Pantoprazole 20mg and 40mg Gastro-resistant Tablets

PL 24668/0058-9

LAY SUMMARY

On 8th February 2010, the MHRA granted Caduceus Pharma Limited Marketing Authorisations (licences) for the medicinal products Pantoprazole 20 and 40mg gastro-resistant tablets (PL 24668/0058-9). These are prescription-only medicines (POM) used to treat acid reflux (a type of heart-burn) and help prevent it from returning.

Pantoprazole Gastro-resistant Tablets may also be given to patients who need to take non-selective non-steroidal anti-inflammatory drugs (NSAIDS) for a continuous period. These patients are at a greater risk of developing an ulcer and associated symptoms. Pantoprazole Gastro-resistant tablets help reduce the risk by preventing an ulcer from developing.

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

PL 24668/0058-9

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Pantoprazole 20 and 40mg Gastro-resistant Tablets (PL 24668/0058-9) on the 8th February 2010.

The product is 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 and prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment.

The applications are according to Article 10(1) of 2001/83/EC, generic applications, as amended. The applications are for the generic products Pantoprazole Gastro-resistant Tablets 20mg and 40mg in duplicate. The reference product is Pantoloc 40mg magensaftresistente Tabletten first authorised for Byk Gulden Lomberg (HIST) Chemische Fabrik GmbH on 23rd August 1994 in Germany. The UK reference product is Protium 20mg & 40mg gastro-resistant tablets registered in the UK since 17th March 2003 (Altana Pharma AG, PL 20141/0001 & 0002). Bioequivalence has been established with the 40mg Pantozol magensaftresistente Tabletten, (Altana Pharma AG) from the German market.

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.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE – PANTOPRAZOLE

INN: Pantoprazole sodium sesquihydrate
Chemical Name: 5-(difluoromethoxy)-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole sodium salt sesquihydrate
Molecular Formula: C_{16}H_{14}F_{2}N_{3}NaO_{4}S.1\frac{1}{2}H_{2}O
Chemical Structure:

The drug substance is the subject of a European Drug Master File (EDMF). A letter of access has been provided by the drug substance manufacturer.

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 pharmaceutical excipients mannitol, sodium carbonate anhydrous, sodium starch glycolate, methacrylic acid copolymer, calcium stearate, Opadry white OY-D-7233 (hypromellose, titanium dioxide, talc, macrogol, sodium lauryl sulphate) and Kollicoat MAE 30 DP yellow (methacrylic acid-ethyl acrylate copolymer dispersion 30%, propylene glycol, yellow iron oxide, titanium dioxide, talc)

All excipients comply with their respective European Pharmacopoeia monograph with the exception of Opadry white OY-D-7233 which complies with in-house specification. A TSE statement from the suppliers of the calcium stearate, the Kollicoat MAE 30DP light yellow and dark yellow and the Opadry White OY-D-7233 has been provided.

Satisfactory Certificates of Analysis have been provided for all excipients.

Pharmaceutical development
Suitable pharmaceutical development data have been provided for these applications. Comparable dissolution and impurity profile are provided for these products versus the originator product.

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 appear 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 supplied in aluminium/aluminium blisters in pack sizes of 2 (40 mg strength only), 7, 14, 15, 28, 30, 50, 56, 60, 84, 90, 100, 112, 140, 280, 500, or 700 tablets.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with current guidelines concerning materials in 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.
Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labelling are pharmaceutically satisfactory.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
The MAA form is pharmaceutically satisfactory.

Expert Report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

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

The pharmacodynamic, pharmacokinetic and toxicological properties of the product are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A preclinical expert report has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of an environmental risk assessment.
CLINICAL ASSESSMENT

TOXICOLOGY
No new toxicological data have been submitted or are required for these applications.

CLINICAL PHARMACOLOGY
The applicant has submitted two bioequivalence studies – one under fasted and another under fed conditions.

Study No. 1 (Report AA 26974)

This was an open-label, randomised, single-dose, 2-way crossover, 2-sequence comparative bioavailability study of Actavis Group hf and Altana Pharma (Pantozol®) 40 mg Pantoprazole Sodium Delayed-Release Tablets in Healthy Adult Male Volunteers under Fasting conditions. The study was conducted by MDS Pharma Services, Montreal, Canada and was performed on 50 healthy non-smoking or moderate smoking (less than 10 cigarettes a day) adult male volunteers. A total of 48 subjects completed the clinical phase of the study. In each period, subjects were housed from at least 12 hours before dosing until after the 12-hour blood draw. Single oral doses of 40mg pantoprazole sodium were separated by a washout period of 14 days.

