Public Assessment Report

Decentralised Procedure

Pantoprazole 20 and 40mg Gastro-resistant Tablets

Pantoprazole sodium sesquihydrate

UK/H/1355-6/01-02/DC

UK licence no: PL 08608/0136-9

Applicant: Olinka UK Limited
LAY SUMMARY

On the 30th April 2010 the MHRA granted Olinka UK Limited Marketing Authorisations (licences) for the medicinal products Pantoprazole 20mg and 40mg Gastro-resistant Tablets. These are prescription-only medicines (POM).

Pantoprazole belongs to a group of medicines called proton pump inhibitors, which work by reducing the amount of acid. This product is used:

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

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 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Pantoprazole 20mg and 40mg Gastro-resistant Tablets</th>
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<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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</table>
| **MA Holder** | Olinka (UK) Limited  
38/40 Chamberlayne Road  
London  
United Kingdom  
NW10 3JE |
| **RMS** | UK |
| **CMS** | UK/H/1355/01/DC: SK, PL, DE, and CZ  
UK/H/1356/02/DC: DE and PL |
| **Procedure Number** | UK/H/1355-6/01-02/DC |
| **Timetable** | Day 210 – 6th April 2010 |
Module 2

UK/H/1355/01/DC

SUMMARY OF PRODUCT CHARACTERISTICS

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

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

3 PHARMACEUTICAL FORM
Gastro-resistant tablet.
Yellow, oval, concave, smooth tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
• For the treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing).
• For long-term management and prevention of relapse in reflux oesophagitis.
• Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment (see section 4.4).

4.2 Posology and method of administration

Method of administration
Pantoprazole 20 mg tablets should not be chewed or crushed, and should be swallowed whole with water before a meal.

Adults and adolescents 12 years of age and above
Treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing)
The recommended dosage is 20 mg pantoprazole daily. Symptom relief is generally accomplished within 2–4 weeks, and a 4-week treatment period is usually required for healing of associated oesophagitis. If this is not sufficient, healing will normally be achieved within a further 4 weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment.

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

Adults
Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk who need continuous NSAID treatment
The recommended dosage is 20 mg pantoprazole daily.

Elderly and patients with renal impairment
A daily dose of 40 mg pantoprazole should not be exceeded in these patient groups.

Patients with hepatic impairment
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment (see section 4.4). In these patients, hepatic enzyme levels should be monitored during the treatment. If hepatic enzyme levels become elevated, treatment with pantoprazole should be discontinued.

Children below 12 years of age
There is no information on the use of pantoprazole in children. Therefore pantoprazole tablets should not be used in children.

4.3 **Contraindications**

Hypersensitivity to pantoprazole or to any of the excipients.

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

4.4 **Special warnings and precautions for use**

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).

The use of Pantoprazole 20 mg for the prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Decreased gastric acidity due to any means – including proton pump inhibitors – increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to a slightly increased risk of gastrointestinal infections, such as *Salmonella* and *Campylobacter*.

Pantoprazole, as all acid-blocking medicinal products, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption in long-term treatment.

Pantoprazole is not intended for treatment of the gastrointestinal disorders accompanying functional dyspepsia.

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

Prior to treatment a malignant disease of the oesophagus or stomach should be excluded as the treatment with pantoprazole may alleviate the symptoms of malignant diseases and can thus delay diagnosis.

Patients who do not respond after 4 weeks should be investigated.

This medicinal product contains 2.93 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 **Interaction with other medicinal products and other forms of interaction**

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

Studies with other proton pump inhibitors have shown a marked reduction in atazanavir exposure during concomitant proton pump inhibitor treatment. Use of proton pump inhibitors is contraindicated during atazanavir treatment.

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

Even though no interactions with pantoprazole and phenprocoumon or warfarin have been observed in clinical pharmacokinetics studies, a few isolated post-marketing cases of INR value changes in concomitant treatment with these substances have been reported. If the patient is using coumarin-type
anticoagulants, measurements of prothrombin time / INR values are recommended after the initiation and discontinuation of pantoprazole and in irregular use of pantoprazole.

There were also no interactions with concomitantly administered antacids

4.6 Pregnancy and lactation

Pregnancy
Clinical experience in pregnant women is limited. Experience with proton pump inhibitors as a class does not indicate an increased risk for major congenital malformations. In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Lactation
There is no information on the excretion of pantoprazole into human breast milk. During pregnancy and breast feeding, pantoprazole tablets should only be used when the benefit to the mother is considered greater than the potential risk to the fetus or child.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive and use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). Under these conditions the ability to react may be decreased.

4.8 Undesirable effects

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Common (≥ 1/100 to &lt; 1/10)</th>
<th>Uncommon (≥ 1/1000 to &lt; 1/10)</th>
<th>Rare (≥ 1/10000 to &lt; 1/100)</th>
<th>Very rare (&lt; 1/10000, incl. isolated reports)</th>
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<tbody>
<tr>
<td><strong>Blood and lymphatic system</strong></td>
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<td>Leukopenia; Thrombocytopenia</td>
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<td><strong>Gastrointestinal Disorders</strong></td>
<td>Upper abdominal pain; Diarrhoea; Constipation; Flatulence</td>
<td>Nausea / Vomiting</td>
<td>Dry mouth</td>
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<td><strong>General disorders and administration site conditions</strong></td>
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<td>Peripheral edema</td>
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<td><strong>Hepatobiliary disorders</strong></td>
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<td></td>
<td>Severe hepatocellular damage leading to jaundice with or without hepatic failure</td>
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<tr>
<td><strong>Immune system disorders</strong></td>
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<td>Anaphylactic reactions including anaphylactic shock</td>
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<td><strong>Investigations</strong></td>
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<td>Increased liver enzymes (transaminases, (\gamma)-GT); Elevated triglycerides; Increased body temperature</td>
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<tr>
<td><strong>Musculoskeletal, connective tissue disorders</strong></td>
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<td>Arthralgia</td>
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<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Headache</td>
<td>Dizziness; Disturbances in vision (blurred)</td>
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<td>Myalgia</td>
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<tr>
<td>Psychiatric disorders</td>
<td>Depression, Hallucination, Disorientation and 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>Renal and urinary disorders</td>
<td>Interstitial nephritis</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Allergic reactions such as pruritus and skin rash</td>
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<td></td>
<td>Urticaria; Angioedema; Severe skin reactions such as Stevens-Johnson Syndrome, Erythema multiforme, Lyell-Syndrome; Photosensitivity</td>
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4.9 Overdose

There are no known symptoms of over dosage in man.

Doses up to 240 mg i.v. were administered over 2 minutes and were well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable.

Cases of overdosage or poisoning should be treated according to the standard treatment practice of toxic conditions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors
ATC code: A02BC02

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

Pantoprazole is converted to its active form in the acidic channel of the parietal cells where it inhibits the H+, K+-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved in 2 weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, the substance can affect hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is administered orally or intravenously.

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

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid and liver enzymes according to results in animal studies.
5.2 Pharmacokinetic properties

General pharmacokinetics

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single oral dose. On average, the maximum serum concentrations are 1–1.5 µg/ml at about 2.0–2.5 hours post-administration, and these values remain constant after multiple administration. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg.

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

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

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

Bioavailability

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

Characteristics in patients/special groups of subjects

No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole can be dialyzed. Although the main metabolite has a moderately delayed half-life (2–3 h), excretion is still rapid and thus accumulation does not occur. However, the daily dose of 40 mg pantoprazole should not be exceeded in patients with impaired renal function.

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

A slight increase in AUC and 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity.

In a two-year carcinogenicity study in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment.

In two-year rodent studies, an increased number of liver tumours was observed in rats (in one rat study only) and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.
A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg) in one two-year study. The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no side effects on the thyroid glands are expected.

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

Investigations revealed no evidence of impaired fertility or teratogenic effects. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, the concentration of pantoprazole in the fetus is increased shortly before birth.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Disodium phosphate anhydrous
Mannitol (75-315 μm)
Cellulose microcrystalline
Crocarmellose sodium
Magnesium stearate (vegetable)
Hypromellose (Type 60cP)
Triethyl citrate
Sodium starch glycolate (Type A)
Methacrylic acid-ethyl acrylate copolymer (1:1), dispersion at 30%
Yellow iron oxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
1. Alu/Alu blister - packed in packs of 14, 15, 28, 30, 56, 60 & 100 tablets
2. HDPE bottle and child-resistant polypropylene cap with desiccant compartment packaged in packs of 14, 15, 28, 30, 56, 60, & 100 tablets.

Not all pack sizes may be marketed.

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

7 MARKETING AUTHORISATION HOLDER
Olinka (UK) Limited
38/40 Chamberlayne Road
London
United Kingdom
NW10 3JE

8 MARKETING AUTHORISATION NUMBER(S)
PL 08608/0136

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/04/2010

10 DATE OF REVISION OF THE TEXT
30/04/2010
NAME OF THE MEDICINAL PRODUCT
Pantoprazole 40 mg Gastro-resistant tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each gastro-resistant tablet contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate). For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Gastro-resistant tablet.

YELLOW, OVAL, CONCAVE, SMOOTH TABLETS

CLINICAL PARTICULARS

4.1 Therapeutic indications
For relieving the symptoms and for short-term treatment of gastrointestinal diseases which require a reduction in acid secretion:
- duodenal ulcer
- gastric ulcer
- moderate and severe reflux oesophagitis
- Zollinger-Ellison syndrome and other hypersecretory conditions.

4.2 Posology and method of administration

Adults and adolescents 12 years of age and above
Moderate and severe reflux oesophagitis
The recommended dosage is 40 mg pantoprazole daily. In some cases this may be doubled 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
Gastric and Duodenal ulcer
The recommended dosage is 40 mg pantoprazole daily. In some cases this may be doubled especially when there has been no response to other treatment. Duodenal ulcers generally heal within two weeks. If a two-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further two weeks. A four-week period is usually required for the treatment of gastric ulcers and reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further four weeks.

