Public Assessment Report

Decentralised Procedure

Pantoprazole 20 and 40mg Gastro-resistant Tablets

Pantoprazole sodium sesquihydrate

UK/H/1932/01-02/DC

UK licence no: PL 29831/0372-3

Applicant: Wockhardt UK Ltd
LAY SUMMARY

On the 25th May 2010, the MHRA granted Wockhardt UK Limited Marketing Authorisations (licences) for the medicinal products Pantoprazole 20mg and 40mg Gastro-resistant Tablets. These medicines are only available on prescription from your doctor.

Pantoprazole Tablets are selective “proton pump inhibitors”, which are medicines that reduce the amount of acid produced in your stomach. They are used for treating acid-related diseases of the stomach and intestine.

Pantoprazole 20mg gastro-resistant tablets is used in the treatment of:

**Adults and adolescents 12 years of age and above**
- Symptomatic gastro-oesophageal reflux disease.
- For long-term management and prevention of relapse in reflux oesophagitis.

**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.

Pantoprazole 40mg gastro-resistant tablets is used in 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 antibiotics therapy in patients with *H. pylori* associated ulcers.
- Gastric and duodenal ulcer.
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Pantoprazole 20mg and 40mg Gastro-resistant Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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## Module 5: Scientific Discussion

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V. Overall conclusion and Benefit-Risk Assessment

Module 6  
Steps taken after initial procedure
## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Pantoprazole 20mg and 40mg Gastro-resistant Tablets</th>
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</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Pantoprazole sodium sesquihydrate</td>
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<tr>
<td><strong>Form</strong></td>
<td>Gastro-resistant Tablets</td>
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<tr>
<td><strong>Strength</strong></td>
<td>20mg and 40mg</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Wockhardt UK Ltd</td>
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<td>Ash Road North</td>
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<td>Wrexham LL13 9UF</td>
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<td>UK</td>
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<td><strong>RMS</strong></td>
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<td><strong>CMS</strong></td>
<td>IE, CY, MT and PL</td>
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<td><strong>Procedure Number</strong></td>
<td>UK/H/1932/01-02/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 28th April 2010</td>
</tr>
</tbody>
</table>
Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Pantoprazole 20 mg Gastro-resistant tablets

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant tablet.

A yellow, oval, biconvex gastro-resistant tablet; plain on both sides.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Adults and adolescents 12 years of age and above
Symptomatic gastro-oesophageal reflux disease.

For long-term management and prevention of relapse in reflux oesophagitis.

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 (see section 4.4).

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

Recommended dose:
Adults and adolescents 12 years of age and above
Symptomatic gastro-oesophageal reflux disease
The recommended oral dosage is one pantoprazole 20 mg gastro-resistant tablet per day. Symptom relief is generally accomplished within two to four weeks. If this is not sufficient, symptom relief will normally be achieved within a further four weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment.

Long-term management and prevention of relapse in reflux oesophagitis
For long-term management, a maintenance dose of one pantoprazole 20 mg gastro-resistant tablet per day is recommended, increasing to 40 mg pantoprazole per day if a relapse occurs. Pantoprazole 40 mg gastro-resistant tablets are available for this case. After healing of the relapse the dosage can be reduced again to 20 mg pantoprazole.

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 pantoprazole 20 mg gastro-resistant tablet per day.

Special populations
Children below 12 years of age:
Pantoprazole 20 mg gastro-resistant tablets are 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 should not be exceeded in patients with severe liver impairment (see section 4.4).

Renal Impairment
No dose adjustment is necessary in patients with impaired renal function.

Elderly
No dose adjustment is necessary in elderly patients.

4.3 Contraindications
Hypersensitivity to the active substance, substituted benzimidazoles, or any of the other excipients.

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).

Co-administration with NSAIDs
The use of pantoprazole 20 mg gastro-resistant tablets 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.

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
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 one 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 20 mg gastro-resistant tablets may lead to a slightly increased risk of gastrointestinal infections caused by bacterial 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 such as ketoconazole, itraconazole, posaconazole and other medicines such as erlotinib.