Table 1  Summary of the main Pharmacokinetic Parameters of 40mg Pantoprazole - Fasted State (N = 48)

<table>
<thead>
<tr>
<th></th>
<th>AUC 0-t* (ng.h/mL)</th>
<th>AUC inf* (ng.h/mL)</th>
<th>Cmax* (ng/mL)</th>
<th>Tmax (h)</th>
<th>Half-life(h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actavis Group hf (A)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4759.50</td>
<td>4908.88</td>
<td>3200.625</td>
<td>2.4666</td>
<td>1.3285</td>
</tr>
<tr>
<td>CV</td>
<td>56.5</td>
<td>63.6</td>
<td>27.3</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>n</td>
<td>48</td>
<td>48</td>
<td>48</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>Altana Pharma (B)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4521.58</td>
<td>4672.35</td>
<td>2794.750</td>
<td>2.5293</td>
<td>1.3884</td>
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<tr>
<td>CV</td>
<td>60.2</td>
<td>66.8</td>
<td>35.8</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>n</td>
<td>48</td>
<td>48</td>
<td>48</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>Ratio of Least-Square Means (A/B)</td>
<td>1.05</td>
<td>1.05</td>
<td>1.14</td>
<td></td>
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<tr>
<td>90% Confidence Intervals (A/B)</td>
<td>0.99</td>
<td>0.99</td>
<td>1.04</td>
<td></td>
<td></td>
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<tr>
<td>lower limit:</td>
<td>1.12</td>
<td>1.11</td>
<td>1.246</td>
<td></td>
<td></td>
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<tr>
<td>upper limit:</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* For in-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
The Test formulation (40mg pantoprazole by Activis Group hf) was shown to be bioequivalent to the Reference formulation (Altana Pharma Pantozol® 40mg ) under fasting conditions following a single oral dose administration.

The essentially linear pharmacokinetics of pantoprazole, particularly at this relatively low dose range, makes it likely that the lower-doses of pantoprazole formulations also are bioequivalent to the corresponding marketed brand formulations although bioequivalence has not been assessed explicitly.

No subject experienced any adverse events attributable to the Test formulation and only one subject experienced minor adverse event attributed to the Reference product. No significant or serious adverse events were reported during the study.

Study Report 1742/08

This was an open-label, randomised, single-dose, 2-way crossover, 2-sequence comparative bioavailability study of pantoprazole 40mg enter coated tablets of Actavis Group PTC ehf and Pantozol® 40 mg Pantoprazole 40 mg enterocoated tablets of Nycomed, Germany. A total of 80 subjects were recruited and 76 completed the study and 75 were evaluated. Three subjects were withdrawn due to protocol violation, one subject dropped out of the study. Another subject was excluded from statistical analysis due to several unquantifiable concentrations in period II. Blood samples were collected frequently up to 24 post-dosing. There was a washout period of 7 days between dosing.

Summary of the main Pharmacokinetic Parameters of 40mg Pantoprazole - Fed State

<table>
<thead>
<tr>
<th></th>
<th>AUC 0-t (µg.h/mL)</th>
<th>AUC inf. (µg.h/mL)</th>
<th>Cmax (µg/mL)</th>
<th>Tmax (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Product</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>6.665</td>
<td>7.037</td>
<td>2.674</td>
<td>8.867</td>
</tr>
<tr>
<td>CV (%)</td>
<td>95.95</td>
<td>104.45</td>
<td>37.71</td>
<td>42.25</td>
</tr>
<tr>
<td>n</td>
<td>75</td>
<td>74</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td><strong>Ref. Product</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7.193</td>
<td>7.684</td>
<td>2.804</td>
<td>8.953</td>
</tr>
<tr>
<td>CV(%)</td>
<td>90.66</td>
<td>111.27</td>
<td>34.25</td>
<td>49.91</td>
</tr>
<tr>
<td>n</td>
<td>75</td>
<td>74</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td><strong>Ratio</strong></td>
<td>0.93</td>
<td>0.92</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td><strong>90% CI</strong></td>
<td>0.87 – 0.99</td>
<td>0.86 – 0.97</td>
<td>0.87 – 1.05</td>
<td></td>
</tr>
</tbody>
</table>

The Test formulation (40mg pantoprazole by Activis Group hf) appears to have been shown to be bioequivalent to the Reference formulation (Nycomed Pantozol® 40mg) under fed conditions following a single oral dose administration.
The essentially linear pharmacokinetics of pantoprazole, particularly at this relatively low dose range, makes it likely that the lower-doses of pantoprazole formulations also are bioequivalent to the corresponding marketed brand formulations although bioequivalence has not been assessed explicitly.

There were nine adverse events reported during the study and all were assessed as mild. No serious adverse events were reported during the study.

*The results of the fasted and fed study demonstrate bioequivalence. The 90% confidence intervals (CI) for the AUC and C_{max} ratios fall within the conventional 80-125% bioequivalence range.*

**Efficacy**

No new efficacy data have been submitted or are required for this submission.

**Safety**

No new data are submitted or needed.

**Expert Report**

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

**Summary of Product Characteristics (SPC)**

These are consistent with the SPC for the reference products and are satisfactory.

**Patient Information Leaflet (PIL)**

The PIL is an accurate reflection of the SPC and complies with the appropriate guidelines.

**Labelling**

These are satisfactory.

**MAA Form**

These are satisfactory.

**Conclusions**

The proposed products are qualitatively and quantitatively equivalent to the reference product. The German reference product is considered to be equivalent to the UK reference product, Protium. Therefore, grant of Marketing Authorisations are recommended.
OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

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

PRECLINICAL
The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Pantoprazole 20mg and 40mg Gastro-resistant Tablets beyond those already described.