Zollinger-Ellison-Syndrome and other hypersecretory conditions
In the treatment of Zollinger-Ellison syndrome and other hypersecretory conditions, the initial dose is 80 mg daily. Thereafter, the dosage can be increased or decreased as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control. Treatment duration in Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.

Elderly
A daily dose of 40 mg pantoprazole should not be.

Patients with renal impairment
The daily dose of 40 mg pantoprazole should not be exceeded in patients with impaired renal function. For this reason, *H. pylori* triple therapy is not appropriate in these patients (see section 4.3).

Patients with hepatic impairment
Patients with severe hepatic impairment should be given 40 mg of pantoprazole every other day (see sections 4.3 and 4.4). In these patients, hepatic enzyme levels should be monitored during the treatment. If hepatic enzyme levels become elevated, treatment with pantoprazole should be discontinued. For this reason, *H. pylori* triple therapy is not appropriate in these patients.
Children below 12 years of age
There is no information on the use of pantoprazole in children. Therefore pantoprazole tablets should not be used in children.

Method of administration
Pantoprazole 40 mg tablets should not be chewed or crushed, and should be swallowed whole with water before a meal.

4.3 Contraindications
Hypersensitivity to pantoprazole or to any of the excipients.

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

Pantoprazole must not be used in combination treatment for eradication of *H. pylori* in patients with moderate to severe hepatic or renal dysfunction since currently no data are available on the efficacy and safety of Pantoprazole in combination treatment of these patients.

4.4 Special warnings and precautions for use
There is no data available to make dose adjustment in patients with moderate and severe renal impairment. For patient with severe hepatic impairment, patients should be given 40 mg of pantoprazole every other day. In patients with severe liver impairment the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise of the liver enzymes, the treatment should be discontinued (see section 4.2 and 4.3).

Decreased gastric acidity due to any means – including proton pump inhibitors – increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to a slightly increased risk of gastrointestinal infections, such as *Salmonella* and *Campylobacter*.

In patients with Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered 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.

Pantoprazole is not intended for treatment of the gastrointestinal disorders accompanying functional dyspepsia.

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

Prior to treatment a malignant disease of the oesophagus or stomach should be excluded as the treatment with pantoprazole may alleviate the symptoms of malignant diseases and can thus delay diagnosis.

Patients who do not respond after 4 weeks should be investigated.

This medicinal product contains 5.85 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

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

Studies with other proton pump inhibitors have shown a marked reduction in atazanavir exposure during concomitant proton pump inhibitor treatment. Use of proton pump inhibitors is contraindicated during atazanavir treatment.

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

Even though no interactions with pantoprazole and phenprocoumon or warfarin have been observed in clinical pharmacokinetics studies, a few isolated post-marketing cases of INR value changes in concomitant treatment with these substances have been reported. If the patient is using coumarin-type anticoagulants, measurements of prothrombin time / INR values are recommended after the initiation and discontinuation of pantoprazole and in irregular use of pantoprazole.

There were also no interactions with concomitantly administered antacids

4.6 Pregnancy and lactation

Pregnancy
Clinical experience in pregnant women is limited. Experience with proton pump inhibitors as a class does not indicate an increased risk for major congenital malformations. In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Lactation
There is no information on the excretion of pantoprazole into human breast milk. During pregnancy and breast feeding, pantoprazole tablets should only be used when the benefit to the mother is considered greater than the potential risk to the fetus or child.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive and use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). Under these conditions the ability to react may be decreased.

4.8 Undesirable effects

Common
≥ 1/100 to < 1/10

Uncommon
≥ 1/1000 to < 1/100

Rare
≥ 1/10 000 to < 1/1000

Very rare < 1/10 000, including isolated reports

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Organ system</th>
<th>common (&gt;1/100, &lt;1/10)</th>
<th>uncommon (&gt;1/1000, &lt;1/100)</th>
<th>rare (&lt;1/1000, &gt;1/10,000)</th>
<th>Very rare (&lt;1/10,000, incl. isolated reports)</th>
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<tbody>
<tr>
<td>Blood and lymphatic system</td>
<td>Leukopenia; Thrombocytopenia</td>
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<td>Immune system disorders</td>
<td>Anaphylactic reactions including anaphylactic shock</td>
<td></td>
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<tr>
<td>Investigations</td>
<td>Increased liver enzymes (transaminases, γ-GT); Elevated triglycerides; Increased body weight</td>
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<tr>
<td>Musculoskeletal, connective tissue disorders</td>
<td>Arthralgia</td>
<td>Myalgia</td>
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<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness; Disturbances in vision (blurred vision)</td>
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<tr>
<td>Psychiatric disorders</td>
<td></td>
<td>Depression, Hallucination, Disorientation and Confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence</td>
<td></td>
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<tr>
<td>Renal and urinary disorders</td>
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<td>Interstitial nephritis</td>
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<td></td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Allergic reactions such as pruritus and skin rash</td>
<td>Urticaria; Angioedema; Severe skin reactions such as Stevens-Johnson Syndrome, Erythema multiforme, Lyell-Syndrome; Photosensitivity</td>
<td></td>
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</tbody>
</table>

4.9 Overdose
There are no known symptoms of over dosage in man.

Doses up to 240 mg i.v. were administered over 2 minutes and were well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable.

Cases of overdosage or poisoning should be treated according to the standard treatment practice of toxic conditions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Proton pump inhibitors
ATC code: A02BC02

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

Pantoprazole is converted to its active form in the acidic channel of the parietal cells where it inhibits the H⁺, K⁺-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved in 2 weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, the substance can affect hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is administered orally or intravenously.

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

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid and liver enzymes according to results in animal studies.

5.2 Pharmacokinetic properties

General pharmacokinetics
Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single oral dose. On average, the maximum serum concentrations are 1–1.5 µg/ml at about 2.0–2.5 hours post-administration, and these values remain constant after multiple administration. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg.

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

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

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

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

Characteristics in patients/special groups of subjects
No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole can be dialyzed. Although the main metabolite has a moderately delayed half-life (2–3h), excretion is still rapid and thus accumulation does not occur. However, the daily dose of 40 mg pantoprazole should not be exceeded in patients with impaired renal function.

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

A slight increase in AUC and 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity.

In a two-year carcinogenicity study in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and
allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment.

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

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

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

Investigations revealed no evidence of impaired fertility or teratogenic effects. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, the concentration of pantoprazole in the fetus is increased shortly before birth.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- Disodium phosphate anhydrous
- Mannitol (75-315 μm)
- Cellulose microcrystalline
- Croscarmellose sodium
- Magnesium stearate (vegetable)
- Hypromellose (Type 6 cP)
- Triethyl citrate
- Sodium starch glycolate (Type A)
- Methacrylic acid-ethyl acrylate copolymer (1:1), dispersion at 30%
- Yellow iron oxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 30ºC.

6.5 Nature and contents of container
1. Alu/Alu blister - packed in packs of 14, 15, 28, 30, 60 & 100 tablets
2. HDPE bottle and child-resistant polypropylene cap with desiccant compartment packaged in packs of 14, 15, 28, 30, 60, & 100 (2x50) tablets.

Not all pack sizes may be marketed.

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

7 MARKETING AUTHORISATION HOLDER
Olinka (UK) Limited
38/40 Chamberlayne Road
London
United Kingdom
NW10 3JE

8 MARKETING AUTHORISATION NUMBER(S)
PL 08608/0137
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/04/2010

10 DATE OF REVISION OF THE TEXT
30/04/2010
UK/H/1356/01/DC

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

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

3 PHARMACEUTICAL FORM
Gastro-resistant tablet.

Yellow, oval, concave, smooth tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
- For the treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing).
- For long-term management and prevention of relapse in reflux oesophagitis.
- Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment (see section 4.4).

4.2 Posology and method of administration

Method of administration
Pantoprazole 20 mg tablets should not be chewed or crushed, and should be swallowed whole with water before a meal.

Adults and adolescents 12 years of age and above
Treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing)
The recommended dosage is 20 mg pantoprazole daily. Symptom relief is generally accomplished within 2–4 weeks, and a 4-week treatment period is usually required for healing of associated oesophagitis. If this is not sufficient, healing will normally be achieved within a further 4 weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment.

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

Adults
Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk who need continuous NSAID treatment
The recommended dosage is 20 mg pantoprazole daily.

Elderly and patients with renal impairment
A daily dose of 40 mg pantoprazole should not be exceeded in these patient groups.

Patients with hepatic impairment
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment (see section 4.4). In these patients, hepatic enzyme levels should be monitored during the treatment. If hepatic enzyme levels become elevated, treatment with pantoprazole should be discontinued.

Children below 12 years of age
There is no information on the use of pantoprazole in children. Therefore pantoprazole tablets should not be used in children.
Method of administration
Pantoprazole 20 mg tablets should not be chewed or crushed, and should be swallowed whole with water before a meal.

4.3 Contraindications
Hypersensitivity to pantoprazole or to any of the excipients.

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

4.4 Special warnings and precautions for use
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).

The use of Pantoprazole 20 mg for the prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Decreased gastric acidity due to any means – including proton pump inhibitors – increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to a slightly increased risk of gastrointestinal infections, such as *Salmonella* and *Campylobacter*.

Pantoprazole, as all acid-blocking medicinal products, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption in long-term treatment.

Pantoprazole is not intended for treatment of the gastrointestinal disorders accompanying functional dyspepsia.

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

Prior to treatment a malignant disease of the oesophagus or stomach should be excluded as the treatment with pantoprazole may alleviate the symptoms of malignant diseases and can thus delay diagnosis.

Patients who do not respond after 4 weeks should be investigated.

This medicinal product contains 2.93 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

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

Studies with other proton pump inhibitors have shown a marked reduction in atazanavir exposure during concomitant proton pump inhibitor treatment. Use of proton pump inhibitors is contraindicated during atazanavir treatment.