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

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

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

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

Results from a range of interaction studies demonstrate that pantoprazole does not effect the metabolism of active substances 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 also 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</th>
<th>System</th>
<th>Organ Class</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood and lymphatic system</td>
<td>disorders</td>
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<tr>
<td></td>
<td>Thrombocytopenia;</td>
<td>Leukopenia</td>
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<td></td>
<td>Immune system disorders</td>
<td>Hypersensitivity (including</td>
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<td></td>
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<td>anaphylactic reactions</td>
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<td>anaphylactic shock</td>
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<td></td>
<td>Metabolism and nutrition</td>
<td>disorders</td>
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<td></td>
<td>Hyperlipidaemias and</td>
<td>lipid increases (triglycerides,</td>
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<td></td>
<td></td>
<td>cholesterol); Weight changes</td>
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<td></td>
<td>Psychiatric disorders</td>
<td>Sleep disorders</td>
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<td>Depression (and all aggressions)</td>
<td>Disorientation (and all aggressions)</td>
<td>Hallucination; Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)</td>
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<tr>
<td></td>
<td>Nervous system disorders</td>
<td>Headache; Dizziness</td>
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<td></td>
<td>Eye disorders</td>
<td>Disturbances in vision /</td>
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<td></td>
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<td>blurred vision</td>
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<td></td>
<td>Gastrointestinal Disorders</td>
<td>Diarrhoea; Nausea/Vomiting;</td>
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<td>Abdominal distension and</td>
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<td></td>
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<td>bloating; Constipation; Dry</td>
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<td></td>
<td></td>
<td>mouth; Abdominal pain and</td>
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<td></td>
<td></td>
<td>discomfort</td>
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<td></td>
<td>Hepatobiliary disorders</td>
<td>Liver enzymes increased</td>
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<td>(transaminases, $\gamma$-GT)</td>
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<td>Skin and subcutaneous tissue</td>
<td>Rash / exanthema / eruption;</td>
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<td>Pruritus</td>
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<td>Urticaria; Angioedema</td>
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<td></td>
<td>Stevens-Johnson syndrome;</td>
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<td>Lyell syndrome; Erythema</td>
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<td>multiforme; Photosensitivity</td>
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<tr>
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<td>Musculoskeletal and connective</td>
<td>tissue disorders</td>
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<td></td>
<td>Athralgia; Myalgia</td>
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<td>Renal and urinary disorders</td>
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<td>Interstitial nephritis</td>
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<td>Reproductive system and</td>
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<td></td>
<td></td>
<td>Gynaecomastia</td>
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</table>
4.9 Overdose
There are no known symptoms of overdose in man. Systemic exposure with up to 240 mg administered intravenously over two minutes was 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: AO2BC02

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 two weeks. As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced 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 (atyypical 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 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.
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 metabolised in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathways 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 recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of are dialysed. Although the main metabolite has a moderately delayed half-life (two to three 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 three and six hours and the AUC values increased by a factor of three to five, 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 to 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 to16 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 tumours 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 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)
Partially pre-gelatinized maize starch
Colloidal anhydrous silica
Sodium carbonate (anhydrous) (E500)(i)
Calcium stearate
Talc (E553b)
Sodium starch glycolate (type A)

Enteric coating
Methacrylic acid – ethyl acrylate copolymer (1:1)
Sodium hydroxide (E524)
Triethyl citrate (E1505)
Talc (E553b)

Coating seal (yellow)
Hypermellose (E464)
Titanium dioxide (E171)
Macrogol 4000
Iron oxide yellow (E172)
Blue indigo carmine aluminium lake (E132).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months (unopened).

6.4 Special precautions for storage
This medicinal product does not require any special temperature storage conditions.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
Blisters (OPA/Aluminium/PVC film and aluminium foil), containing 14 tablets, and outer cardboard carton.

Pack size: 28 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
U.K.

8 MARKETING AUTHORISATION NUMBER(S)

PL 29831/0372

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/05/2010

10 DATE OF REVISION OF THE TEXT

24/05/2010
1 NAME OF THE MEDICINAL PRODUCT
Pantoprazole 40 mg Gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One gastro-resistant 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.

A yellow, oval, biconvex gastro-resistant tablet; 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 antibiotics 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 one hour before a meal with some water.

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

- twice daily one Pantoprazole 40 mg gastro-resistant tablet
  + twice daily 1000 mg amoxicillin
  + twice daily 500 mg clarithromycin

- twice daily one Pantoprazole 40 mg gastro-resistant tablet
  + twice daily 400 – 500 mg metronidazole (or 500 mg tinidazole)
  + twice daily 250 – 500 mg clarithromycin

- twice daily one Pantoprazole 40 mg gastro-resistant tablet
  + 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 40 mg gastro-resistant tablet should be taken one hour before the evening meal. The combination therapy is implemented for seven days in general and can be prolonged for a further seven 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 pantoprazole 40 mg gastro-resistant tablets per day.