EFFICACY
No new data have been submitted and none are required for an application of this type.

Pantoprazole 20mg and 40mg Gastro-resistant Tablets is the generic version of Protium 20 & 40 mg Tablets (Altana Pharma AG, PL 20141/0001-2). The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredients, pantoprazole.

The 90% confidence intervals for the test/reference lie within the acceptance criteria specified in the CPMP/EWP/QWP/1401/98 Notes for Guidance on the Investigation of Bioavailability and Bioequivalence. Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria.

No new safety data are supplied or required for this generic application. Pantoprazole have well-established side-effect profiles and are generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s product and the innovator product are interchangeable. 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.
## STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 30&lt;sup&gt;th&lt;/sup&gt; April 2007</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 16&lt;sup&gt;th&lt;/sup&gt; July 2007</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information on 23/10/2007 for the quality part and on 8&lt;sup&gt;th&lt;/sup&gt; February, 29&lt;sup&gt;th&lt;/sup&gt; December 2008 and 22&lt;sup&gt;nd&lt;/sup&gt; June 2009 for the clinical parts of the dossier</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 23&lt;sup&gt;rd&lt;/sup&gt; November 2007 for the quality sections, and 8&lt;sup&gt;th&lt;/sup&gt; February 2008, 3&lt;sup&gt;rd&lt;/sup&gt; June 2008, 22&lt;sup&gt;nd&lt;/sup&gt; April 2009 and 29&lt;sup&gt;th&lt;/sup&gt; July 2009 for the Clinical sections.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 8&lt;sup&gt;th&lt;/sup&gt; February 2010</td>
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</tbody>
</table>
Pantoprazole 20mg and 40mg Gastro-resistant Tablets

PL 24668/0058-9

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<tr>
<td></td>
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</tbody>
</table>
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 22.58 mg)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant tablet

Elliptical, biconvex, light yellow gastro-resistant tablet

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

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

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

Note:
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver
impairment.
No dose adjustment is necessary in elderly patients or in those with impaired renal function.
There is no experience in children.

General instructions:
Pantoprazole 20 mg gastro-resistant tablets should not be chewed or crushed, and should be
swallowed whole with liquid before a meal.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
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 Pantoprazole 20mg gastro-resistant tablets should be discontinued.

The use of Pantoprazole 20mg gastro-resistant tablets as a preventitive of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications.

The increased risk should be assessed according to individual risk factors, e.g. high age >65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

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

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

Note:
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.

There is no experience in children.

4.5 Interaction with other medicinal products and other forms of interaction

Pantoprazole 20mg gastro-resistant tablets may reduce or increase the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole).

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

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

There were also no interactions with concomitantly administered antacids.

4.6 Pregnancy and lactation

Clinical experience in pregnant women is limited. In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg. There is no information on the excretion of pantoprazole into human breast milk. Pantoprazole tablets should only be used when the benefit to the mother is considered greater than the potential risk to the foetus/baby.
4.7 Effects on ability to drive and use machines
Pantoprazole 20mg gastro-resistant tablets have no influence on the ability to drive and use machines.

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

<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 ( &gt;1/10,000, &lt;1/1000)</th>
<th>Very rare ( &lt;1/10,000, incl. isolated reports)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood and lymphatic system</td>
<td></td>
<td></td>
<td></td>
<td>Leukopenia; Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal Disorders</td>
<td>Upper abdominal pain;</td>
<td>Nausea/Vomiting</td>
<td>Dry mouth</td>
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<tr>
<td></td>
<td></td>
<td>Diarrhoea; Constipation;</td>
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<tr>
<td></td>
<td></td>
<td>Flatulence</td>
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<tr>
<td></td>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
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<td>Peripheral oedema</td>
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<tr>
<td></td>
<td>Hepatobiliary disorders</td>
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<td></td>
<td></td>
<td>Severe hepatocellular damage leading to jaundice with or without hepatic failure</td>
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<tr>
<td></td>
<td>Immune system disorders</td>
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<td></td>
<td>Anaphylactic reactions including anaphylactic shock</td>
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<td>Investigations</td>
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<td>Increased liver enzymes (transaminases, γ-GT); Elevated triglycerides; Increased body temperature</td>
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<td>Musculoskeletal, connective tissue disorders</td>
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<td>Athralgia</td>
<td>Myalgia</td>
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<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness; Disturbances in vision (blurred vision)</td>
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<tr>
<td></td>
<td>Psychiatric disorders</td>
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<td>Mental depression</td>
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<td>Renal and urinary disorders</td>
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<td></td>
<td>Interstitial nephritis</td>
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<td></td>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Allergic reactions such as pruritus and skin rash</td>
<td>Urticaria; Angioedema; Severe skin reactions such as Stevens Johnson Syndrome, Erythema Multi-forme, Lyell-Syndrome; Photosensitivity</td>
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</tr>
</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.

In the case of over-dosage with clinical signs of intoxication, the usual rules of intoxication therapy apply

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: proton pump inhibitors, ATC code: A02BC02

Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells.
Pantoprazole is converted to its active form in the acidic canaliculi of the parietal cells where it inhibits the H⁺, K⁺-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved 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 given orally or intravenously.