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

Even though no interactions with pantoprazole and phenprocoumon or warfarin have been observed in clinical pharmacokinetics studies, a few isolated post-marketing cases of INR value changes in concomitant treatment with these substances have been reported. If the patient is using coumarin-type
anticoagulants, measurements of prothrombin time / INR values are recommended after the initiation
and discontinuation of pantoprazole and in irregular use of pantoprazole.

There were also no interactions with concomitantly administered antacids

4.6 Pregnancy and lactation

Pregnancy
Clinical experience in pregnant women is limited. Experience with proton pump inhibitors as a class
does not indicate an increased risk for major congenital malformations. In animal reproduction studies,
signs of slight fetotoxicity were observed at doses above 5 mg/kg (see section 5.3). Caution should be
exercised when prescribing to pregnant women.

Lactation
There is no information on the excretion of pantoprazole into human breast milk. During pregnancy
and breast feeding, pantoprazole tablets should only be used when the benefit to the mother is
considered greater than the potential risk to the fetus or child.

4.7 Effects on ability to drive and use machines
There are no known effects on the ability to drive and use machines. Adverse drug reactions such as
dizziness and visual disturbances may occur (see section 4.8). Under these conditions the ability to
react may be decreased.

4.8 Undesirable effects
Common ≥ 1/100 to < 1/10
Uncommon ≥ 1/1000 to < 1/100
Rare ≥ 1/10 000 to ≤ 1/1000
Very rare < 1/10 000, including isolated reports

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Organ system</th>
<th>common (&gt;1/100, &lt;1/10)</th>
<th>uncommon (&gt;1/1000, &lt;1/100)</th>
<th>rare (&lt;1/1000, &gt;1/10,000)</th>
<th>Very rare (&lt;1/10,000, incl. Isolated reports)</th>
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<tbody>
<tr>
<td>Blood and lymphatic system</td>
<td>Leukopenia; Thrombocytopenia</td>
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<tr>
<td>Gastrointestinal Disorders</td>
<td>Upper abdominal pain; Diarrhoea; Constipation; Flatulence</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Nausea / Vomiting</td>
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<td></td>
<td>Dry mouth</td>
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<td></td>
<td>Peripheral edema</td>
<td></td>
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<tr>
<td>Hepatobiliary disorders</td>
<td>Severe hepatocellular damage leading to jaundice with or without hepatic failure</td>
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<tr>
<td>Immune system disorders</td>
<td>Anaphylactic reactions including anaphylactic shock</td>
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<td>Dizziness; Disturbances in vision (blurred)</td>
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</tbody>
</table>
Psychiatric disorders

Depression, Hallucination, Disorientation and Confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Renal and urinary disorders

Interstitial nephritis

Skin and subcutaneous tissue disorders

Allergic reactions such as pruritus and skin rash

Urticaria; Angioedema; Severe skin reactions such as Stevens-Johnson Syndrome, Erythema multiforme, Lyell-Syndrome; Photosensitivity

4.9 Overdose

There are no known symptoms of over dosage in man.

Doses up to 240 mg i.v. were administered over 2 minutes and were well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable.

Cases of overdosage or poisoning should be treated according to the standard treatment practice of toxic conditions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pantoprazole is converted to its active form in the acidic channel of the parietal cells where it inhibits the H+, K+-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved in 2 weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, the substance can affect hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is administered orally or intravenously.

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

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid and liver enzymes according to results in animal studies.
5.2 Pharmacokinetic properties

General pharmacokinetics
Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single oral dose. On average, the maximum serum concentrations are 1–1.5 µg/ml at about 2.0–2.5 hours post-administration, and these values remain constant after multiple administration. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg.

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

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

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

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

Characteristics in patients/special groups of subjects
No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole can be dialyzed. Although the main metabolite has a moderately delayed half-life (2–3h), excretion is still rapid and thus accumulation does not occur. However, the daily dose of 40 mg pantoprazole should not be exceeded in patients with impaired renal function.

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

A slight increase in AUC and 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity.

In a two-year carcinogenicity study in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment.

In two-year rodent studies, an increased number of liver tumours was observed in rats (in one rat study only) and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.
A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg) in one two-year study. The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no side effects on the thyroid glands are expected.

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

Investigations revealed no evidence of impaired fertility or teratogenic effects. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, the concentration of pantoprazole in the fetus is increased shortly before birth.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Disodium phosphate anhydrous
Mannitol (75-315 μm)
Cellulose microcrystalline
Crocarmellose sodium
Magnesium stearate (vegetable)
Hypermellose (Type 6 cP)
Triethyl citrate
Sodium starch glycolate (Type A)
Methacrylic acid-ethyl acrylate copolymer (1:1), dispersion at 30%
Yellow iron oxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
1. Alu/Alu blister - packed in packs of 14, 15, 28, 30, 60 & 100 tablets
2. HDPE bottle and child-resistant polypropylene cap with desiccant compartment packaged in packs of 14, 15, 28, 30, 60, & 100 tablets.

Not all pack sizes may be marketed.

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

7 MARKETING AUTHORISATION HOLDER
Olinka (UK) Limited
38/40 Chamberlayne Road
London
United Kingdom
NW10 3JE

8 MARKETING AUTHORISATION NUMBER(S)
PL 08608/0138

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/04/2010

10 DATE OF REVISION OF THE TEXT
30/04/2010
1 NAME OF THE MEDICINAL PRODUCT
Pantoprazole 40 mg Gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 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.

Yellow, oval, concave, smooth tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
For relieving the symptoms and for short-term treatment of gastrointestinal diseases which require a reduction in acid secretion:
- duodenal ulcer
- gastric ulcer
- moderate and severe reflux oesophagitis
- Zollinger-Ellison syndrome and other hypersecretory conditions.

4.2 Posology and method of administration

Adults and adolescents 12 years of age and above

Gastric and Duodenal ulcer
The recommended dosage is 40 mg pantoprazole daily. In some cases this may be doubled 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.

Elderly
A daily dose of 40 mg pantoprazole should not be exceeded.

Patients with renal impairment
The daily dose of 40 mg pantoprazole should not be exceeded in patients with impaired renal function.
For this reason, H. pylori triple therapy is not appropriate in these patients (see section 4.3).

Patients with hepatic impairment
Patients with severe hepatic impairment should be given 40 mg of pantoprazole every other day (see sections 4.3 and 4.4). In these patients, hepatic enzyme levels should be monitored during the treatment. If hepatic enzyme levels become elevated, treatment with pantoprazole should be discontinued. For this reason, H. pylori triple therapy is not appropriate in these patients.
There is no information on the use of pantoprazole in children. Therefore pantoprazole tablets should not be used in children.

**Method of administration**
Pantoprazole 40 mg tablets should not be chewed or crushed, and should be swallowed whole with water before a meal.

**4.3 Contraindications**
Hypersensitivity to pantoprazole or to any of the excipients.
Pantoprazole like other proton pump inhibitors should not be administered with atazanavir (see section 4.5).
Pantoprazole must not be used in combination treatment for eradication of *H. pylori* in patients with moderate to severe hepatic or renal dysfunction since currently no data are available on the efficacy and safety of Pantoprazole in combination treatment of these patients.

**4.4 Special warnings and precautions for use**
There is no data available to make dose adjustment in patients with moderate and severe renal impairment. For patient with severe hepatic impairment, patients should be given 40 mg of pantoprazole every other day. In patients with severe liver impairment the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise of the liver enzymes, the treatment should be discontinued (see section 4.2 and 4.3).

Decreased gastric acidity due to any means – including proton pump inhibitors – increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to a slightly increased risk of gastrointestinal infections, such as *Salmonella* and *Campylobacter*.

In patients with Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered 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.

Pantoprazole is not intended for treatment of the gastrointestinal disorders accompanying functional dyspepsia.

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

Prior to treatment a malignant disease of the oesophagus or stomach should be excluded as the treatment with pantoprazole may alleviate the symptoms of malignant diseases and can thus delay diagnosis.

Patients who do not respond after 4 weeks should be investigated.

This medicinal product contains 5.85 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

**4.5 Interaction with other medicinal products and other forms of interaction**
Pantoprazole may reduce the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole, itraconazole, atazanavir).

Studies with other proton pump inhibitors have shown a marked reduction in atazanavir exposure during concomitant proton pump inhibitor treatment. Use of proton pump inhibitors is contraindicated during atazanavir treatment.

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

Even though no interactions with pantoprazole and phenprocoumon or warfarin have been observed in clinical pharmacokinetics studies, a few isolated post-marketing cases of INR value changes in concomitant treatment with these substances have been reported. If the patient is using coumarin-type anticoagulants, measurements of prothrombin time / INR values are recommended after the initiation and discontinuation of pantoprazole and in irregular use of pantoprazole.

There were also no interactions with concomitantly administered antacids.

4.6 Pregnancy and lactation

Pregnancy
Clinical experience in pregnant women is limited. Experience with proton pump inhibitors as a class does not indicate an increased risk for major congenital malformations. In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Lactation
There is no information on the excretion of pantoprazole into human breast milk. During pregnancy and breast feeding, pantoprazole tablets should only be used when the benefit to the mother is considered greater than the potential risk to the fetus or child.

4.7 Effects on ability to drive and use machines
There are no known effects on the ability to drive and use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). Under these conditions the ability to react may be decreased.

4.8 Undesirable effects

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Organ system</th>
<th>common (&gt;1/100, &lt;1/10)</th>
<th>uncommon (&gt;1/1,000, &lt;1/100)</th>
<th>rare (&lt;1/1,000, &gt;1/10,000)</th>
<th>Very rare (&lt;1/10,000, incl. isolated reports)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system</td>
<td>Leukopenia; Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Upper abdominal pain; Diarrhoea; Constipation; Flatulence</td>
<td></td>
<td>Nausea / Vomiting</td>
<td>Dry mouth</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td>Peripheral edema</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
<td>Severe hepatocellular damage leading to jaundice with or without hepatic failure</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Anaphylactic reactions including anaphylactic shock</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
<td>Increased liver enzymes (transaminases, (\gamma)-GT); Elevated triglycerides;</td>
<td></td>
</tr>
</tbody>
</table>
### 4.9 Overdose
There are no known symptoms of overdose in man.