In individual cases the dose may be doubled (increase to two tablets daily) especially when there has been no response to other treatment. A four week period is usually required for the treatment of gastric ulcers. If this is not sufficient, healing will usually be achieved within a further four weeks.

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

**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 (two 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 dosage above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control.

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

**Special populations**

**Children below 12 years of age:**
Pantoprazole 40 mg gastro-resistant tablets are 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 (one tablet of 40 mg pantoprazole) should not be exceeded in patients with severe liver impairment. Pantoprazole gastro-resistant tablets 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 gastro-resistant tablets in combination treatment of these patients (see section 4.4).

**Renal Impairment**
No dose adjustment is necessary in patients with impaired renal function. Pantoprazole gastro-resistant tablets 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 gastro-resistant tablets in combination treatment for these patients.

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

### 4.3 Contraindications
Hypersensitivity to the active substance, substituted benzimidazoles, or to any of the other excipients or of the combination partners.

### 4.4 Special warnings and precautions for use

#### Hepatic Impairment
In patients with severe liver impairment, the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise in liver enzymes, 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 the 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 with 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 one 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. someazole antifungals such as ketoconazole, itraconazole, posaconazole and other medicines such as erlotinib.

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

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

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

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

Results from a range of interaction studies demonstrate that pantoprazole does not effect the metabolism of active substances 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>
<thead>
<tr>
<th>Frequency Class</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td>Thrombocytopenia; Leukopenia</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (including anaphylactic reactions and anaphylactic shock)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes</td>
<td></td>
<td>Hyponatraemia</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)</td>
</tr>
</tbody>
</table>
### 4.9 Overdose

There are no known symptoms of overdose in man. Systemic exposure with up to 240 mg administered intravenously over two minutes was 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 two 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 the stimulation by other substances (acetylcholine, histamine, gastrin).

Pantoprazole has the same effect whether administered orally or intravenously.

The fasting gastrin values increased 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 concentrations 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 metabolised in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathways 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 recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialysed. Although the main metabolite has a moderately delayed half-life (two to three 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 seven and nine hours and the AUC values increased by a factor of five to seven, 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 to 16 years AUC and Cmax were in the range of corresponding values in adults. Following administration of single intravenous doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 to 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 tumours was observed in rats and in female mice and was interpreted as being due to pantoprazole’s high metabolic rate in the liver.

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

In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg. Investigations revealed no evidence of impaired fertility or teratogenic effects. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablet core
Mannitol (E421)
Partially pre-gelatinized maize starch
Colloidal anhydrous silica
Sodium carbonate (anhydrous) (E500)(i)
Calcium stearate
Talc (E553b)
Sodium starch glycolate (type A)

Enteric coating
Methacrylic acid – ethyl acrylate copolymer (1:1)
Sodium hydroxide (E524)
Triethyl citrate (E1505)
Talc (E553b)

Coating seal (yellow)
Hypermellose (E464)
Titanium dioxide (E171)
Macrogol 4000
Iron oxide yellow (E172)
Blue indigo carmine aluminium lake (E132).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months (unopened).

6.4 Special precautions for storage
This medicinal product does not require any special temperature storage conditions.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
Blisters (OPA/Aluminium/PVC film and aluminium foil), containing 14 tablets, and outer cardboard carton.

Pack size: 28 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
U.K.

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0373

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/05/2010

10 DATE OF REVISION OF THE TEXT
24/05/2010
PAR Pantoprazole 20mg and 40mg Gastro-resistant Tablets

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pantoprazole 20mg Gastro-resistant Tablets
Parizezole

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

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

1. What Pantoprazole Tablets are and what they are used for

Pantoprazole Tablets are selective proton pump inhibitors, which are medicines that reduce the amount of acid produced in your stomach. They are used for treating acid-related diseases of the stomach and intestine.

Pantoprazole Tablets are used for:
- Adults and adolescents 12 years of age and above.
- Treating symptoms (e.g. heartburn, acid regurgitation, pain on swallowing) associated with gastro-oesophageal reflux disease caused by reflux of acid from the stomach.
- Long-term management of reflux oesophagitis (inflammation of the oesophagus accompanied by regurgitation of stomach acid) and preventing its return.