The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the normal upper limit. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments (see Section 5.3) can be ruled out for humans for a 1-year treatment period.

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 20 mg oral dose. On average at about 2.0 h - 2.5 h p.a. the maximum serum concentrations of about 1-1.5 µg/ml are achieved, and these values remain constant after multiple administration. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg.

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

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

Pantoprazole's serum protein binding is about 98%. The substance is almost exclusively metabolized in the liver. Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole, the rest 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.
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.

5.3 Preclinical safety data
Preclinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In the 2-year carcinogenicity studies (corresponding to lifetime treatment) in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats in one study. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment.

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

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg) in one 2-year study. The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no side effects on the thyroid glands are expected.

From mutagenicity studies, cell transformation tests and a DNA binding study 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, concentration of pantoprazole in the foetus is increased shortly before birth.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Mannitol
Sodium carbonate anhydrous
Sodium starch glycolate, Type A
Methacrylic acid copolymer
Calcium stearate
Opadry white OY-D-7233 (hypromellose, titanium dioxide, talc, macrogol, sodium lauryl sulphate)
Kollicoat MAE 30 DP yellow (methacrylic acid-ethyl acrylate copolymer dispersion 30%, propylene glycol, yellow iron oxide, titanium dioxide, talc)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.
6.5 **Nature and contents of container**
Pantoprazole 20mg gastro-resistant tablets are provided in aluminium/aluminium blister packs of 7, 14, 15, 28, 30, 50, 56, 60, 84, 90, 100, 112, 140, 280, 500, or 700 tablets.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements

7 **MARKETING AUTHORISATION HOLDER**
Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF
UK

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 24668/0058

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
08/02/2010

10 **DATE OF REVISION OF THE TEXT**
08/02/2010
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 45.16 mg)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant tablet

Elliptical, biconvex, dark yellow gastro-resistant tablet

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux oesophagitis
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions

4.2 Posology and method of administration
The recommended dosage in duodenal ulcer, gastric ulcer and gastro-oesophageal reflux is one enteric-coated tablet per day. Pantoprazole 40mg gastro-resistant tablets should not be chewed or crushed, and should be swallowed whole with water either before or during breakfast.

The safety of longer-term use is generally well established. Long-term administration of pantoprazole has a safety profile similar to that observed with short-term treatment, and is well tolerated. Except for patients with Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions, the treatment with pantoprazole 40mg gastro-resistant tablets should not exceed 8 weeks, as experience with long-term administration in man is insufficient.

In most patients, freedom from symptoms is achieved rapidly. Except for patients with pathological hypersecretory conditions including Zollinger-Ellison syndrome, the treatment with pantoprazole 40mg gastro-resistant tablets should not exceed 8 weeks, as experience in man is insufficient. In a few instances, there may be benefit in extending treatment beyond 8 weeks to ensure healing.

Duodenal ulcer:
Duodenal ulcers generally heal within 2 weeks. If a 2-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Gastric ulcer:
A 4-week period is usually required for the treatment of gastric ulcers. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Gastro-Oesophageal Reflux:
A 4-week period is usually required for the treatment of gastro-oesophageal reflux. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Long-term management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions:
For the long-term management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions patients should start their treatment with a daily dose of 80 mg (2 pantoprazole 40 mg gastro-resistant tablets). Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage
above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control.

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

**Elderly:**
No dose adjustment is necessary in the elderly. However, the daily dose of 40 mg pantoprazole should not be exceeded. An exception is combination therapy for eradication of *H. pylori*, where elderly patients should receive the usual pantoprazole dose (2 x 40 mg/day) during 1 week treatment.

**Patients with impaired renal function:**
No dose adjustment is necessary in patients with impaired renal function. However, the daily dose of 40mg pantoprazole should not be exceeded. For this reason, *H. pylori* triple therapy is not appropriate in these patients.

**Patients with hepatic cirrhosis:**
Due to an increased AUC and a modified metabolism of pantoprazole in patients with hepatic cirrhosis, the dose regimen should be reduced to one tablet every other day. For this reason, *H. pylori* triple therapy is not appropriate in these patients.

**Children:**
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 the active substance or to any of the excipients.

### 4.4 Special warnings and precautions for use
In patients with severe liver impairment, particularly those on long-term use, liver enzymes should be monitored regularly during treatment with pantoprazole. In the case of a rise in liver enzymes, pantoprazole 40mg gastro-resistant tablets should be discontinued.

To date, there has been no experience with treatment in children.

Note:
Prior to treatment of gastric ulcer, the possibility of malignancy should be excluded as treatment with pantoprazole 40mg gastro-resistant tablets may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

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 if respective clinical symptoms are observed.

### 4.5 Interaction with other medicinal products and other forms of interaction
As with other acid secretion inhibitors, changes in absorption may be observed when drugs whose absorption is pH-dependent, e.g. ketoconazole, are taken concomitantly

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. Although studies have shown that pantoprazole has no significant effect on cytochrome P450, an interaction of pantoprazole with other drugs or compounds, which are metabolised using the same enzyme system, cannot be excluded.
However, no clinically significant interactions were observed in specific tests with a number of such drugs/compounds, namely antipyrine, carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and an oral contraceptive. There were also no interactions with concomitantly administered antacids.