Doses up to 240 mg i.v. were administered over 2 minutes and were well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable.

Cases of overdosage or poisoning should be treated according to the standard treatment practice of toxic conditions.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

<table>
<thead>
<tr>
<th>Pharmacotherapeutic group: Proton pump inhibitors</th>
<th>ATC code: A02BC02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells.</td>
<td></td>
</tr>
<tr>
<td>Pantoprazole is converted to its active form in the acidic channel of the parietal cells where it inhibits the H⁺, K⁺-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved in 2 weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, the substance can affect hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is administered orally or intravenously.</td>
<td></td>
</tr>
<tr>
<td>The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the normal upper limit. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal, connective tissue disorders</th>
<th>Arthralgia</th>
<th>Myalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness; Disturbances in vision (blurred vision)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Depression, Hallucination, Disorientation and Confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Interstitial nephritis</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Allergic reactions such as pruritus and skin rash</td>
<td></td>
</tr>
</tbody>
</table>

Urticaria; Angioedema; Severe skin reactions such as Stevens-Johnson Syndrome, Erythema multiforme, Lyell Syndrome; Photosensitivity
long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far (see section 5.3), the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids can be ruled out for humans.

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid and liver enzymes according to results in animal studies.

5.2 Pharmacokinetic properties

General pharmacokinetics

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single oral dose. On average, the maximum serum concentrations are 1–1.5 µg/ml at about 2.0–2.5 hours post-administration, and these values remain constant after multiple administration. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg.

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

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

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

Bioavailability

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

Characteristics in patients/special groups of subjects

No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole can be dialyzed. Although the main metabolite has a moderately delayed half-life (2–3h), excretion is still rapid and thus accumulation does not occur. However, the daily dose of 40 mg pantoprazole should not be exceeded in patients with impaired renal function.

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

A slight increase in AUC and 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity.

In a two-year carcinogenicity study in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and
allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment.

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

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

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

Investigations revealed no evidence of impaired fertility or teratogenic effects. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, the concentration of pantoprazole in the fetus is increased shortly before birth.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Disodium phosphate anhydrous
Mannitol (75-315 μm)
Cellulose microcrystalline
Crocarmellose sodium
Magnesium stearate (vegetable)
Hypermellose (Type 6 cP)
Triethyl citrate
Sodium starch glycolate (Type A)
Methacrylic acid-ethyl acrylate copolymer (1:1), dispersion at 30%
Yellow iron oxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
1. Alu/Alu blister - packed in packs of 14, 15, 28, 30, 60 & 100 tablets
2. HDPE bottle and child-resistant polypropylene cap with desiccant compartment packaged in packs of 14, 15, 28, 30, 60, & 100 (2x50) tablets.

Not all pack sizes may be marketed.

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

7 MARKETING AUTHORISATION HOLDER
Olinka (UK) Limited
38/40 Chamberlayne Road
London
United Kingdom
NW10 3JE

8 MARKETING AUTHORISATION NUMBER(S)
PL 08608/0139
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pantoprazole 20 mg Gastro-resistant Tablets
Pantoprazole (as pantoprazole sodium sesquihydrate)

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 become 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 store Pantoprazole Tablets
6. Further information

1. WHAT PANTOPRAZOLE TABLETS ARE AND WHAT THEY ARE USED FOR
Pantoprazole belongs to a group of medicines called proton pump inhibitors, which work by reducing the amount of acid your stomach makes.
- You have been given Pantoprazole, because you have a condition caused by too much acid in the stomach. Pantoprazole reduces the amount of acid your stomach makes and is used: In the treatment of mild forms of oesophageal disease caused by reflux of acid from the stomach (with or without mild inflammation of the oesophagus (gullet)) and the associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing).
- in the long-term management of reflux oesophagitis (inflammation of the oesophagus accompanied by the regurgitation of stomach acid) and preventing its return.
- In preventing duodenal (part of the small bowel) and stomach ulcers caused by 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 any of the other ingredients in the tablets. Check the ingredients listed in section 6.
- if you are taking atazanavir (used to treat HIV infection).

Take special care with Pantoprazole Tablets
Please tell your doctor if any of the following apply to you:
- you have severe liver disease, as your doctor may need to monitor your liver function while you are taking Pantoprazole
- you have been diagnosed with vitamin B12 deficiency
- you are also taking painkillers called non-steroidal anti-inflammatory medicines (NSAIDs) – please also read the package leaflets of these medicines carefully
- you have been taking Pantoprazole for over a year. Your doctor will probably keep you under close supervision and you should report any new or worrying symptoms.
Please tell your doctor if you have, or have recently had, any of the following symptoms:

- unintentional weight loss
- recurrent vomiting
- vomiting blood (this may look dark like “coffee grounds”)
- black, tarry stools (faeces).

Your doctor may perform additional tests (e.g. endoscopy (visual inspection of the gullet, stomach, and upper intestine) to exclude the possibility of serious illness.

Please also tell your doctor if your symptoms persist despite adequate treatment with this medicine.

**Taking other medicines**

If you are taking other medicines with Pantoprazole they can sometimes interfere with, and alter the effect of, each other. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is particularly important to tell your doctor if you are taking any of the following:

- ketoconazole or itraconazole which are used to treat fungal infections of the skin and nails
- anticoagulants (medicines used to thin the blood) e.g. warfarin. You may need to have clotting tests done more frequently.
- atazanavir for the treatment of HIV infection.

**Taking Pantoprazole with food and drink**
Pantoprazole tablets should be taken on an empty stomach (before meals). You should swallow the tablet(s) whole, with water.

**Pregnancy and breast-feeding**

Ask your doctor or pharmacist for advice before taking any medicine. Experience with the use of pantoprazole in pregnant women is limited. There is no information on the excretion of pantoprazole into human breast milk. If you are pregnant, or if you are breast-feeding, you should use this medicine only if your treating physician considers the benefit to you is greater than any potential risk for your unborn child or baby.

**Driving and using machines**
Pantoprazole tablets do not normally affect the ability to drive and use machines. However, if you experience side effects such as dizziness, blurred vision or fatigue, your ability to react may be decreased. This should be taken into account when driving or using machines.

**Important information about some of the ingredients of Pantoprazole Tablets**

This product contains 2.93 mg of sodium per tablet. You should take this into account if you are on a controlled sodium diet.

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.

- Pantoprazole tablets should be taken on an empty stomach (before meals).
- You should swallow the tablet(s) whole, with water.

Do not crush, break or chew the tablet(s) as this will prevent them from working properly. The usual doses of Pantoprazole 20 mg are given below. Sometimes your doctor may prescribe you a different dose.

**Adults and adolescents 12 years of age and above**

For treating mild forms of oesophageal disease caused by reflux of acid from the stomach and the associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing):
The recommended dose is one 20 mg tablet every day for 2-4 weeks (extended for another 4 weeks if necessary). Your doctor will tell you how long to continue taking the medicine. After this any recurring symptoms can be controlled by taking one tablet daily, as needed.

For long-term management and for preventing the return of reflux oesophagitis:
The recommended dose is one 20 mg tablet a day.
If symptoms return, the dose may be doubled to 40 mg daily, in which case you can use Pantoprazole 40 mg tablets instead, one a day. After healing, you can reduce the dose back again to one tablet (20 mg) a day.

Adults
Prevention of gastric and duodenal ulcers caused by anti-inflammatory drugs:
The recommended dose is one 20 mg tablet every day for as long as prescribed by your doctor.

Elderly and patients with renal impairment
A daily dose of 40 mg should not be exceeded.

Patients with hepatic impairment
A daily dose of 20 mg should not be exceeded.

Children under 12 years of age
Pantoprazole tablets are not recommended for use in children under 12 years of age.

If you take more Pantoprazole Tablets than you should
If you take more Pantoprazole tablets than you have been told to, consult your doctor or pharmacist immediately.

If you forget to take Pantoprazole Tablets
Do not take a double dose to make up for a forgotten dose. If you do forget to take a dose, take it as soon as you remember unless it is almost time for your next dose.

If you stop taking Pantoprazole tablets
You should continue to take this medicine for as long as your doctor has told you. Do not stop just because you feel better. If you stop taking your tablets too soon, your symptoms may return.

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

4. POSSIBLE SIDE EFFECTS
Like all medicines, Pantoprazole tablets can cause side effects, although not everybody will experience them.

You should stop taking Pantoprazole and seek immediate medical advice if you experience any of the following symptoms as they could be due to a severe allergic reaction:
• a swollen face, mouth, tongue and/or throat
• difficulty swallowing
• an itchy rash (hives) and difficulty breathing

Common (less than 1 in 10 but more than 1 in 100 people treated)
• stomach-ache, diarrhoea, constipation or wind
• headaches.

Uncommon (less than 1 in 100 but more than 1 in 1,000 people treated)
• nausea (feeling sick)
• vomiting (being sick)
• dizziness
• blurred vision
• allergic reactions such as itchy skin and rash.

Rare (Less than 1 in 1000 but more than 1 in 10,000 people treated)
• dry mouth
• joint pain
• depression, hallucination, disorientation, confusion.

Very rare (Less than 1 in 10,000 people treated)
• a fall in the number of white cells or platelets in the blood.
• swollen legs
• muscle pain
• liver damage and jaundice (yellowing of the skin) which can be serious
• allergic reactions (these may be accompanied by a skin rash and can be severe, causing swelling of the face or mouth). This can cause difficulty breathing (see warning at the beginning of this section)
• raised body temperature
• kidney inflammation (nephratitis)
• severe skin reactions (Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis or Lyell’s disease)
• increased sensitivity of the skin to sunlight (photosensitivity)
• an increase in liver enzymes and raised blood triglycerides (a type of fat in the blood).