Adolescents:
- Providing increased protection for patients who are taking non-steroidal anti-inflammatory drugs (NSAIDs), for example ibuprofen in patients at risk who need to take NSAIDs continuously.

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 (see section 4).
- If you are allergic to milk proteins 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. He will check your liver enzymes more frequently, especially when you are taking Pantoprazole Tablets as a long-term treatment. In case of a rise of liver enzymes the treatment should be stopped.
- If you need to take medicines called NSAIDs continuously and receive Pantoprazole Tablets because you have an increased risk of developing stomach and intestinal complications. Any increased risk will be assessed according to your personal risk factors such as your age (65 years or more), a history of stomach or duodenal ulcers or of stomach or intestinal bleeding.
- If you have reduced body stores or risk factors for reduced vitamin B12 and receive Pantoprazole Tablets as a 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 alazanavir (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 look pale and feel weak (anaemia)
- you notice blood in your stools
- severe and/or persistent diarrhea, as Pantoprazole Tablets have been associated with a small increase in infectious diarrhea.

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 also monitor your symptoms and report any new and exceptional symptoms and circumstances whenever he sees you.

Taking other medicines
Pantoprazole Tablets may influence the effectiveness of other medicines, so tell your doctor if you are taking:
- Medicines such as beta-blockers, tetracycline and potassium chloride (used to treat fungal infections) or omeprazole (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.
- Azathioprine (used to treat HIV-infection).

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

Pregnancy and breastfeeding
There are no adequate data from the use of pantoprazole in pregnant women. Exposure to human milk has been reported. If you are pregnant, or think you may be pregnant, or if you are breastfeeding, you should use this medicine only if your doctor considers the benefit 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 machinery
If you experience side effects like dizziness or disturbed vision, you should not drive or operate machinery.

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 tablet(s) 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 symptoms (e.g. heartburn, acid regurgitation, pain on swallowing) associated with gastro-oesophageal reflux disease.
  - The usual dose is one tablet a day. This dose usually brings relief within 2 – 4 weeks – in most after 1 1/2 – 2 weeks. If symptoms persist, tell your doctor.
  - After healing, you can reduce the dose back to one tablet a day after 1 tablet 20mg a day.

Adults:
- To prevent duodenal and stomach ulcers in patients who need to take NSAIDs continuously.
- The usual dose is one tablet a day.

Special patient groups
- If you suffer from severe liver problems, you should not take more than one 20mg tablet a day.
- Children under 12 years. These tablets are not recommended for use in children below 12 years.

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PAR Pantoprazole 20mg and 40mg Gastro-resistant Tablets

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 next 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 Tablets can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:
- very common (affects more than 1 in 10 common (affects 1 to 10 in 100)
- uncommon (affects 1 to 10 in 1,000)
- rare (affects 1 to 10 in 10,000)
- very rare (affects less than 1 in 10,000)
- 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 unknown): swelling of the tongue or throat, difficulty in swallowing, hives (itchy rash), difficulty in breathing, allergic facial swelling, severe dizziness with very fast heartbeat and heavy sweating.
- Serious skin conditions (frequency not known): blistering of the skin with rapid deterioration of your general condition, acne (including severe bleeding) of the eyes, nose, mouth, lips or genitals (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 liver damage) jaundice or fever, rash, enlarged glands sometimes with painful urination and lower back pain (serious inflammation of the kidneys).

Other side effects are:
- Uncommon (affects 1 to 10 in 1,000): headache, dizziness, diarrhoea, feeling sick, vomiting, blurring of vision, constipation, dry mouth, abdominal pain and discomfort, skin rash, exanthema, urticaria, itching, feeling weak, exhausted or generally unwell, sleep disturbances.
- Rare (affects 1 to 10 in 10,000): 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; breast enlargement in males.
- Very Rare (affects less than 1 in 10,000): diarrhoea.
- Not known (frequency cannot be estimated from the available data): hallucinations, confusion (especially in patients with a history of these symptoms), decreased sodium levels in blood.

Side effects identified through blood tests:
- Uncommon (affects 1 to 10 in 1,000): an increase in liver enzymes.
- Rare (affects 1 to 10 in 10,000): an increase in bilirubin, increased fats in the blood.
- Very Rare (affects less than 1 in 10,000): 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 get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Pantoprazole Tablets

Keep out of the reach and sight of children.

