Public Assessment Report

Decentralised Procedure

Pantoprazole 40 mg Gastro-Resistant Tablets

Procedure No: UK/H/2111/002/DC

UK Licence No: PL 08137/0189

Neolab Limited
LAY SUMMARY

On 10 February 2011, Ireland and the UK agreed to grant a Marketing Authorisation to Neolab Limited for the medicinal product Pantoprazole 40 mg Gastro-Resistant Tablets (PL 08137/0189; UK/H/2111/002/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 05 April 2011.

This is a prescription-only medicine (POM) used in the treatment of:

**Adults and adolescents 12 years of age and above:**
- Reflux oesophagitis, which is 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.

Pantoprazole 40 mg Gastro-Resistant Tablets contain the active ingredient pantoprazole (as pantoprazole sodium sesquihydrate). 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.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Pantoprazole 40 mg Gastro-Resistant Tablets outweigh the risks and a Marketing Authorisation was granted.
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Module 1
Information about the initial procedure

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Module 2
Summary of Product Characteristics

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate).

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant tablet.

Tablets are yellow coloured, capsule-shaped, (10 mm x 5 mm) biconvex tablets, plain on both sides.

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 dose:
Adults and adolescents 12 years of age and above:
Reflux oesophagitis
One tablet of Pantoprazole 40 mg per day. In individual cases the dose may be doubled (increase to 2 tablets pantoprazole 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:

a) twice daily one tablet pantoprazole
   + twice daily 1000 mg amoxicillin
   + twice daily 500 mg clarithromycin

b) twice daily one tablet pantoprazole
   + twice daily 400 - 500 mg metronidazole (or 500 mg tinidazole)
   + twice daily 250 - 500 mg clarithromycin

c) twice daily one tablet pantoprazole
   + twice daily 1000 mg amoxicillin
   + twice daily 400 - 500 mg metronidazole (or 500 mg tinidazole)

In combination therapy for eradication of H. pylori infection, the second pantoprazole 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 monotherapy:

**Treatment of gastric ulcer**

One tablet of pantoprazole per day. In individual cases the dose may be doubled (increase to 2 tablets pantoprazole 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 per day. In individual cases the dose may be doubled (increase to 2 tablets pantoprazole 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 80 mg (2 tablets of Pantoprazole 40 mg). Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dose above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control

Treatment duration in Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.

**Special populations**

**Children below 12 years of age**

Pantoprazole is not recommended for use in children below 12 years of age due to limited data on safety and efficacy in this age group.

**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 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 in combination treatment of these patients (see section 4.4).

**Renal Impairment**

No dose adjustment is necessary in patients with impaired renal function. Pantoprazole 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 in combination treatment for these patients.

**Elderly:**

No dose adjustment is necessary in elderly patients.

### 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 of the liver enzymes, the treatment 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 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 metabolized 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 affect the metabolism of active substances metabolised 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 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 should be made taking into account the benefit of breast-feeding to the child and the benefit of pantoprazole 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

<table>
<thead>
<tr>
<th>Frequency System Organ Class</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known</th>
</tr>
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<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td>Thrombocytopenia; Leukopenia</td>
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<tr>
<td>Immune system disorders</td>
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<td>Hypersensitivity (including anaphylactic reactions and anaphylactic shock)</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Sleep disorders</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>
</tbody>
</table>
Frequency System Organ Class | Uncommon | Rare | Very rare | Not known
--- | --- | --- | --- | ---
Nervous system disorders | Headache; Dizziness |  |  |  |
Eye disorders | Disturbances in vision/blurred vision |  |  |  |
Gastrointestinal disorders | Diarrhoea; Nausea/vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort |  |  |  |
Hepatobiliary disorders | Liver enzymes increased (transaminases, γ-GT) | Bilirubin increased | Hepatocellular injury; Jaundice; Hepatocellular failure |  |
Skin and subcutaneous tissue disorders | Rash/exanthema/eruption; Pruritus | Urticaria; Angioedema | Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity |  |
Musculoskeletal and connective tissue disorders |  | Arthralgia; Myalgia |  |  |
Renal and urinary disorders |  |  | Interstitial nephritis |  |
Reproductive system and breast disorders |  | Gynaecomastia |  |  |
General disorders and administration site conditions | Asthenia, fatigue and malaise | Body temperature increased; Oedema peripheral |  |  |

4.9 Overdose

There are no known symptoms of over dosage in man.