If any of the side effects become 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.
Store below 30°C.
Do not use Pantoprazole tablets after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Pantoprazole Tablets contain
• The active substance is Pantoprazole, each gastro-resistant tablet contains, 20mg Pantoprazole (as pantoprazole sodium sesquihydrate 22.6 mg)
• The other ingredients are Disodium Phosphate Anhydrous, Mannitol, Cellulose Microcrystalline. Croscarmellose Sodium, Magnesium Stearate (vegetable), Hypermellose, Triethyl Citrate, Sodium Starch Glycolate (Type A), Methacrylic acid-Ethyl acrylate copolymer, Yellow Iron Oxide.

What Pantoprazole Tablets look like and contents of the pack
Pantoprazole 20 mg gastro-resistant tablets are oval, yellow tablets and are available in aluminium/aluminium blister packs of 14, 15, 28, 50, 56, 60 & 100 tablets or HDPE containers with child resistant closure of 14, 15, 28, 30, 56, 60, & 100 tablets*.
*Not all pack sizes may be marketed

Marketing Authorisation Holder and Manufacturer
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Manufacturer
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Polígono Industrial Mahpica,
calle C. Número 4,
50016, ZARAGOZA,
Spain
Tel: 00 34 976 57 17 84

This leaflet was last approved in {MM/YYYY}.
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.
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- in the treatment of duodenal and stomach ulcers
- to treat Zollinger-Ellison syndrome and other conditions producing too much acid in the stomach.

Pantoprazole, which is contained in these tablets, may also be authorised to treat other conditions which are not mentioned in this leaflet. Ask your doctor or pharmacist if you have further questions.

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- you have been taking Pantoprazole for over a year. Your doctor will probably keep you under close supervision and you should report any new or worrying symptoms.

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Please also tell your doctor if your symptoms persist despite adequate treatment with this medicine.

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If you are taking other medicines with Pantoprazole they can sometimes interfere with, and alter the effect of, each other. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is particularly important to tell your doctor if you are taking any of the following:
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• You should swallow the tablet(s) whole, with water.
Do not crush, break or chew the tablet(s) as this will prevent them from working properly. The usual doses of Pantoprazole 40 mg are given below. Sometimes your doctor may prescribe you a different dose.

Adults and adolescents 12 years of age and above
Reflux oesophagitis:
The recommended dose is one 40 mg tablet per day for 4-8 weeks. Your doctor may then change your dose depending on how you respond.
Adults
Stomach or duodenal ulcer:
The recommended dose is one 40 mg tablet per day. The treatment period for stomach ulcers is usually 4-8 weeks. The treatment period for duodenal ulcers is usually 2-4 weeks.

Zollinger-Ellison syndrome (a condition where your stomach constantly makes too much acid):
The initial dose is two 40 mg tablets every day. Your doctor may then change your dose depending on how you respond. If prescribed more than two tablets a day, take the tablets in two equal doses.

Elderly and patients with renal impairment
A daily dose of 40 mg should not be exceeded.

Patients with hepatic impairment
On 40 mg tablet should be given every other day.

Children under 12 years of age
Pantoprazole tablets are not recommended for use in children under 12 years of age.

If you take more Pantoprazole Tablets than you should
If you take more Pantoprazole tablets than you have been told to, consult your doctor or pharmacist immediately.

If you forget to take Pantoprazole Tablets
Do not take a double dose to make up for a forgotten dose. If you do forget to take a dose, take it as soon as you remember unless it is almost time for your next dose.

If you stop taking Pantoprazole tablets
You should continue to take this medicine for as long as your doctor has told you. Do not stop just because you feel better. If you stop taking your tablets too soon, your symptoms may return.

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

4. POSSIBLE SIDE EFFECTS
Like all medicines, Pantoprazole tablets can cause side effects, although not everybody will experience them.

You should stop taking Pantoprazole and seek immediate medical advice if you experience any of the following symptoms as they could be due to a severe allergic reaction:
• a swollen face, mouth, tongue and/or throat
• difficulty swallowing
• an itchy rash (hives) and difficulty breathing

Common (less than 1 in 10 but more than 1 in 100 people treated)
• stomach-ache, diarrhoea, constipation or wind
• headaches.

Uncommon (less than 1 in 100 but more than 1 in 1,000 people treated)
• nausea (feeling sick)
• vomiting (being sick)
• dizziness
• blurred vision
• allergic reactions such as itchy skin and rash.

Rare (Less than 1 in 1000 but more than 1 in 10,000 people treated)
• dry mouth
• joint pain
• depression, hallucination, disorientation, confusion.

Very rare (Less than 1 in 10,000 people treated)
• a fall in the number of white cells or platelets in the blood.
• swollen legs
• muscle pain
• liver damage and jaundice (yellowing of the skin) which can be serious
• allergic reactions (these may be accompanied by a skin rash and can be severe, causing swelling of the face or mouth). This can cause difficulty breathing (see warning at the beginning of this section)
• raised body temperature
• kidney inflammation (nephritis)
• severe skin reactions (Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis or Lyell’s disease)
• increased sensitivity of the skin to sunlight (photosensitivity)
• an increase in liver enzymes and raised blood triglycerides (a type of fat in the blood).

If any of the side effects become 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.
Store below 30°C.
Do not use Pantoprazole tablets after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Pantoprazole Tablets contain
• The active substance is Pantoprazole, each gastro-resistant tablet contains, 40mg Pantoprazole (as pantoprazole sodium sesquihydrate 45.1 mg)
• The other ingredients are Disodium Phosphate Anhydrous, Mannitol, Cellulose Microcrystalline, Croscarmellose Sodium, Magnesium Stearate (vegetable), Hypromellose, Triethyl Citrate, Sodium Starch Glycolate (Type A), Methacrylic acid-Ethyl acrylate copolymer, Yellow Iron Oxide.

What Pantoprazole Tablets look like and contents of the pack
Pantoprazole 40 mg gastro-resistant tablets are oval, yellow tablets and are available in either aluminium/aluminium blister packs of 14, 15, 28, 30, 60 & 100 tablets or HDPE containers with child resistant closure of 14, 15, 28, 30, 56, 60 & 100 (2x50) tablets*. *Not all pack sizes may be marketed

Marketing Authorisation Holder and Manufacturer
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Manufacturer

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Poligono Industrial Malpica, calle C, Numero 4, 50016, ZARAGOZA, Spain
Tel: 00 34 976 57 17 84

This leaflet was last approved in {MM/YYYY}.
PACKAGE LEAFLET: INFORMATION FOR THE USER

Pantoprazole 20 mg Gastro-resistant Tablets
Pantoprazole (as pantoprazole sodium sesquihydrate)

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 become 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 store Pantoprazole Tablets
6. Further information

1. WHAT PANTOPRAZOLE TABLETS ARE AND WHAT THEY ARE USED FOR
Pantoprazole belongs to a group of medicines called proton pump inhibitors, which work by reducing the amount of acid your stomach makes.

- You have been given Pantoprazole, because you have a condition caused by too much acid in the stomach. Pantoprazole reduces the amount of acid your stomach makes and is used: In the treatment of mild forms of oesophageal disease caused by reflux of acid from the stomach (with or without mild inflammation of the oesophagus (gullet)) and the associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing).
- In the long-term management of reflux oesophagitis (inflammation of the oesophagus accompanied by the regurgitation of stomach acid) and preventing its return.
- In preventing duodenal (part of the small bowel) and stomach ulcers caused by 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 any of the other ingredients in the tablets. Check the ingredients listed in section 6.

- if you are taking atazanavir (used to treat HIV infection).

Take special care with Pantoprazole Tablets

Please tell your doctor if any of the following apply to you:

- you have severe liver disease, as your doctor may need to monitor your liver function while you are taking Pantoprazole
- you have been diagnosed with vitamin B12 deficiency
- you are also taking painkillers called non-steroidal anti-inflammatory medicines (NSAIDs) – please also read the package leaflets of these medicines carefully
- you have been taking Pantoprazole for over a year. Your doctor will probably keep you under close supervision and you should report any new or worrying symptoms.
Please tell your doctor if you have, or have recently had, any of the following symptoms:

- unintentional weight loss
- recurrent vomiting
- vomiting blood (this may look dark like “coffee grounds”)
- black, tarry, stools (faeces).

Your doctor may perform additional tests (e.g. endoscopy (visual inspection of the gullet, stomach, and upper intestine) to exclude the possibility of serious illness.

Please also tell your doctor if your symptoms persist despite adequate treatment with this medicine.

**Taking other medicines**

If you are taking other medicines with Pantoprazole they can sometimes interfere with, and alter the effect of, each other. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is particularly important to tell your doctor if you are taking any of the following:

- ketokonazole oritraconazole which are used to treat fungal infections of the skin and nails
- anticoagulants (medicines used to thin the blood) e.g. warfarin. You may need to have clotting tests done more frequently.
- atazanavir for the treatment of HIV infection.

**Taking Pantoprazole with food and drink**

Pantoprazole tablets should be taken on an empty stomach (before meals). You should swallow the tablet(s) whole, with water.

**Pregnancy and breast-feeding**

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

Experience with the use of pantoprazole in pregnant women is limited. There is no information on the excretion of pantoprazole into human breast milk. If you are pregnant, or if you are breast-feeding, you should use this medicine only if your treating physician considers the benefit to you is greater than any potential risk for your unborn child or baby.

**Driving and using machines**

Pantoprazole tablets do not normally affect the ability to drive and use machines.

However, if you experience side effects such as dizziness, blurred vision or fatigue, your ability to react may be decreased. This should be taken into account when driving or using machines.

**Important information about some of the ingredients of Pantoprazole Tablets**

This product contains 2.93 mg of sodium per tablet. You should take this into account if you are on a controlled sodium diet.

**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.

- Pantoprazole tablets should be taken on an empty stomach (before meals).
- You should swallow the tablet(s) whole, with water.

Do not crush, break or chew the tablet(s) as this will prevent them from working properly. The usual doses of Pantoprazole 20 mg are given below. Sometimes your doctor may prescribe you a different dose.

*Adults and adolescents 12 years of age and above*

For treating mild forms of oesophageal disease caused by reflux of acid from the stomach and the associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing):
The recommended dose is one 20 mg tablet every day for 2-4 weeks (extended for another 4 weeks if necessary). Your doctor will tell you how long to continue taking the medicine. After this any recurring symptoms can be controlled by taking one tablet daily, as needed.