Do not use Pantoprazole Tablets after the expiry date, which is stated on the label and blister. The expiry date refers to the last day of that month.

This medicinal product does not require any special temperature storage conditions. Store in the original container to protect from moisture.

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 protect the environment.

6. Further information

What Pantoprazole Tablets contain
- The active ingredient is pantoprazole. Each gastro-resistant tablet contains 20mg of pantoprazole (as sodium sesquihydrate).
- The other ingredients are: Coating: hydroxypropylmethyl cellulose (E464), titanium dioxide (E171), lactose monohydrate (E901), sodium carbonate anhydrous (E529), sodium starch glycolate (E462), magnesium stearate (E467), yellow iron oxide (E172), citric acid (E336), talc (E426), sodium hydroxide (E525), sodium metasilicate pentahydrate (E952), titanium dioxide (E171), anhydrous citric acid (E330), yellow iron oxide (E172), and white and blue food colouring (E133).

What Pantoprazole Tablets look like and the contents of the pack
- A yellow, oval, bisacetyl gastro-resistant tablet, plain on both sides.
- Pack size: blister pack and outer carton.

Pantoprazole Tablets are available in a pack size of 28 tablets.

Marketing Authorisation Holder
- Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK

Manufacturer
- CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK

Other formats
- For the Republic of Ireland please call 0800 166 5000 (UK Only)

Please be ready to give the following information:

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<thead>
<tr>
<th>Product name</th>
<th>Reference number</th>
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<tbody>
<tr>
<td>Pantoprazole 20 mg gastro-resistant tablets</td>
<td>298310372</td>
</tr>
</tbody>
</table>

This is a service provided by the Royal National Institute of Blind People.

For the Republic of Ireland please call +353 52 326523.

This medicinal product is authorised in the following Member States in the EEA, under the following names:
- Cyprus - Pantoprazole Wockhardt 20 mg Gastro-resistant Tablets
- Malta - Pantoprazole 20mg Gastro-resistant Tablets
- Poland - Wockhardt Pantoprazole 20 mg Gastro-resistant Tablets
- Republic of Ireland - Pantoprazole 20mg Gastro-resistant Tablets
- United Kingdom - Pantoprazole 20mg Gastro-resistant Tablets

PAR Pantoprazole 20mg and 40mg Gastro-resistant Tablets

UK/H/1932/01-02/DC

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pantoprazole 40mg Gastro-resistant Tablets
Pantoprazole

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

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

1. What Pantoprazole Tablets are and what they are used for

Pantoprazole Tablets are selective "proton pump inhibitors", which are medicines that reduce the amount of acid produced in your stomach. They are used for treating acid-related diseases of the stomach and intestine.

Pantoprazole Tablets are 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.
- Gastro-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 (see section 4).
- If you are allergic to medicines containing other proton pump inhibitors.

Take special care with Pantoprazole Tablets:
- If you have severe liver problems. Please tell your doctor if you ever had problems with your liver in the past. He will check your liver enzymes more frequently, especially when you are taking Pantoprazole Tablets as a long-term treatment. In the case of a rare liver enzyme the treatment should be stopped.
- If you have reduced body stores or risk factors for reduced vitamin B12 and receive Pantoprazole Tablets as a 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 alfacalcid (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 unusual loss of weight
- repeated vomiting
- difficulty in swallowing
- swelling of the lower limbs
- you look pale and feel weak (anaemia)
- you notice blood in your stools
- severe and/or persistent diarrhoea, as Pantoprazole Tablets have 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 Tablets may influence the effectiveness of other medicines, so tell your doctor if you are taking:
- Medicines such as ketorolac, tramadol and propamochol (used to treat fungal infections) or erlotinib (used for certain types of cancer) because pantoprazole may stop those and other medicines from working properly.
- Warfarin and phenprocoumon, which affect the thickening, or thinning of the blood. You may need further checks.
- Alfacalcid (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 breastfeeding
There are no adequate data from the use of pantoprazole in pregnant women. Excretion into human milk has been reported. If you are pregnant, or think you may be pregnant, or if you are breastfeeding, you should use this medicine only if your doctor considers the benefit 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 machinery
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: Take the tablets once 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 bacteria called Helicobacter pylori in patients with duodenal ulcers and stomach ulcers in combination with two antibiotics (Eradicating therapy).
  - One tablet twice a day for 10 days. Your doctor may tell you to increase to 2 tablets daily. The treatment period for Helicobacter pylori is usually between 4 and 8 weeks. Your doctor will tell you how long to take your medicine.