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

4.6 Pregnancy and lactation
Clinical experience in pregnant women is limited. In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg. There is no information on the excretion of pantoprazole into human breast milk.

During pregnancy and breastfeeding, pantoprazole 40mg gastro-resistant tablets should only be used when the benefit exceeds the potential risk.

4.7 Effects on ability to drive and use machines
Pantoprazole 40mg gastro-resistant tablets have no influence on the ability to drive and use machines.

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

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Common (&gt;1/100, &lt;1/10)</th>
<th>Uncommon (&gt;1/1000, &lt;1/100)</th>
<th>Rare (&gt;1/10,000, &lt;1/1000)</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>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Upper abdominal pain; Diarrhoea; Constipation; Flatulence</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 oedema</td>
</tr>
<tr>
<td>Hepatobiliary disorders</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>Anaphylactic reactions including anaphylactic shock</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td>Increased liver enzymes (transaminases, γ-GT); Elevated triglycerides; Increased body temperature</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td>Athralgia Myalgia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness; Disturbances in vision (blurred vision)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.9 Overdose
There are no known symptoms of over dosage in man. However, pantoprazole is very specific in action and no particular problems are anticipated. Doses up to 240 mg i.v. were administered without obvious adverse effects. As pantoprazole is extensively protein bound, it is not readily dialysable. Apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: proton pump inhibitors, ATC code: A02BC02

Pantoprazole is a proton pump inhibitor, i.e. it inhibits specifically and dose-proportionally the gastric H⁺/K⁺-ATPase enzyme, which is responsible for acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole, which accumulates, in the acidic environment of the parietal cells after absorption. There it is converted into the active form, a cyclic sulphenamide, which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distally to the receptor level, it can inhibit gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it can only exert its full effect in a strongly acidic environment (pH<3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological and thus therapeutic effect can only be achieved in the acid-secretory parietal cells. By means of a feedback mechanism, this effect is diminished at the same rate as acid secretion is inhibited.

Pantoprazole has the same effect whether administered orally or intravenously.

Following intravenous or oral administration, pantoprazole inhibits the pentagastrin-stimulated gastric acid secretion. In volunteers, acid secretion was inhibited by 56% following the first i.v. administration of 30 mg and by 99% after 5 days. With an oral dose of 40 mg, inhibition was 51% on day 1 and 85% on day 7. Basal 24-hour acidity was reduced by 37% and 98%, respectively.

The fasting gastrin values increased under pantoprazole but in most cases they did not exceed the normal upper limit. Following completion of a course of oral treatment, the median gastrin levels clearly declined again.

5.2 Pharmacokinetic properties
General pharmacokinetics
Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40 mg oral dose. On average, the maximum serum concentrations are
approximately 2-3 μg/ml about 2.5 hours post-administration and these values remain constant after multiple administration. Terminal half-life is about 1 hour. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg. There were a few cases of subjects with delayed elimination. Because of the specific activation within the parietal cell, the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

Pharmacokinetics does not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

Studies with pantoprazole in humans reveal no interaction with the cytochrome P450-system of the liver. There was no induction of the P450-system seen as tested after chronic administration with antipyrine as a marker. Also, no inhibition of metabolism was observed after concomitant administration of pantoprazole with either antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenprocoumon, phenytoin, piroxicam, theophylline and oral contraceptives. Concomitant administration of pantoprazole with warfarin has no influence on warfarin's effect on the coagulation factors.

The absolute bioavailability of the tablet is about 77%. Concomitant intake of food or antacids had no influence on AUC, maximum serum concentrations and thus bioavailability.

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

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

Although for patients with hepatic cirrhosis (classes A and B according to Child) the half-time values increased to between 7 and 9 hours and the AUC values increased by a factor of 5 to 7, the maximum plasma concentration only increased slightly by a factor of 1.5 compared with healthy subjects. Therefore the dose regimen in patients with hepatic cirrhosis should be reduced to one tablet every other day.

No dose reduction is required when pantoprazole is administered to patients with impaired kidney function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialysed. Although the main metabolite has a moderately delayed half-life (2-3 hours), excretion is still rapid and thus accumulation does not occur.

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

### 5.3 Preclinical safety data

**Acute toxicity**

In acute toxicity studies in mice, the LD50 values were found to be 370 mg/kg bodyweight for i.v. administration and around 700 mg/kg bodyweight for oral administration.

In the rat, the corresponding values were around 240 mg/kg for i.v. administration and 900 mg/kg for oral administration.

**Chronic toxicity**

Hypergastrinaemia and morphologic changes of the mucosa were observed in studies investigating repeated administration for up to 12 months in the rat and dog. Most of the effects were reversible and attributable solely to the drug action, i.e. suppression of acid secretion.
In long-term studies in the rat and dog, there was an increase in stomach and liver weights; the increase being reversible after the substance was discontinued. The increase in liver weight following highly toxic doses was seen as a result of the induction of drug-metabolising enzymes.