For long-term management and for preventing the return of reflux oesophagitis:
The recommended dose is one 20 mg tablet a day.
If symptoms return, the dose may be doubled to 40 mg daily, in which case you can use Pantoprazole 40 mg tablets instead, one a day. After healing, you can reduce the dose back again to one tablet (20 mg) a day.

Adults
Prevention of gastric and duodenal ulcers caused by anti-inflammatory drugs:
The recommended dose is one 20 mg tablet every day for as long as prescribed by your doctor.

Elderly and patients with renal impairment
A daily dose of 40 mg should not be exceeded.

Patients with hepatic impairment
A daily dose of 20 mg should not be exceeded.

Children under 12 years of age
Pantoprazole tablets are not recommended for use in children under 12 years of age.

If you take more Pantoprazole Tablets than you should
If you take more Pantoprazole tablets than you have been told to, consult your doctor or pharmacist immediately.

If you forget to take Pantoprazole Tablets
Do not take a double dose to make up for a forgotten dose. If you do forget to take a dose, take it as soon as you remember unless it is almost time for your next dose.

If you stop taking Pantoprazole tablets
You should continue to take this medicine for as long as your doctor has told you. Do not stop just because you feel better. If you stop taking your tablets too soon, your symptoms may return.

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

4. POSSIBLE SIDE EFFECTS
Like all medicines, Pantoprazole tablets can cause side effects, although not everybody will experience them.

You should stop taking Pantoprazole and seek immediate medical advice if you experience any of the following symptoms as they could be due to a severe allergic reaction:
- a swollen face, mouth, tongue and/or throat
- difficulty swallowing
- an itchy rash (hives) and difficulty breathing

Common (less than 1 in 10 but more than 1 in 100 people treated)
- stomach-ache, diarrhoea, constipation or wind
- headaches.

Uncommon (less than 1 in 100 but more than 1 in 1,000 people treated)
- nausea (feeling sick)
- vomiting (being sick)
- dizziness
- blurred vision
- allergic reactions such as itchy skin and rash.

**Rare (Less than 1 in 1000 but more than 1 in 10,000 people treated)**
- dry mouth
- joint pain
- depression, hallucination, disorientation, confusion.

**Very rare (Less than 1 in 10,000 people treated)**
- a fall in the number of white cells or platelets in the blood.
- swollen legs
- muscle pain
- liver damage and jaundice (yellowing of the skin) which can be serious
- allergic reactions (these may be accompanied by a skin rash and can be severe, causing swelling of the face or mouth). This can cause difficulty breathing (see warning at the beginning of this section)
- raised body temperature
- kidney inflammation (nephritis)
- severe skin reactions (Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis or Lyell’s disease)
- increased sensitivity of the skin to sunlight (photosensitivity)
- an increase in liver enzymes and raised blood triglycerides (a type of fat in the blood).

If any of the side effects become 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.
Store below 30°C.
Do not use Pantoprazole tablets after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

**6. FURTHER INFORMATION**

**What Pantoprazole Tablets contain**
- The active substance is Pantoprazole, each gastro-resistant tablet contains, 20mg Pantoprazole (as pantoprazole sodium sesquihydrate 22.6 mg)
- The other ingredients are Disodium Phosphate Anhydrous, Mannitol, Cellulose Microcrystalline, Croscarmellose Sodium, Magnesium Stearate (vegetable), Hydroxypropyl, Triethyl Citrate, Sodium Starch Glycolate (Type A), Methacrylic acid-Ethyl acrylate copolymer, Yellow Iron Oxide.

**What Pantoprazole Tablets look like and contents of the pack**
Pantoprazole 20 mg gastro-resistant tablets are oval, yellow tablets and are available in aluminium/aluminium blister packs of 14, 15, 28, 30, 56, 60 & 100 tablets or HDPE containers with child resistant closure of 14, 15, 28, 30, 56, 60 & 100 tablets*.
*Not all pack sizes may be marketed

**Marketing Authorisation Holder and Manufacturer**
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Tel: 00 34 976 57 17 84

This leaflet was last approved in {MM/YYYY}.
PACKAGE LEAFLET: INFORMATION FOR THE USER

Pantoprazole 40 mg Gastro-resistant Tablets
Pantoprazole (as pantoprazole sodium sesquihydrate)

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 become 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 store Pantoprazole Tablets
6. Further information

1. WHAT PANTOPRAZOLE TABLETS ARE AND WHAT THEY ARE USED FOR
Pantoprazole belongs to a group of medicines called proton pump inhibitors, which work by reducing the amount of acid your stomach makes.
• You have been given Pantoprazole, because you have a condition caused by too much acid in the stomach. Pantoprazole reduces the amount of acid your stomach makes and is used: in the treatment of moderate to severe forms of reflux oesophagitis (an inflammation of your oesophagus accompanied by the regurgitating of stomach acid).
• in the treatment of duodenal and stomach ulcers
• to treat Zollinger-Ellison syndrome and other conditions producing too much acid in the stomach.

Pantoprazole, which is contained in these tablets, may also be authorised to treat other conditions which are not mentioned in this leaflet. Ask your doctor or pharmacist if you have further questions.

2. BEFORE YOU TAKE PANTOPRAZOLE TABLETS

Do not take Pantoprazole Tablets
• if you are allergic (hypersensitive) to pantoprazole or any of the other ingredients in the tablets. Check the ingredients listed in section 6.
• if you are taking atazanavir (used to treat HIV infection).

Take special care with Pantoprazole Tablets
Please tell your doctor if any of the following apply to you:
• you have severe liver disease, as your doctor may need to monitor your liver function while you are taking Pantoprazole
• you have been diagnosed with vitamin B12 deficiency
• you are also taking painkillers called non-steroidal anti-inflammatory medicines (NSAIDs) – please also read the package leaflets of these medicines carefully
• you have been taking Pantoprazole for over a year. Your doctor will probably keep you under close supervision and you should report any new or worrying symptoms.

Please tell your doctor if you have, or have recently had, any of the following symptoms:

45
unintentional weight loss
- recurrent vomiting
- vomiting blood (this may look dark like “coffee grounds”)
- black, tarry, stools (faeces).
Your doctor may perform additional tests (e.g. endoscopy (visual inspection of the gut, stomach, and upper intestine) to exclude the possibility of serious illness.

Please also tell your doctor if your symptoms persist despite adequate treatment with this medicine.

Taking other medicines
If you are taking other medicines with Pantoprazole they can sometimes interfere with, and alter the effect of, each other. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is particularly important to tell your doctor if you are taking any of the following:
- ketoconazole or itraconazole which are used to treat fungal infections of the skin and nails
- anticoagulants (medicines used to thin the blood) e.g. warfarin. You may need to have clotting tests done more frequently.
- atazanavir for the treatment of HIV infection.

Taking Pantoprazole with food and drink
Pantoprazole tablets should be taken on an empty stomach (before meals). You should swallow the tablet(s) whole, with water.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Experience with the use of pantoprazole in pregnant women is limited. There is no information on the excretion of pantoprazole into human breast milk. If you are pregnant, or if you are breast-feeding, you should use this medicine only if your treating physician considers the benefit to you is greater than any potential risk for your unborn child or baby.

Driving and using machines
Pantoprazole tablets do not normally affect the ability to drive and use machines. However, if you experience side effects such as dizziness, blurred vision or fatigue, your ability to react may be decreased. This should be taken into account when driving or using machines.

Important information about some of the ingredients of Pantoprazole Tablets
This product contains 5.85 mg of sodium per tablet. You should take this into account if you are on a controlled sodium diet.

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.
- Pantoprazole tablets should be taken on an empty stomach (before meals).
- You should swallow the tablet(s) whole, with water.

Do not crush, break or chew the tablet(s) as this will prevent them from working properly.
The usual doses of Pantoprazole 40 mg are given below. Sometimes your doctor may prescribe you a different dose.

Adults and adolescents 12 years of age and above
Reflux oesophagitis:
The recommended dose is one 40 mg tablet per day for 4-8 weeks. Your doctor may then change your dose depending on how you respond.
**Adults**
**Stomach or duodenal ulcer:**  
The recommended dose is one 40 mg tablet per day. The treatment period for stomach ulcers is usually 4-8 weeks. The treatment period for duodenal ulcers is usually 2-4 weeks.

**Zollinger-Ellison syndrome (a condition where your stomach constantly makes too much acid):**  
The initial dose is two 40 mg tablets every day. Your doctor may then change your dose depending on how you respond. If prescribed more than two tablets a day, take the tablets in two equal doses.

**Elderly and patients with renal impairment**  
A daily dose of 40 mg should not be exceeded.

**Patients with hepatic impairment**  
On 40 mg tablet should be given every other day.

**Children under 12 years of age**  
Pantoprazole tablets are not recommended for use in children under 12 years of age.

**If you take more Pantoprazole Tablets than you should**  
If you take more Pantoprazole tablets than you have been told to, consult your doctor or pharmacist immediately.

**If you forget to take Pantoprazole Tablets**  
Do not take a double dose to make up for a forgotten dose. If you do forget to take a dose, take it as soon as you remember unless it is almost time for your next dose.

**If you stop taking Pantoprazole tablets**  
You should continue to take this medicine for as long as your doctor has told you. Do not stop just because you feel better. If you stop taking your tablets too soon, your symptoms may return.

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

**4. POSSIBLE SIDE EFFECTS**  
Like all medicines, Pantoprazole tablets can cause side effects, although not everybody will experience them.

**You should stop taking Pantoprazole and seek immediate medical advice if you experience any of the following symptoms as they could be due to a severe allergic reaction:**
- a swollen face, mouth, tongue and/or throat
- difficulty swallowing
- an itchy rash (hives) and difficulty breathing

**Common (less than 1 in 10 but more than 1 in 100 people treated)**
- stomach-ache, diarrhoea, constipation or wind
- headaches.