- For 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.

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

If you forget to take a dose:
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.
PAR Pantoprazole 20mg and 40mg Gastro-resistant Tablets

UK/H/1932/01-02/DC

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

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

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

If you stop taking Pantoprazole Tablets
Do not stop taking these tablets without first 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 Tablets can cause side effects, although not everyone gets them.

The frequency of possible side effects listed below is defined using the following convention:
- very common (affects more than 1 user in 10)
- common (affects 1 to 10 users in 100)
- uncommon (affects 1 to 10 users in 1,000)
- rare (affects 1 to 10 users in 10,000)
- very rare (less than 1 user in 10,000)
- 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 rate): swelling of the tongue and/or throat, difficulty in swallowing, hives (hives rash), difficulties in breathing, allergic facial swelling (Quincke’s oedema), angioedema, severe diarrhoea 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 extensive swelling of the eyes, nose, mouth, lips, or penis (Steinmann-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 or rash, and enlarged kidneys sometimes with painful urination and lower back pain (various inflammation or damage in the kidneys).

Other side effects are:
- Uncommon (affects 1 to 10 users in 1,000) headache, dizziness, diarrhoea, feeling sick, vomiting, bloating, and flatulence (wind), constipation, dry mouth, abdominal pain and discomfort, skin rash, urticaria, urination, itching, feeling thirsty, exhaustion, or generally unwell, sleep disorders.
- Rare (affects 1 to 10 users in 10,000) dizziness, feelings of depression, skin rash, urticaria, increased appetite, weight gain, raised body temperature, swelling of the extremities (peripheral oedema), allergic reactions, depression, breast enlargement in males.
- Very rare: (affects less than 1 user in 10,000) disconnection.
- Not known: (frequency cannot be estimated from the available data) hallucination, confusion (especially in patients with a history of these symptoms), decreased blood level in blood.

Side effects identified through blood tests:
- Uncommon (affects 1 to 10 users in 1,000) an increase in liver enzymes.
- Rare (affects 1 to 10 users in 10,000) an increase in blood glucose; increased fats in the blood.
- Very rare: (affects less than 1 user in 10,000) a reduction in the number of blood platelets, which can 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 get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Pantoprazole Tablets

Keep out of the reach and sight of children.

Do not use Pantoprazole Tablets after the expiry date, which is stated on the label and blister. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions. Store in the original container to protect from moisture.

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 protect the environment.

6. Further information

What Pantoprazole Tablets contain
- The active ingredient is pantoprazole. Each gastro-resistant tablet contains 40mg of pantoprazole (as sodium bisulfate).
- The other ingredients are:
  - Corn: mannitol (E421), partially pre-gelatinised maize starch, colloidal anhydrous silica, sodium croscarmellose (E501) itself, sodium dextrate, talc (E553m), sodium starch glycolate (susp A).
  - Coating: methacrylic acid – ethyl acrylate copolymer, sodium hydroxide (E320), sodium chloride (E330), tamarind gum (E417), hydrated lime (E551), iron oxide yellow (E172), and blue indigo carmine aluminium lake (E132).

What Pantoprazole Tablets look like and the contents of the pack
A yellow, oval, biconvex gastro-resistant tablet, plain on both sides.
Posed blister pack and outer cardboard carton.

Pantoprazole Tablets are available in a pack size of 20 tablets.

Marketing Authorisation Holder
B. Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 2UF, UK.

Manufacturer
CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 2UF, UK.

Other formats:
To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge, 0800 192 5002 (UK only).

Please be ready to give the following information:

<table>
<thead>
<tr>
<th>Product name</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantoprazole 40 mg gastro-resistant tablets</td>
<td>2933103730</td>
</tr>
</tbody>
</table>

This is a service provided by the Royal National Institute of Blind People.

For the Republic of Ireland please call +353 52 362553.

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

- Cyprus: Pantoprazole Wockhardt 40mg Gastro-resistant Tablets
- Malta: Pantoprazole 40mg Gastro-resistant Tablets
- Poland: Wockhardt Pantoprazole 40mg Gastro-resistant Tablets
- Republic of Ireland: Pantoprazole 40mg Gastro-resistant Tablets
- United Kingdom: Pantoprazole 40mg Gastro-resistant Tablets


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211677
CPH
Module 4
Labelling
Module 5

Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the MHRA considers that the applications for Pantoprazole 20mg and 40mg Gastro-resistant Tablets, in the treatment of erosive esophagitis associated with gastroesophageal reflux disease, maintenance of healing of erosive esophagitis and pathological hypersecretory conditions including Zollinger-Ellison-Syndrome could be approved.