Thyroid activation in two rat experiments is due to the rapid metabolism of thyroid hormones in the liver and has also been described in a similar form for other drugs. Changes in the thyroid and associated reduced degradation of cholesterol have been observed in one-year studies in the rat and dog. Hypertrophy of the thyroid and increases in cholesterol levels are reversible.

In studies in the dog, a species-specific pulmonary oedema was observed. The animal-specific metabolite, which was responsible for the oedema, could not be identified in man.

**Carcinogenicity**

In a 2-year carcinogenicity study in rats - which corresponds to lifetime treatment for rats - ECL cell carcinoids were found. 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 treatment. In addition, rats have more ECL cells in the mucosa of the glandular stomach than man, so that a larger number of responder cells for the increased gastrin values can become active.

ECL cell neoplasms were not observed in either the study in mice (24 months) or in long-term studies in the dog. In clinical studies (40 - 80 mg for 1 year), ECL cell density slightly increased.

In the two-year studies, an increased number of neoplastic changes of the liver was observed in rats and female mice and was interpreted as being due to pantoprazole's high rate of metabolism in the liver.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose. The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. In man, no changes in the thyroid hormones T3, T4 and TSH were observed. This high dose phenomenon in the rat is therefore not relevant for man.

**Mutagenicity**

In mutagenicity studies, there were no indications of a mutagenic action in vivo or in vitro.

**Reproduction toxicology**

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 foetus is increased shortly before birth, regardless of the route of administration.

In humans, there is no experience of the use of the drug during pregnancy.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

- Mannitol
- Sodium carbonate anhydrous
- Sodium starch glycolate, Type A
- Methacrylic acid copolymer
- Calcium stearate
- Opadry white OY-D-7233 (hypromellose, titanium dioxide, talc, macrogol, sodium lauryl sulphate)
- Kollicoat MAE 30 DP yellow (methacrylic acid-ethyl acrylate copolymer dispersion 30%, propylene glycol, yellow iron oxide, titanium dioxide, talc)
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

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

6.5 Nature and contents of container
Pantoprazole 40mg gastro-resistant tablets are provided in aluminium/aluminium blister packs of 2, 7, 14, 15, 28, 30, 50, 56, 60, 84, 90, 100, 112, 140, 280, 500, or 700 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0059

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
08/02/2010

10 DATE OF REVISION OF THE TEXT
08/02/2010
UKPAR Pantoprazole 20mg and 40mg Gastro-resistant Tablets

Pantoprazole 20 mg
Gastro-resistant Tablets

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

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

In this leaflet:

1. What Pantoprazole 20 mg Gastro-resistant Tablets are and what they are used for
2. Before you take Pantoprazole 20 mg Gastro-resistant Tablets
3. How to take Pantoprazole 20 mg Gastro-resistant Tablets
4. Possible side effects
5. How to store Pantoprazole 20 mg Gastro-resistant Tablets
6. Further information

1. WHAT PANTOPRAZOLE 20 mg GASTRO-RESISTANT TABLETS ARE AND WHAT THEY ARE USED FOR

Pantoprazole 20 mg Gastro-resistant Tablets are used to treat acid reflux (a type of heartburn) and help prevent it from returning. Pantoprazole 20 mg Gastro-resistant Tablets may also be given to patients who need to take non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for a continuous period. These patients are at a greater risk of developing an ulcer and associated symptoms. Pantoprazole 20 mg Gastro-resistant Tablets help reduce the risk by preventing an ulcer from developing.

2. BEFORE YOU TAKE PANTOPRAZOLE 20 mg GASTRO-RESISTANT TABLETS

Do not take Pantoprazole 20 mg Gastro-resistant Tablets
- If you are allergic (hypersensitive) to pantoprazole or any of the other ingredients of Pantoprazole 20mg Gastro-resistant Tablets.

Take special case with Pantoprazole 20 mg Gastro-resistant Tablets
- If you have a liver disease

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

This applies particularly for:
- ketoconazole (to treat fungal infections of the skin and nails)

Inform your doctor if you are taking medicines to thin your blood, such as warfarin, phenprocoumon or acenocoumarol.

Taking vitamin supplements
Please tell your doctor or pharmacist if you are taking Vitamin B supplements as Pantoprazole 20mg Gastro-resistant Tablets may affect how well Vitamin B is absorbed.

Taking Pantoprazole 20 mg Gastro-resistant Tablets with food and drink
Pantoprazole 20 mg Gastro-resistant Tablets should be taken before a meal with water. Do not crush, break or chew the tablets.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Pantoprazole 20 mg Gastro-resistant Tablets must only be used during pregnancy and lactation if clearly advised by your doctor.

Driving and using machines
Pantoprazole 20 mg Gastro-resistant Tablets do not affect the ability to drive and use machines.

3. HOW TO TAKE PANTOPRAZOLE 20 mg GASTRO-RESISTANT TABLETS

Always take Pantoprazole 20 mg Gastro-resistant Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is:

Mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing)

The recommended oral dosage is one Pantoprazole 20 mg Gastro-resistant Tablet per day. Symptom relief is generally accomplished within 2-4 weeks, and a 4-week treatment period is usually required for healing of associated oesophagitis. If this is not sufficient, healing will normally be achieved within a further 4 weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment.