Systemic exposure with up to 240 mg 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 µg/ml are achieved, and these values remain constant after multiple administration.

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. 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 serum protein binding is about 98%. Volume of distribution is about 0.15 l/kg.

Elimination
The substance is almost exclusively metabolized 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 is excreted with the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 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 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.

Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 7 and 9 h and the AUC values increased by a factor of 5-7, the maximum serum concentration only increased slightly by a factor of 1.5 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 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:
Sodium carbonate anhydrous
Mannitol (E421)
Crospovidone
Calcium stearate
Hydroxypropyl cellulose (E463)

Seal coating:
Hypromellose (E464)
Titanium dioxide (E171)
Yellow iron oxide (E172)
Propylene glycol (E1520).

Enteric coating:
Methacrylic acid-ethyl acrylate copolymer (1:1) 30% dispersion
Triethyl citrate (E1505).
6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container
Pantoprazole gastro-resistant tablets are packed in Alu/Alu blister strips containing 28 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Neolab Ltd
57 High Street
Odiham
Hampshire
RG29 1LF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 08137/0189

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/04/2011

10 DATE OF REVISION OF THE TEXT
05/04/2011
Pantoprazole 40 mg Gastro-Resistant Tablets
UK/H/2111/002/DC

PATIENT INFORMATION LEAFLET
PANTOPRAZOLE 40 mg GASTRO-RESISTANT TABLETS
(pantoprazole as sodium bisulphate)

The name of this medicine is Pantoprazole 40 mg Gastro-Resistant Tablets, which will be referred to as Pantoprazole Tablets throughout this leaflet.

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 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 worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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.
  - 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 in Pantoprazole Tablets (these are listed in section 6. Further Information).
- 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 have ever had problems with your liver in the past. He will check your liver enzymes more frequently, especially when you are taking Pantoprazole Tablets as a long-term treatment. In the case of liver enzyme levels 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 azithromycin (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 pale and feel weak (anaemia)
- you notice blood in your stools
- severe, persistent diarrhea, 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.

Taking other medicines

Pantoprazole may influence the effectiveness of other medicines, so tell your doctor if you are taking:

- Medicines such as ketoconazole, itraconazole and posaconazole (used to treat fungal infections) or antifungals used for certain types of cancer because pantoprazole may stop these and other medicines from working properly.
- Warfarin and phenprocoumon, which affect the thickening, or thinning, of the blood. You may need further checks.
- Azithromycin (used to treat HIV-infection).

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

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 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

If you experience side effects like dizziness or disturbed vision, you should not drive or operate machines.

3. HOW TO TAKE PANTOPRAZOLE TABLETS

Always take Pantoprazole 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 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

The usual dose is one tablet a day. 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 trimoxazole), each to be taken two times a day with your Pantoprazole Tablets. Take the first Pantoprazole Tablet 1 hour before breakfast and the second Pantoprazole Tablet 1 hour before 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.
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 6 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 ten times 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:
Tell 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 normal dose at the usual time.

If you stop taking Pantoprazole 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 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)
common (affects 1 to 10 in 100 people)
uncommon (affects 1 to 10 in 1,000 people)
rare (affects 1 to 10 in 10,000 people)
very rare (affects less than 1 in 10,000 people)
not known (frequency cannot be estimated from the available data)

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 (frequency not known): swelling of the tongue and/or throat, difficulty in swallowing, hives (urticaria), difficulties in breathing, allergic facial swelling (Quincke’s oedema), angioedema, severe dizziness with very fast heartbeat and heavy sweating.
- Serious skin conditions (frequency not known): blistering of the skin and rapid deterioration of your general condition, oedema (including tight swelling of eyes, nose, mouth, lips or genitalia (Stevens-Johnson-Syndrome, Lyell-Syndrome, erythema multiforme) and sensitivity to light.
- Other serious conditions (frequency not known): yellowing of the skin or whites of the eyes (severe damage to liver cells, jaundice) or fever, rash, and enlarged lymph nodes sometimes with painful urination and loss of blood (serious inflammation of the kidneys).