These applications have been submitted under article 10(1) of Directive 2001/83/EC, as amended, as generic medicinal products, claiming essential similarity to the brand-leader, Pantozol® 20mg and 40mg gastro-resistant tablets which were first granted to Altana Pharma AG, The Netherlands on 6th June 1995.

With UK as the Reference Member State (RMS) in these Decentralised Procedures, Wockhardt UK Ltd is applying for the Marketing Authorisations for Pantoprazole 20mg & 40mg Gastro-resistant Tablets. The Concerned Member States (CMSs) are CY, IE, MT and PL.

Pantoprazole is a proton pump inhibitor, i.e. it inhibits specifically and dose-proportionally the gastric H⁺/K⁺-ATPase enzyme, which is responsible for acid secretion in the parietal cells of the stomach. It is used for the treatment of acid related disease like upper gastrointestinal ulceration and oesophageal reflux disease and – in conjunction with antibiotics – for the eradication of Helicobacter pylori.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

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

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 28th April 2010. The Marketing Authorisation was granted in the UK on 25th May 2010.
### ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Pantoprazole 20mg and 40mg Gastro-resistant Tablets</th>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Pantoprazole sodium sesquihydrate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>A02BC02 Proton pump inhibitors</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Gastro-resistant Tablets</td>
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<td>Reference numbers for the Mutual Recognition Procedure</td>
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<td>Reference Member State</td>
<td>United Kingdom</td>
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<tr>
<td>Concerned Member States</td>
<td>CY, IE, MT and PL</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 29831/0372-3</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Wockhardt UK Ltd</td>
</tr>
<tr>
<td></td>
<td>Ash Road North, Wrexham LL13 9UF, UK</td>
</tr>
</tbody>
</table>
SCIENTIFIC OVERVIEW AND DISCUSSION
II. QUALITY ASPECTS
DRUG SUBSTANCE
INN: Pantoprazole sodium sesquihydrate
Chemical Name: 5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridinyl)methyl]sulphinyl] - 1H-benzimidazole sodium salt sesquihydrate

Structure:

Molecular Formula: C_{16}H_{14}F_{2}N_{3}NaO_{4}S.3/2H_{2}O
Molecular Weight: 432.38 g/mol
Appearance: White to off-white powder. It is freely soluble in water and ethanol (96%), practically insoluble in hexane.

Synthesis of the drug substance from the designated starting material 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.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificate of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with foodstuffs.

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

DRUG PRODUCT
Other ingredients
Other ingredients consist of the pharmaceutical excipients mannitol (E421), partially pre-gelatinized maize starch, colloidal anhydrous silica, sodium carbonate (anhydrous) (E500)(i), calcium stearate, talc (E553b), sodium starch glycolate (type A), methacrylic acid – ethyl acrylate copolymer (1:1), sodium hydrosiloxe (E524), triethyl citrate (E1505), talc (E553b), OPADRY 04F82842 yellow which consists of hypromellose (E464), titanium dioxide (E171), macrogol 4000, iron oxide yellow (E172) and blue indigo carmine aluminium lake (E132)).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of OPADRY 04F82842 yellow which complies with an in-house specification.
Satisfactory Certificates of Analysis have been provided for all excipients.

**Pharmaceutical Development**
Suitable pharmaceutical development data have been provided for these applications.

The physico-chemical properties of the drug product have been compared with that of the originator product and these are similar.

**Manufacture**
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory, based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results are satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**
The finished product is packed in Blisters (OPA/Aluminium/PVC film and aluminium foil) in pack sizes of 28 tablets. Specifications and Certificates of Analysis for all packaging materials have been provided. All primary packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 18 months has been set for the product, with a storage instruction ‘Store in the original package in order to protect from moisture’.

**Bioequivalence**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Bioequivalence has been demonstrated between the test and reference products (see clinical assessment).

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SPC, 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. 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.

**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.
A suitable justification has been provided for not submitting a risk management plan for these products.

**Conclusion**

It is recommended that Marketing Authorisations are granted for these applications.

The requirements for a generic product of the originator product have been met with respect to qualitative and quantitative content of the active substance. In addition, similar physico-chemical properties have been demonstrated for the proposed and originator product.