Long-term management and prevention of relapse in reflux oesophagitis

For long-term management, a maintenance dose of one Pantoprazole 20 mg Gastro-resistant Tablet per day is recommended, increasing to 40 mg pantoprazole per day if a relapse occurs. Pantoprazole 40 mg Gastro-resistant Tablets are available for this case. After healing of the relapse the dosage can be reduced again to 20 mg pantoprazole.

Prevention of gastrooesophageal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment

The recommended oral dosage is one Pantoprazole 20 mg Gastro-resistant Tablet per day.

Elderly:
No dose adjustment is necessary. Follow your doctor's instructions.
Children:
Pantoprazole 20 mg Gastro-resistant Tablets are not recommended for children.

Reduced kidney function:
No dose adjustment is necessary. Follow your doctor’s instructions

Reduced liver function:
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment.

General instructions:
Pantoprazole 20 mg Gastro-resistant Tablets should not be chewed or crushed, and should be swallowed whole with liquid before a meal.

If you take more Pantoprazole 20 mg Gastro-resistant Tablets than you should
Contact your doctor, emergency room or pharmacist
If you have taken more Pantoprazole 20 mg Gastro-resistant Tablets than stated in this leaflet or more than your doctor has prescribed.

If you forget to take Pantoprazole 20 mg Gastro-resistant Tablets
Do not take a double dose to make up for a forgotten tablet.

If you stop taking Pantoprazole 20 mg Gastro-resistant Tablets
Keep taking the tablets until you have finished the course of treatment or until your doctor tells you to stop. 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 20 mg Gastro-resistant Tablets can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Common (they occur in between one and ten per 100 patients who receive treatment)
Stomach pain, diarrhoea, constipation, wind, headache.

Uncommon (they occur in between one and ten per 1000 patients who receive treatment)
Nausea, vomiting, dizziness, blurred vision, allergic reactions.

Rare (they occur in between one and ten per 10,000 patients who receive treatment)
Dry mouth, joint pain.

Very rare (they occur in less than one per 10,000 patients who receive treatment)
Reduction in some cells in your blood, swollen ankles, liver damage leading to jaundice with or without liver failure, anaphylactic reactions, fever, muscle pain, mental depression, inflammation of the kidneys, nettle rash, severe skin reactions with blistering of the skin.

5. HOW TO STORE PANTOPRAZOLE 20 mg GASTRO-RESISTANT TABLETS
Keep out of the reach and sight of children.
This medicinal product requires no special storage conditions.
Do not take Pantoprazole 20 mg Gastro-resistant Tablets after the expiry date which is stated on the label and carton after EXPIRY. 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 20 mg Gastro-resistant Tablets contain
- The active substance is pantoprazole (as pantoprazole sodium sesquifilrate).
Each tablet contains 20 mg pantoprazole
- The other ingredients are:
Mannitol
Sodium carbonate anhydrous
Sodium stearic glycolate
Methacrylic acid copolymer
Calcium stearate
Opadry white OY-D-7233 (hypromellose 3cp; titanium dioxide, talc, macrogol, sodium lauryl sulphate)
Kollcoat MAE 30 DP yellow (methacrylic acid-ethyl acrylate copolymer dispersion, 30%, propylene glycol, yellow iron oxide, titanium dioxide, talc)

What Pantoprazole 20 mg Gastro-resistant Tablets look like and contents of the pack
Pantoprazole 20 mg Gastro-resistant Tablets are elliptical, biconvex, light yellow, gastro-resistant tablets.

Pack sizes:
(only the actual marketed pack sizes will be stated on the leaflet)
Pantoprazole 20 mg Gastro-resistant Tablets are supplied in blister packs of 7, 14, 15, 28, 30, 50, 60, 84, 90, 100, 112, 140, 280, 500, or 700 tablets.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
CADUCEUS PHARMA LIMITED
6th Floor
94 Wigmore Street
London
W1U 3BF
UK

Manufacturer:
Actavis hf
Reykjavikursargar 78
15-220 Reykjavik 1
Iceland

Actavis Ltd
BL8016 Bulebel Industrial Estate
Zejtun ZTN 3000
Malta

*(the actual leaflet will only refer to the batch release site that is utilised)

This leaflet was last approved in 03/2009.
Pantoprazole 40 mg Gastro-resistant Tablets

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

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

In this leaflet:

1. What Pantoprazole 40 mg Gastro-resistant Tablets are and what they are used for
2. Before you take Pantoprazole 40 mg Gastro-resistant Tablets
3. How to take Pantoprazole 40 mg Gastro-resistant Tablets
4. Possible side effects
5. How to store Pantoprazole 40 mg Gastro-resistant Tablets
6. Further information

1. WHAT PANTOPRAZOLE 40 mg GASTRO-RESISTANT TABLETS ARE AND WHAT THEY ARE USED FOR

Pantoprazole 40 mg Gastro-resistant Tablets are used to treat acid reflux (a type of heartburn) and ulcers in the stomach (gastric ulcer) and in the upper part of the intestine (duodenal ulcer). Pantoprazole 40 mg Gastro-resistant Tablets are also used for the long-term treatment of people who secrete too much acid in conditions such as Zollinger-Ellison syndrome.