Other side effects are:
- Uncommon (affects 1 to 10 in 1,000 people)
  - Headache, dizziness, nausea, feeling sick, vomiting, diarrhoea and belching (wind), constipation, dry mouth, abdominal pain and discomfort, skin rash, exanthema, urticaria, itching, feeling weak, exhaustion or general weakness, sleep disorders.
- Rare (affects 1 to 10 in 10,000 people)
  - Disturbances of vision such as blurred vision, hives, pain in the joints, muscle pain, weight changes, raised blood pressure, swelling of the extremities (peripheral oedema), allergic reactions, depression, breast enlargement in males.
  - Very Rare (affects less than 1 in 10,000 people)
    - Disorientation.
    - Not known (frequency cannot be estimated from the available data)
      - Nausea, vomiting (especially in patients with a history of these symptoms); decreased sodium level in blood.

Side effects identified through blood tests:
- Uncommon (affects 1 to 10 in 1,000 people)
  - An increase in liver enzymes.
- Rare (affects 1 to 10 in 10,000 people)
  - An increase in blood lipids, increased fats in the blood.
- Very Rare (affects less than 1 in 10,000 people)
  - 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.

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.

9. HOW TO STORE PANTOPRAZOLE TABLETS
Keep out of the reach of children. Do not use pantoprazole tablets after the expiry date, which is stated on the carton and blister pack after EXP. The expiry date refers to the last day of that month.
Store in the original package to protect from moisture. This medicinal product does not require any special temperature storage conditions. Do not use if your tablets are broken or crushed, return them to your pharmacist.

For practical or medical reasons, medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

8. FURTHER INFORMATION
What Pantoprazole 40 mg Tablets contain:
The active ingredient is pantoprazole. One tablet contains 40 mg of pantoprazole (as sodium bisulphate).
The other ingredients are:
Tablets core: Sodium carbonate anhydrous, mannitol (E421), croscarmellose, calcium stearate, hypromellose (E464), colloidal silicon dioxide (E572), yellow iron oxide (E172), propylene glycol (E438), blue pigment: Potassium iron oxalate, E153.
Tablets blister pack: Methacrylate acid-ethyl acrylate copolymer (1:1) 30% dispersion, ethyl cellulose (E903).

What Pantoprazole 40 mg tablets look like and contents of the pack:
Pantoprazole Tablets are yellow coloured, capsule shaped, blister packs plain on both sides. Tabled dimensions: length 10 mm; width 5 mm. Your medicine is available in blisters containing 20 tablets.

Marketing Authorisation Holder:
Nactlab Ltd, 57 High Street, Oldham, Hampshire, RO20 1LF, UK.
This information is available in alternative formats upon request.
This leaflet was last approved in March 2011.
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Pantoprazole 40 mg Gastro-Resistant Tablets (PL 08137/0189; UK/H/2111/002/DC) could be approved. The product is a prescription-only medicine (POM) indicated for the treatment of:

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.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Ireland as Concerned Member State (CMS). The application was submitted under Article 10.1 of 2001/83/EC, as amended, claiming to be a generic medicinal product of Somac 40 mg Gastro-Resistant Tablets (Nycomed GmbH, Germany), which was first approved in Finland on 07 November 1994. The corresponding reference product in the UK is Protium 40 mg gastro-resistant tablets (Nycomed GmbH, Germany) which was first authorised on 04 June 1996.

The active ingredient pantoprazole (as pantoprazole sodium sesquihydrate) is a substituted benzimidazole that 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. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole causes reduced acidity in the stomach and thereby increases 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 and gastrin).