**Uncommon (less than 1 in 100 but more than 1 in 1,000 people treated)**
- nausea (feeling sick)
- vomiting (being sick)
- dizziness
- blurred vision
- allergic reactions such as itchy skin and rash.

**Rare (Less than 1 in 1000 but more than 1 in 10,000 people treated)**
• dry mouth
• joint pain
• depression, hallucination, disorientation, confusion.

Very rare (Less than 1 in 10,000 people treated)
• a fall in the number of white cells or platelets in the blood.
• swollen legs
• muscle pain
• liver damage and jaundice (yellowing of the skin) which can be serious
• allergic reactions (these may be accompanied by a skin rash and can be severe, causing swelling of the face or mouth). This can cause difficulty breathing (see warning at the beginning of this section)
• raised body temperature
• kidney inflammation (nephritis)
• severe skin reactions (Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis or Lyell’s disease)
• increased sensitivity of the skin to sunlight (photosensitivity)
• an increase in liver enzymes and raised blood triglycerides (a type of fat in the blood).

If any of the side effects become 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.
Store below 30°C.
Do not use Pantoprazole tablets after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Pantoprazole Tablets contain
• The active substance is Pantoprazole, each gastro-resistant tablet contains, 40mg Pantoprazole (as pantoprazole sodium sesquihydrate 45.1 mg)
• The other ingredients are Disodium Phosphate Anhydrous, Mannitol, Cellulose Microcrystalline, Croscarmellose Sodium, Magnesium Stearate (vegetable), Hypromellose, Triethyl Citrate, Sodium Starch Glycolate (Type A), Methacrylic acid-Ethyl acrylate copolymer, Yellow Iron Oxide.

What Pantoprazole Tablets look like and contents of the pack
Pantoprazole 40 mg gastro-resistant tablets are oval, yellow tablets and are available in either aluminium/aluminium blister packs of 14, 15, 28, 30, 60 & 100 tablets or HDPE containers with child resistant closure of 14, 15, 28, 30, 56, 60 & 100 (2x50) tablets*.
*Not all pack sizes may be marketed

Marketing Authorisation Holder and Manufacturer
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Manufacturer

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Tel: 00 34 976 57 17 84

This leaflet was last approved in {MM/YYYY}. 48
Module 4

Labelling

UK/H/1355/01/DC

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole 20 mg Gastro-resistant Tablets [and associated names]
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg Pantoprazole (as pantoprazole sodium sesquihydrate)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
15 tablets
28 tablets
30 tablets
56 tablets
60 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:
9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Olinka (UK) Limited
38/40 Chamberlayne Road
London
United Kingdom
NW10 3JE

12. MARKETING AUTHORIZATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed Nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Do not crush or chew
Swallow whole with water before a meal.
Take as directed by your doctor.

16. INFORMATION IN BRAILLE

[To be completed Nationally]
### PARTICULARS TO APPEAR ON THE INNER PACKAGING

HDPE Label

### 1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole 20 mg Gastro-resistant Tablets [and associated names]
Pantoprazole

### 2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains 20 mg Pantoprazole

### 3. LIST OF EXCIPIENTS

### 4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets  
15 tablets  
28 tablets  
30 tablets  
56 tablets  
60 tablets  
100 tablets.

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read leaflet before use.  
Oral use.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

EXP:

### 9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

### 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Olinka (UK) Limited, London, UK

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Do not crush or chew
Swallow whole with water before a meal.
Take as directed by your doctor.

16. INFORMATION IN BRAILLE
MINIMUM PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Blist Carton

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole 20 mg Gastro-resistant Tablets [and associated names]
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg Pantoprazole (as pantoprazole sodium sesquihydrate)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
15 tablets
28 tablets
30 tablets
56 tablets
60 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S) IF NECESSARY

8. EXPIRY DATE

[To be completed nationally]

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNSUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
Olinka (UK) Limited
38/40 Chamberlayne Road
London
United Kingdom
NW10 3JE

[To be completed nationally]

[To be completed nationally]

[To be completed nationally]

Medicinal product subject to medical prescription.

Do not crush or chew
Swallow whole with liquid before a meal.
Take as directed by your doctor.

[To be completed nationally]
MINIMUM PARTICULARS TO APPEAR ON BLISTERS
Alu/Alu blister

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<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olinka UK Limited</td>
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<table>
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<th>3. EXPIRY DATE</th>
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<thead>
<tr>
<th>5. OTHER</th>
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</table>
UK/H/1355/02/DC

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
HDPE Bottle Carton

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole 40 mg Gastro-resistant Tablets
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg Pantoprazole (as pantoprazole sodium sesquihydrate)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
15 tablets
28 tablets
30 tablets
60 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store below 30ºC.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Olinka (UK) Limited
38/40 Chamberlayne Road
London
United Kingdom
NW10 3JE

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed Nationally]

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed Nationally]
Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Do not crush or chew
Swallow whole with water before a meal.
Take as directed by your doctor.

16. INFORMATION IN BRAILLE

[To be completed Nationally]
PARTICULARS TO APPEAR ON THE INNER PACKAGING
HDPE Label

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

2. STATEMENT OF ACTIVE SUBSTANCES
Each tablet contains 40 mg Pantoprazole

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
14 tablets
15 tablets
28 tablets
30 tablets
56 tablets
60 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Read leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP:

9. SPECIAL STORAGE CONDITIONS
Store below 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Olinka (UK) Limited, London, UK

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Do not crush or chew
Swallow whole with water before a meal.
Take as directed by your doctor.

16. INFORMATION IN BRAILLE
MINIMUM PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Blist carton

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole 40 mg Gastro-resistant Tablets
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg Pantoprazole (as pantoprazole sodium sesquihydrate)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
15 tablets
28 tablets
30 tablets
60 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use..

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S) IF NECESSARY

8. EXPIRY DATE

[To be completed nationally]

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNSUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
12. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

13. BATCH NUMBER

[To be completed nationally]

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Do not crush or chew
Swallow whole with liquid before a meal.
Take as directed by your doctor.

16. INFORMATION IN BRAILLE

[To be completed nationally]
MINIMUM PARTICULARS TO APPEAR ON BLISTERS
Alu/Alu blister

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

2. NAME OF THE MARKETING AUTHORISATION HOLDER
Olinka UK Limited

3. EXPIRY DATE
[To be completed nationally]

4. BATCH NUMBER
[To be completed nationally]

5. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

HDPE Bottle Carton

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole 20 mg Gastro-resistant Tablets
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg Pantoprazole (as pantoprazole sodium sesquihydrate)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
15 tablets
28 tablets
30 tablets
60 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store below 30ºC.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed Nationally]

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed Nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Do not crush or chew Swallow whole with water before a meal. Take as directed by your doctor.

16. INFORMATION IN BRAILLE

[To be completed Nationally]
PARTICULARS TO APPEAR ON THE INNER PACKAGING
HDPE Label

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

2. STATEMENT OF ACTIVE SUBSTANCES
Each tablet contains 20 mg Pantoprazole

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
14 tablets
15 tablets
28 tablets
30 tablets
60 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Read leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP:

9. SPECIAL STORAGE CONDITIONS
Store below 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Do not crush or chew
Swallow whole with water before a meal.
Take as directed by your doctor.

16. INFORMATION IN BRAILLE
MINIMUM PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**Blister Carton**

<table>
<thead>
<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></th>
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</thead>
<tbody>
<tr>
<td>Pantoprazole 20 mg Gastro-resistant Tablets</td>
</tr>
<tr>
<td>Pantoprazole 40 mg Gastro-resistant Tablets</td>
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</tbody>
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<table>
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<tr>
<th><strong>2. STATEMENT OF ACTIVE SUBSTANCE(S)</strong></th>
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<tbody>
<tr>
<td>Each tablet contains 20 mg Pantoprazole (as pantoprazole sodium sesquihydrate)</td>
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<tr>
<th><strong>3. LIST OF EXCIPIENTS</strong></th>
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<tr>
<th><strong>4. PHARMACEUTICAL FORM AND CONTENTS</strong></th>
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</thead>
<tbody>
<tr>
<td>14 tablets</td>
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<tr>
<td>30 tablets</td>
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<td>60 tablets</td>
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<td>100 tablets</td>
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<tr>
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<tbody>
<tr>
<td>Read the package leaflet before use.</td>
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<tr>
<td>Oral use.</td>
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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
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<th><strong>7. OTHER SPECIAL WARNING(S) IF NECESSARY</strong></th>
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<th><strong>9. SPECIAL STORAGE CONDITIONS</strong></th>
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<tbody>
<tr>
<td>Store below 30°C.</td>
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<tr>
<th><strong>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNSUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</strong></th>
</tr>
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12. MARKETING AUTHORISATION NUMBER
[To be completed nationally]

13. BATCH NUMBER
[To be completed nationally]

14. GENERAL CLASSIFICATION FOR SUPPLY
[To be completed nationally]
Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE
Do not crush or chew
Swallow whole with liquid before a meal.
Take as directed by your doctor.

16. INFORMATION IN BRAILLE
[To be completed nationally]
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS

| Alu/Alu blister |

### 1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole 20 mg Gastro-resistant Tablets
Pantoprazole

### 2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

### 3. EXPIRY DATE

[To be completed nationally]

### 4. BATCH NUMBER

[To be completed nationally]

### 5. OTHER
UK/H/1356/02/DC

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
HDPE Bottle Carton

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole 40 mg Gastro-resistant Tablets
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg Pantoprazole (as pantoprazole sodium sesquihydrate)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
15 tablets
28 tablets
30 tablets
60 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store below 30ºC.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed Nationally]

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed Nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Do not crush or chew
Swallow whole with water before a meal.
Take as directed by your doctor.

16. INFORMATION IN BRAILLE

[To be completed Nationally]
**PARTICULARS TO APPEAR ON THE INNER PACKAGING**
HDPE Label

**1. NAME OF THE MEDICINAL PRODUCT**

Pantoprazole 40 mg Gastro-resistant Tablets
Pantoprazole

**2. STATEMENT OF ACTIVE SUBSTANCES**

Each tablet contains 40 mg Pantoprazole

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

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<td>28</td>
<td>30</td>
</tr>
<tr>
<td>60</td>
<td>100</td>
</tr>
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</table>

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read leaflet before use.
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP:

**9. SPECIAL STORAGE CONDITIONS**

Store below 30°C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Do not crush or chew
Swallow whole with water before a meal.
Take as directed by your doctor.