2. BEFORE YOU TAKE PANTOPRAZOLE 40 mg GASTRO-RESISTANT TABLETS

Do not take Pantoprazole 40 mg Gastro-resistant Tablets

- If you are allergic (hypersensitive) to pantoprazole or any of the other ingredients of Pantoprazole 40 mg Gastro-resistant Tablets.

Take special care with Pantoprazole 40 mg Gastro-resistant Tablets

- If you have liver disease

Taking other medicines

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

This applies particularly for:
- ketoconazole (to treat fungal infections of the skin and nails)
- Inform your doctor if you are taking medicines to thin your blood, such as warfarin, phenprocoumon or acenocoumarol.

Taking vitamin supplements

Please tell your doctor or pharmacist if you are taking Vitamin B supplements as Pantoprazole 40 mg Gastro-resistant Tablets may affect how well Vitamin B is absorbed.

Taking Pantoprazole 40 mg Gastro-resistant Tablets with food and drink

Pantoprazole 40 mg Gastro-resistant Tablets should be taken before a meal with water. Do not crush, break or chew the tablet.

Pregnancy and breast-feeding

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

Pantoprazole 40 mg Gastro-resistant Tablets must only be used during pregnancy and lactation if clearly advised by your doctor.

Driving and using machines

Pantoprazole 40 mg Gastro-resistant Tablets do not affect the ability to drive and use machines.

3. HOW TO TAKE PANTOPRAZOLE 40 mg GASTRO-RESISTANT TABLETS

Always take Pantoprazole 40 mg Gastro-resistant Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is:

- The usual dose for the treatment of acid reflux, a gastric and duodenal ulcer is one tablet taken in the morning, with or without food.

- The usual starting dose for the treatment of Zollinger-Ellison syndrome is one tablet taken twice a day. You should take the first tablet in the morning and the second tablet just before your evening meal. Your doctor may then adjust the dosage, depending on how much medicine is required for your treatment.

Ask your doctor or pharmacist if you are unsure about anything.

Elderly:

No dose adjustment is necessary. However, the daily dose of 40 mg pantoprazole should not be exceeded. An exception is combination therapy for eradication of H. pylori, where elderly patients should receive the usual pantoprazole dose (1 x 40 mg/day) during a 1 week treatment.

Children:

Pantoprazole 40 mg Gastro-resistant Tablets are not recommended for use in children below 12 years.

Patients with impaired kidney function:

No dose adjustment is necessary. However, the daily dose of 40 mg pantoprazole should not be exceeded. For this reason, H. pylori triple therapy is not appropriate in these patients.

Patients with liver cirrhosis:

The dose should be reduced to one tablet every other day. For this reason, H. pylori triple therapy is not appropriate in these patients.

General instructions:

Pantoprazole 40 mg Gastro-resistant Tablets should not be chewed or crushed, and should be swallowed whole with liquid.

If you take more Pantoprazole 40 mg Gastro-resistant Tablets than you should

Contact your doctor, emergency room or pharmacist if you have taken more Pantoprazole 40 mg Gastro-resistant Tablets than stated in this leaflet or more than your doctor has prescribed.
If you forget to take Pantoprazole 40 mg Gastro-resistant Tablets
If you forget to take a dose, take it as soon as you remember, unless it is almost time for your next dose. If it is, do not take the missed dose at all. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Pantoprazole 40 mg Gastro-resistant Tablets
Keep taking the tablets until you have finished the course of treatment or until your doctor tells you to stop. 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 40 mg Gastro-resistant Tablets can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Common (they occur in between one and ten per 100 patients who receive treatment)
- Stomach pain, diarrhoea, constipation, wind, headache.

Uncommon (they occur in between one and ten per 1000 patients who receive treatment)
- Nausea, vomiting, dizziness, blurred vision, allergic reactions.

Rare (they occur in between one and ten per 10,000 patients who receive treatment)
- Dry mouth, joint pain.

Very rare (they occur in less than one per 10,000 patients who receive treatment)
Reduction in some cells in your blood, swollen ankles, liver damage leading to jaundice with or without liver failure, anaphylactic reactions, fever, muscle pain, mental depression, inflammation of the kidneys, nettle rash, severe skin reactions with blistering of the skin.

5. HOW TO STORE PANTOPRAZOLE 40 mg GASTRO-RESISTANT TABLETS

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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

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  - Mannitol
  - Sodium carbonate anhydrous
  - Sodium starch glycolate
  - Methacrylic acid copolymer
  - Calcium stearate
  - Opadry white OY-D-7233 (hypromellose 3cP, titanium dioxide, talc, macrogol, sodium lauryl sulphate)
  - Kollicoat MAE 30 DP yellow (methacrylic acid-ethyl acrylate copolymer dispersion 30%, propylene glycol, yellow iron oxide, titanium dioxide, talc)

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Iceland

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