No non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Two single-dose bioequivalence studies (one fasting and one fed) were submitted to support this application, comparing the test product Pantoprazole 40 mg Gastro-Resistant Tablets (Neolab Limited, UK) versus the reference product Protium 40 mg gastro-resistant tablets (Nycomed GmbH, Germany). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP). With the exception of these bioequivalence studies, no new clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this
product. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, 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 and CMS considered that the application could be approved at the end of procedure (Day 210) on 10 February 2011. After a subsequent national phase, the licence was granted in the UK on 05 April 2011.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Pantoprazole 40 mg Gastro-Resistant Tablets |
| Name(s) of the active substance(s) (INN)          | Pantoprazole sodium sesquihydrate |
| Pharmacotherapeutic classification (ATC code)    | Proton Pump Inhibitors, (ATC code: A02B C02) |
| Pharmaceutical form and strength(s)              | Gastro-resistant tablet 40 mg |
| Reference numbers for the Decentralised Procedure| UK/H/2111/002/DC |
| Reference Member State (RMS)                     | United Kingdom |
| Concerned Member States (CMS)                    | Ireland |
| Marketing Authorisation Number                   | PL 08137/0189 |
| Name and address of the authorisation holder     | Neolab Limited, 57 High Street, Odiham, Hampshire, RG29 1LF, UK |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Pantoprazole sodium sesquihydrate

Chemical name: Sodium 5-(difluoromethoxy)-2-[(RS)-[(3,4-dimethoxy-2-yl)methyl]sulphinyl]benzimidazol-1-ide sesquihydrate

Structure:

Molecular formula: $\text{C}_{16}\text{H}_{14}\text{F}_2\text{N}_3\text{NaO}_4\text{S}, \frac{11}{2}\text{H}_2\text{O}$
Molecular Mass: 432.4
Appearance: A white to off-white powder, freely soluble in water and 96% ethanol and practically insoluble in hexane.

Pantoprazole sodium sesquihydrate is the subject of a European Pharmacopoeia 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 specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is 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 specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

MEDICINAL PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients in the tablet core and coatings (seal and enteric), namely anhydrous sodium carbonate, mannitol (E421), crospovidone, calcium stearate, hydroxypropyl cellulose (E463), hypromellose (E464), titanium dioxide (E171), yellow iron oxide (E172), propylene glycol (E1520), methacrylic acid-ethyl acrylate copolymer (1:1) 30% dispersion and triethyl citrate (E1505). Appropriate justifications for the inclusion of each excipient have been provided.
With the exception of yellow iron oxide (E172), which is controlled to a suitable in-house specification, all excipients comply with their respective European Pharmacopoeia monograph.

Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of calcium stearate, none of the excipients contain materials of animal or human origin. The supplier of calcium stearate has provided a Certificate of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that calcium stearate manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**
The objective of the development programme was to formulate a safe, efficacious, stable product that could be considered a generic medicinal product of the reference product Protium 40 mg gastro-resistant tablets (Nycomed GmbH, Germany).

Suitable pharmaceutical development data have been provided for this application.

Comparative *in-vitro* dissolution and impurity profiles have been provided for this product and the reference product Protium 40 mg gastro-resistant tablets (Nycomed GmbH, Germany).

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Control of Finished Product**
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**
The product is packaged in aluminium/aluminium blisters. These are packed into cardboard cartons with patient information leaflets in pack sizes of 28 gastro-resistant tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuff.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with the storage conditions “Store in the original package to protect from moisture.”
Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**Bioequivalence/Bioavailability**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA Form**
The MAA form is pharmaceutically satisfactory.

**Expert Report**
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
The grant of a Marketing Authorisation is recommended.
III.2 NON-CLINICAL ASPECTS
PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of pantoprazole sodium sesquihydrate are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

The clinical pharmacology of pantoprazole sodium sesquihydrate is well-known. With the exception of data from the below bioequivalence studies, no new pharmacodynamic or pharmacokinetic data are provided or required for this application.

Pharmacokinetics

In support of the application, the Marketing Authorisation Holder submitted the following bioequivalence studies:

Fasting Study

A randomised, open-label, two-treatment, two-sequence, two-period, single-dose, crossover study comparing the pharmacokinetics of the test product Pantoprazole 40 mg Gastro-Resistant Tablets (Neolab Limited, UK) and the reference product Protium 40 mg gastro-resistant tablets (Nycomed GmbH, Germany) in healthy adult subjects under fasting conditions.

