aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in a pack size of 28 tablets.

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, using product stored in the packaging proposed for marketing. These data support the applied shelf-life of 24 months. Storage instructions are ‘Do not store above 25°C’.

Quality Overall Summary

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

Product Information

The approved Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The labelling fulfils the statutory requirements for Braille.

The PIL is in line with the SmPC and is satisfactory. PIL user-testing has been accepted based on bridging to the successful user-testing of the ‘parent’ PIL for Pantoprazole 20 mg gastro-resistant tablets (UK/H/3355/001/DC). The text, content and layout of the proposed PIL are considered to be sufficiently similar to the approved PIL for the stated product. The bridging is accepted.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. There are no objections to approval of Pantoprazole 40 mg gastro-resistant tablets from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS
Pantoprazole is a proton pump inhibitor, the first drug of this class, omeprazole, having been developed in the 1980s and launched in Europe and the US between 1988 and 1990. Lansoprazole, rabeprazole, pantoprazole and esomeprazole have since been developed. Pantoprazole, which was first licensed in 1995, is currently marketed in over 60 countries for the treatment of gastroduodenal ulcer (including NSAID-related ulcers), as well as in gastric oesophageal reflux disease, Zollinger-Ellison syndrome and (in combination with appropriate antibiotics) the eradication of *Helicobacter pylori*. Because pantoprazole is acid-labile, it is formulated as a delayed-release gastro-resistant product.

Specific non-clinical studies have not been performed, which is acceptable considering that this is an application for a generic version of a product that has been licensed for more than 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of pantoprazole, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the innovator product, Protium 40 mg gastro-resistant tablets (Nycomed GmbH).

There are no objections to approval of Pantoprazole 40 mg gastro-resistant tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS
INDICATIONS
Pantoprazole 40 mg gastro-resistant tablets are indicated for:

- the treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing)
- long-term management and prevention of relapse in reflux oesophagitis
- prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment

The indications are consistent with those for the innovator product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the innovator product and is satisfactory.

TOXICOLOGY
The toxicology of pantoprazole is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY
The clinical pharmacology of pantoprazole is well-known. With the exception of the bioequivalence studies, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for this application.
Pharmacokinetics – bioequivalence studies

The application is supported by 2 bioequivalence studies – one under fasted conditions (Study A), one under fed conditions (Study B) – comparing the pharmacokinetic profile of the test product, Pantoprazole 40 mg gastro-resistant tablets, to that of the reference product, Protium 40 mg gastro-resistant tablets (Nycomed GmbH). The studies were of an appropriate design and were conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for both test and reference products.

The primary pharmacokinetic parameters for the studies were $C_{\text{max}}$, $\text{AUC}_{0-t}$ and $\text{AUC}_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) of the ratio of the test and reference products fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed $C_{\text{max}}$, $\text{AUC}_{0-t}$ and $\text{AUC}_{0-\infty}$ for pantoprazole.

Study A – fasted, single dose

This was an open-label, randomised, two-period, two-sequence, two-treatment, single-dose crossover bioequivalence study conducted in healthy adult human male subjects under fasting conditions. A single 40 mg dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 7 days was maintained between the dosing days in each group.

Blood samples were taken pre-dose and at specified time points up to 24.0 hours after administration of test or reference product. Plasma levels of pantoprazole were quantified by a validated LC-MS/MS method.

Results:

An appropriate number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

Safety - There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Reference product (X)</td>
<td>Test product (Y)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>3404.49</td>
<td>3453.27</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$ (ng.h/ml)</td>
<td>7764.59</td>
<td>7753.00</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (ng.h/ml)</td>
<td>7990.81</td>
<td>7981.20</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ maximum plasma concentration
$\text{AUC}_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
$\text{AUC}_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

Conclusion

Bioequivalence has been demonstrated between the test and reference products for a single-dose study conducted under fasting conditions.
Study B – fed, single dose

This was an open-label, randomised, two-period, two-sequence, two-treatment, single-dose crossover bioequivalence study conducted in healthy adult human subjects under fed conditions. Following an overnight fast, subjects were given a high-calorie, high-fat breakfast and then a single 40 mg dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 7 days was maintained between the dosing days in each group.

Blood samples were taken pre-dose and at specified time points up to 36.0 hours after administration of test or reference product. Plasma levels of pantoprazole were quantified by a validated LC-MS/MS method.

Results:

An appropriate number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

Safety - There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:

**Summary pharmacokinetic data for pantoprazole for a randomised, open-label, 2-way, single-dose crossover study; healthy subjects, dosed fed; t=36 hours; washout period: 7 days**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Reference product (X)</th>
<th>Test product (Y)</th>
<th>Ratio (Y/X)</th>
<th>90% CI (Parametric)</th>
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<tbody>
<tr>
<td>C(_\text{max}) (ng/ml)</td>
<td>2105.50</td>
<td>2096.00</td>
<td>99.55</td>
<td>92.43-107.22%</td>
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<td>AUC(_0-\text{t}) (ng.h/ml)</td>
<td>5326.50</td>
<td>5313.47</td>
<td>99.76</td>
<td>95.23-104.50%</td>
</tr>
<tr>
<td>AUC(_0-\infty) (ng.h/ml)</td>
<td>5442.80</td>
<td>5524.06</td>
<td>101.49</td>
<td>97.61-105.53%</td>
</tr>
</tbody>
</table>

\(C\(_\text{max}\)\) maximum plasma concentration

AUC\(_0-\text{t}\) area under the plasma concentration-time curve from time zero to \(t\) hours

AUC\(_0-\infty\) area under the plasma concentration-time curve from time zero to infinity

Conclusion

Bioequivalence has been demonstrated between the test and reference products for a single-dose study conducted under fed conditions.

Discussion on Bioequivalence

The results of the bioequivalence studies show that Pantoprazole 40 mg gastro-resistant tablets and Protium 40 mg gastro-resistant tablets (Nycomed GmbH) are bioequivalent, as the confidence intervals for \(C\(_\text{max}\), AUC\(_0-\text{t}\), and AUC\(_0-\infty\) fall within the acceptance criteria ranges of 80-125% in line with the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence” (CPMP/EWP/QWP/1401/98).

Clinical efficacy

No new data have been submitted and none are required. The reference product is established and the application depends upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of pantoprazole is well-established from its extensive use in clinical practice.
Clinical safety
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of pantoprazole is well-known.

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

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The approved SmPC is consistent with that for the reference product and is acceptable.

Patient Information Leaflet
The final PIL is in line with the approved SmPC and is satisfactory.

Labelling
The labelling text is satisfactory.

CONCLUSIONS
Sufficient clinical information has been submitted to support this application. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was, therefore, recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Pantoprazole 40 mg 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Pantoprazole 40 mg gastro-resistant tablets, and the reference product, Protium 40 mg gastro-resistant tablets (Nycomed GmbH).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC is consistent with that for the UK reference product and is satisfactory.

The PIL is in line with the SmPCs and is satisfactory. PIL user-testing has been accepted based on bridging to the successful user-testing of the ‘parent’ PIL for Pantoprazole 20 mg gastro-resistant tablets (UK/H/3355/001/DC). The results show that the 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.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies and their conclusions support the claim that the applicant’s Pantoprazole 40 mg gastro-resistant tablets is a generic version of the reference product, Protium 40 mg gastro-resistant tablets (Nycomed GmbH). Extensive clinical experience with pantoprazole is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is 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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