16. INFORMATION IN BRAILLE
MINIMUM PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Blister Carton

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole 40 mg Gastro-resistant Tablets
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg Pantoprazole (as pantoprazole sodium sesquihydrate)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
15 tablets
28 tablets
30 tablets
60 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S) IF NECESSARY

8. EXPIRY DATE

[To be completed nationally]

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNSUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
12. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

13. BATCH NUMBER

[To be completed nationally]

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Do not crush or chew
Swallow whole with liquid before a meal.
Take as directed by your doctor.

16. INFORMATION IN BRAILLE

[To be completed nationally]
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS</th>
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<td>Alu/Alu blister</td>
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<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>Pantoprazole 40 mg Gastro-resistant Tablets</td>
</tr>
<tr>
<td>Pantoprazole</td>
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</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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<tbody>
<tr>
<td>[To be completed nationally]</td>
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<table>
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<tr>
<th>3. EXPIRY DATE</th>
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<td>[To be completed nationally]</td>
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<table>
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<th>4. BATCH NUMBER</th>
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<td>[To be completed nationally]</td>
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<tr>
<th>5. OTHER</th>
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Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Pantoprazole 20mg and 40mg Gastro-resistant Tablets, in the treatment of mild reflux disease and associated symptoms, long-term management and prevention of relapse in reflux oesophagitis and for prevention of gastroduodenal ulcers by non-selective non-steroidal anti-inflammatory drugs in patients at risks with a need for continuous NSAID treatment, could be approvable.

These are decentralised application concerns a generic version of Pantoprazole submitted under Article 10.1. The applications make reference to the German product Pantozol 40mg.

Pantozol 20mg and 40mg are marketed under the German MA (held by Nycomed GmbH). These are equivalent to Protium 20mg and 40mg marketed in the UK under PL 20141/0001-2 held by Altana Pharma AG.

With the UK as the Reference Member State in this Decentralised Procedure, Olinka (UK) Ltd is applying for the Marketing Authorisations for Pantoprazole 20mg Gastro-resistant tablets and Pantoprazole 40mg Gastro-resistant Tablets in the following CMSs:

**UK/H/1355/01-02/DC:** CZ, DE, PL and SK.

**UK/H/1356/01-02/DC:** DE and PL.

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

The submitted dossier is of an acceptable standard.

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

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Pantoprazole 20mg and 40mg Gastro-resistant</th>
</tr>
</thead>
<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</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Gastro-resistant tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/1355-6/01-02/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States Concerned</td>
<td>UK/H/1355/01-02/DC: SK, PL, DE and CZ</td>
</tr>
<tr>
<td></td>
<td>UK/H/1356/01-02/DC: DE and PL</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 08608/0136-9</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Olinka UK Limited, 38/40 Chamberlayne Road, London, NW10 3JE, UK</td>
</tr>
</tbody>
</table>
SCIENTIFIC OVERVIEW AND DISCUSSION

II. QUALITY ASPECTS

DRUG SUBSTANCE

INN: Pantoprazole sodium sesquihydrate

Chemical Name: 5-(difluoromethoxy)-2-[(R,S)-[3,4-dimethoxypyridin-2-yl)methyl]sulphinyl] benzimidazol-1-ide.

Structure:

![Structure Diagram]

Molecular Formula: C_{16}H_{15}F_{2}N_{3}NaO_{4}S

Molecular Weight: 406.4

Appearance: a white or almost white, crystalline powder. It is soluble in water (up to 384mg/mL) giving alkaline solutions. It is very soluble in methanol and very soluble 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 food.

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 disodium phosphate anhydrous, mannitol (75-315 μm), Cellulose microcrystalline, Croscarmellose sodium, Magnesium stearate (vegetable), Hypromellose (Type 6 cP), Triethyl citrate, Sodium starch glycolate (Type A), Methacrylic acid-ethyl acrylate copolymer (1:1), dispersion at 30% and Yellow iron oxide.

All excipients comply with their respective European Pharmacopoeia monographs except Yellow iron oxide which complies with National formulae. Satisfactory Certificates of Analysis have been provided for all excipients. Magnesium stearate is from a vegetable source. None of the other excipients are of human origin.

Pharmaceutical Development
Suitable pharmaceutical development data have been provided for this application.

The physico-chemical properties of the drug product have been compared with that of the originator product. These data demonstrate that the proposed product can be considered a generic medicinal product of Pantozol 40mg Gastro-resistant tablets.

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 Alu/Alu blister and HDPE bottle with child-resistant polypropylene cap.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set for the unopened product, with the storage instruction ‘Store below 30 C’.

Bioequivalence/bioavailability
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. Satisfactory bioequivalence is seen between the test and reference product.
SPC, PIL, Labels
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.

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 40mg Tablets, which has been licensed within the EU for over 10 years.

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

IV. CLINICAL ASPECTS
1. Introduction

1.1. Type of Application and Regulatory Background
These are decentralised abridged applications submitted under article 10(1) of the Directive 2001/83/EC. The applications make reference to the German products Pantozol 40mg.

Pantozol 20mg and 40mg are marketed under the German MA 43404.00.00 and 40718.00.00 (held by Nycomed GmbH). These are equivalent to Protium 20mg and 40mg marketed in the UK under the MA 20141/0001 and 20141/0001 held by Altana Pharma AG.

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

1.3. Indications
- For the treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing).
- For long-term management and prevention of relapse in reflux oesophagitis.
- Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment (see section 4.4).
1.4. Posology and method of administration

Method of administration
Pantoprazole 20 mg tablets should not be chewed or crushed, and should be swallowed whole with water before a meal.

Adults and adolescents 12 years of age and above
Treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing)
The recommended dosage is 20 mg pantoprazole daily. Symptom relief is generally accomplished within 2–4 weeks, and a 4-week treatment period is usually required for healing of associated oesophagitis. If this is not sufficient, healing will normally be achieved within a further 4 weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment.

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

Adults
Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk who need continuous NSAID treatment
The recommended dosage is 20 mg pantoprazole daily.

Elderly and patients with renal impairment
A daily dose of 40 mg pantoprazole should not be exceeded in these patient groups.

Patients with hepatic impairment
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment (see section 4.4). In these patients, hepatic enzyme levels should be monitored during the treatment. If hepatic enzyme levels become elevated, treatment with pantoprazole should be discontinued.

Children below 12 years of age
There is no information on the use of pantoprazole in children. Therefore pantoprazole tablets should not be used in children.

2. Clinical Pharmacology

2.1. Pharmacokinetics
The two bioequivalence studies were:

1. Bioequivalence study on two pantoprazole formulations (gastro-resistant tablets) at a single oral dose of 40 mg, in healthy fasting volunteers.

2. Bioequivalence study on two pantoprazole formulations (gastro-resistant tablets) at a single oral dose of 40 mg, after breakfast, in healthy volunteers.
2.2. Bioequivalence

**Study design**
These were both single-dose, open-label, randomised, two-period cross-over studies in healthy male and female subjects who fulfilled standard entry criteria. A minimum one week washout period separated doses. Each subject received a single dose of the 40mg test or reference product, according to the randomisation schedule.

**Blood Sampling schedule**

**PAN-2006/007 Fasting**
Blood samples for assay of plasma pantoprazole were taken pre-dose, then at the following times post dosing:
1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 11 and 12 h.

**PAN-2006/006 Food Interaction**
Blood samples for assay of plasma pantoprazole were taken pre-dose, then at the following times post dosing:
1.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 11, 12, 13, 14 and 15 h.

**Table 1: Pharmacokinetic Ratios - log-transformed data in fasting study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ratio [%Ref]</th>
<th>90% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>92.04</td>
<td>86.15-98.33</td>
</tr>
<tr>
<td>AUClast h.ng/ml</td>
<td>96.60</td>
<td>91.66-101.81</td>
</tr>
<tr>
<td>AUC 0-inf h.ng/ml</td>
<td>97.00</td>
<td>91.95 – 102.33</td>
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The comparative analyses of the PK parameters for both formulations fell within the standard 80-125% intervals, therefore these data confirm that, under fasting conditions, the proposed (test) product is bioequivalent to the reference product.

**Table 2: PAN-2006/006 Food Interaction - Pharmacokinetic ratios – MAIN ANALYSIS SET- log transformed data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ratio [%Ref]</th>
<th>90% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>102.20</td>
<td>89.38-116.87</td>
</tr>
<tr>
<td>AUClast h.ng/ml</td>
<td>101.79</td>
<td>92.80-111.65</td>
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<tr>
<td>AUC 0-inf h.ng/ml</td>
<td>103.21</td>
<td>93.55-113.87</td>
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These data show that for the main analysis which *excludes predefined outliers*, the proposed formulation (test) remains bioequivalent to the reference product despite concomitant food intake.

The Applicant has also conducted an analysis with *all the data* (including outliers). These findings are consistent with those from the primary analysis and show that the formulations remain bioequivalent.
2.3. Pharmacodynamics
The pharmacodynamic characteristics of pantoprazole have been well-studied in the past. There would be no particular concerns for a generic medicinal product.

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

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

5. 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.

6. Conclusion
Based on the submitted bioequivalence studies Pantoprazole 40mg gastroresistant tablets are considered to be bioequivalent to the originator, Pantozol 40mg gastroresistant tablets.

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

Module 1 – Administrative information

MAA forms
The MAA forms are medically satisfactory.

Summary of Product Characteristics (SPC)
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.

V . OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Pantoprazole 20mg and 40mg Gastro-resitant 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
No new or unexpected safety concerns arise from these applications.

The SPC and PIL are satisfactory and consistent with that of the reference product.
RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with Pantoprazole is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
**Module 6**

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

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