The subjects were administered one tablet of test or reference product after at least a 10-hour fast. Blood samples were collected before and up to 48 hours after each administration. The washout period between the treatment arms was 7 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Parameters (units)</th>
<th>Pantoprazole 40 mg (Test)</th>
<th>Protium 40 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;t&lt;/sub&gt;</td>
<td>9996.29</td>
<td>10543.87</td>
<td>94.81</td>
<td>88.42-101.66</td>
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<td>AUC&lt;sub&gt;inf&lt;/sub&gt;</td>
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<td>10945.57</td>
<td>93.27</td>
<td>85.03-102.30</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>3383.99</td>
<td>3757.84</td>
<td>90.05</td>
<td>84.55-95.91</td>
</tr>
</tbody>
</table>

AUC<sub>t</sub> area under the plasma concentration-time curve from time zero to t hours
AUC<sub>inf</sub> area under the plasma concentration-time curve from time zero to infinity
C<sub>max</sub> maximum plasma concentration
Ratios and 90% CI calculated from ln-transformed data

Fed Study

A randomised, open-label, two-treatment, two-sequence, two-period, single-dose, crossover study comparing the pharmacokinetics of the test product Pantoprazole 40 mg Gastro-Resistant Tablets (Neolab Limited, UK) and the reference product Protium 40 mg gastro-resistant tablets (Nycomed GmbH, Germany) in healthy adult male subjects under fed conditions.

The subjects fasted for at least 10 hours prior to a standard high-fat breakfast, after which they were administered one tablet of test or reference product with 240 ml water. Blood samples were collected before and up to 48 hours after each administration. The washout period between the treatment arms was 7 days. The pharmacokinetic results are presented below:
Pharmacokinetic parameters (geometric means, ratios and confidence intervals [CI]) of pantoprazole sodium sesquihydrate

<table>
<thead>
<tr>
<th>Parameters (units)</th>
<th>Pantoprazole 40 mg (Test)</th>
<th>Protium 40 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
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<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.hr/ml)</td>
<td>6655.34</td>
<td>6885.31</td>
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<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng.hr/ml)</td>
<td>6770.52</td>
<td>6990.65</td>
<td>96.85</td>
<td>92.28-101.65</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>2946.40</td>
<td>2990.39</td>
<td>98.53</td>
<td>92.53-104.92</td>
</tr>
</tbody>
</table>

AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
AUC<sub>0-inf</sub> area under the plasma concentration-time curve from time zero to infinity
C<sub>max</sub> maximum plasma concentration
Ratios and 90% CI calculated from ln-transformed data

The *Guidance on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1) defines the 90% confidence limits as 80% to 125% for C<sub>max</sub> and AUC values. The 90% confidence intervals of the test/reference ratio of geometric means for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> lie within the acceptable limits for both studies. Thus, the data support the claim that the test product Pantoprazole 40 mg Gastro-Resistant Tablets (Neolab Limited, UK) is bioequivalent to the UK reference product Protium 40 mg gastro-resistant tablets (Nycomed GmbH, Germany) under both fed and fasting conditions.

**Efficacy**
The efficacy of pantoprazole sodium sesquihydrate is well-known. No new efficacy data have been submitted and none are required for an application of this type.

**Safety**
With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues were raised by the bioequivalence data.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labels are clinically acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

**Clinical Expert Report**
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Pharmacovigilance System and Risk Management Plan**
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant 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.

**Conclusion**
The grant of a Marketing Authorisation is 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. As the pharmacokinetics, pharmacodynamics and toxicology of pantoprazole sodium sesquihydrate are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence studies, no new data were submitted and none are required for this type of application.

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, Germany).

SAFETY
With the exception of the bioequivalence studies, no new data were submitted and none are required for this type of application. As the safety profile of pantoprazole sodium sesquihydrate is well-known, no additional data were required. No new or unexpected concerns arose from the safety data from the bioequivalence studies.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory, and consistent with those for the reference product, where appropriate, along with current guidelines.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with pantoprazole sodium sesquihydrate is considered to have demonstrated the therapeutic value of the product. The benefit/risk is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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