**III. PRE-CLINICAL ASPECTS**

These applications claim to be generic medicinal products of Pantozol 20 and 40mg Gastro-resistant Tablets, which has been licensed within the EU for over 10 years.

No new preclinical data have been supplied with these applications. However, a preclinical expert report summarising relevant non-clinical studies has been included in the dossier. This is satisfactory.

A suitable justification has been provided for non-submission of a detailed environmental risk assessment.

There are no objections to the approval of these products from a preclinical viewpoint.

**IV. CLINICAL ASPECTS**

**Clinical Pharmacology**

**Pharmacokinetics**

In support of these applications, the marketing authorisation has submitted two bioequivalence studies performed under fasting and fed conditions.

1. A randomized, single dose, open-label, two-treatment, two period, two-sequence, crossover bioavailability study on Pantoprazole sodium 40mg Gastro resistant tablets (Wockhardt Limited, India) compared with Protium 40mg (Altana Pharma AG, Germany) Gastro resistant tablets in 44 normal, adult, human subjects under fasting condition.

**Results**

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Geometric mean</th>
<th>Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-t} (ratio test/reference)</td>
<td>96.24</td>
<td>87.19-106.23</td>
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<tr>
<td>AUC_{0-∞} (ratio test/reference)</td>
<td>97.68</td>
<td>91.01-104.85</td>
</tr>
<tr>
<td>C_{max} (ratio test/reference)</td>
<td>103.48</td>
<td>91.68-116.81</td>
</tr>
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The fasting bioequivalence study passed with the results falling within the conventional bioequivalence criteria of 80 – 125% with low variability, compared with Protium® 40mg delayed-release tablets, Altana Pharma AG, Germany.
2. A randomized, single dose, open-label, two-treatment, four-period, two-sequence, replicate, crossover comparative bioavailability study on Pantoprazole sodium 40mg Gastro resistant tablet (Wockhardt Limited, India) compared with Protium 40mg Gastro resistant tablet (Altana Pharma AG, Germany) in 52 normal, adult, human subjects under fed condition.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Geometric mean</th>
<th>Confidence limits</th>
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<tbody>
<tr>
<td>AUC$_0$-t (ratio test/reference)</td>
<td>96.13</td>
<td>87.49 – 105.63</td>
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<tr>
<td>AUC$_{0-\infty}$ (ratio test/reference)</td>
<td>100.25</td>
<td>91.32 – 110.06</td>
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<tr>
<td>C$_{\text{max}}$ (ratio test/reference)</td>
<td>97.89</td>
<td>86.30 – 111.04</td>
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The fed bioequivalence study passed with the results falling within the conventional bioequivalence criteria of 80 – 125 % for the parameters C$_{\text{max}}$, AUC$_0$-t and AUC$_{0-\infty}$ compared with Protium® 40mg Gastro resistant tablets, Altana Pharma AG, Germany.

The 90% confidence intervals for C$_{\text{max}}$, AUC$_{0-\text{t}}$ and AUC$_{0-\infty}$ were within the bioequivalence acceptance range of 80.00% - 125.00% for the fasting and fed studies. Bioequivalence has been demonstrated.

The results of the study with the 40mg formulation can be extrapolated to the 20mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Pharmacodynamics
The pharmacodynamic characteristics of pantoprazole have been well-studied in the past. There would be no particular concerns for a generic medicinal product. No new data have been submitted and none are required.

Clinical Efficacy
No new data have been submitted and none are required.

Clinical Safety
No new data have been submitted and none are required.

Expert Reports
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, non-critical summary of Module 5.

Module 1 – Administrative information
Marketing Authorisation Application forms (MAA)
The MAA forms are medically satisfactory.

Summary of Product Characteristics (SmPC)
The SPCs are medically satisfactory and consistent with that for the reference product.

Patient Information Leaflet (PIL)
The PIL is medically satisfactory and consistent with the SPC.
Packaging
The packaging are medically satisfactory.

Conclusion
The grant of marketing authorisations is recommended.

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

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

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Pantoprazole sodium 40mg delayed-release tablet and its respective reference product. As the 20mg strength of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 40mg strength can be extrapolated to the other strength of tablet.

No new or unexpected safety concerns arise from these applications.

The SPC and PIL are satisfactory and consistent with that of the reference product. Satisfactory labelling has also been submitted.

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

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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