PANTOPRAZOLE 20 MG GASTRO-RESISTANT TABLETS
PANTOPRAZOLE 40 MG GASTRO-RESISTANT TABLETS

(Pantoprazole sodium sesquihydrate)

PL 19156/0041-2

UKPAR

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PANTOPRAZOLE 20 MG GASTRO-RESISTANT TABLETS
PANTOPRAZOLE 40 MG GASTRO-RESISTANT TABLETS

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LAY SUMMARY

The MHRA granted Jubilant Pharmaceuticals NV Marketing Authorisations (licences) for the medicinal products Pantoprazole 20 mg and 40 mg gastro-resistant tablets on 11 August 2011. These products are prescription-only medicines (POM) used for treating acid-related diseases of the stomach and intestine.

Pantoprazole 20 mg gastro-resistant tablets are used:
- in the treatment of mild gastro-oesophageal reflux disease (a condition in which gastric content may rise up to the oesophagus and which can be associated with oesophagitis) caused by acid secretion, and the associated symptoms, such as heartburn, acidic belches and pains on swallowing
- in the long-term treatment and in the prevention of relapse in reflux oesophagitis (a condition in which backwash of gastric content in oesophagus leads to inflammation and pain)
- in the prevention of gastric and duodenal ulcers caused by anti-inflammatory drugs in high-risk patients needing continuous treatment with anti-inflammatory drugs

Pantoprazole 40 mg gastro-resistant tablets are used in the treatment and to relieve the symptoms of:
- duodenal ulcer
- gastric ulcer
- oesophagitis (inflammation of oesophagus) caused by acid secretion

Additionally, the preparation is used in the long-term treatment of conditions where gastric acid is constantly being secreted too much (e.g. Zollinger-Ellison syndrome)

Pantoprazole belongs to a group of medicines called proton pump inhibitors. Proton pump inhibitors reduce the amount of acid that your stomach makes.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Pantoprazole 20 mg and 40 mg gastro-resistant tablets outweigh the risks, hence Marketing Authorisations has been granted.
PANTOPRAZOLE 20 MG GASTRO-RESISTANT TABLETS
PANTOPRAZOLE 40 MG GASTRO-RESISTANT TABLETS

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Jubilant Pharmaceuticals NV, Marketing Authorisations for the medicinal products Pantoprazole 20 mg and 40 mg gastro-resistant tablets (PL 19156/0041-2) on 11 August 2011. These products are prescription-only medicines (POM).

Pantoprazole 20 mg gastro-resistant tablets are indicated:
- 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.
- for 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 of SmPC).

Pantoprazole 40 mg gastro-resistant tablets are indicated for relieving the symptoms and for 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.

These are abridged applications submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to Pantozol 40mg magnesiumresistent Tablette (Byk Gulden Lomberg, Germany), which has been authorised in the EEA since 23 August 1994. The corresponding reference products in the UK are Protium 20 mg and 40 mg Gastro-resistant Tablets (Nycomed GmBH), which were first authorised on 04 June 1996.

Pantoprazole belongs to a group of medicines called proton pump inhibitors. It 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 in the parietal cells, where it inhibits the H⁺, K⁺-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent, and affects both basal and stimulated acid secretion.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

Three single-dose, bioequivalence studies under fasting (20 mg and 40 mg) and fed conditions (40 mg only) were submitted to support these applications, comparing the test products Pantoprazole 20 mg and 40 mg gastro-resistant tablets (Jubilant Pharmaceuticals NV, Belgium) and the reference products Zurcale 20 mg and 40 mg tablets (Altana Pharma AG, Germany). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new clinical studies were performed, which is acceptable given that the applications were based on being a generic medicinal products of originator products that have been in clinical use for over 10 years.
No new or unexpected safety concerns were raised during the assessment of these applications and it was, therefore, judged that the benefits of taking Pantoprazole 20 mg and 40 mg gastro-resistant tablets outweigh the risks; hence Marketing Authorisations have been granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Pantoprazole
Chemical name: Sodium 5-(difluoromethoxy)-2-[(RS)-[(3,4-dimethoxypyridin-2-yl)methyl] sulphinyl] benzimidazol-1-ide sesquihydrate

Structure:

Molecular formula: $\text{C}_{16}\text{H}_{14}\text{F}_{2}\text{N}_{3}\text{NaO}_{4}\text{S}.1\frac{1}{2}\text{ H}_{2}\text{O}$
Molecular weight: 432.4
Appearance: Pantoprazole is a white to off-white crystalline powder which is freely soluble in water. Pantoprazole sodium sesquihydrate contains no chiral carbons but it does contain an asymmetric sulphur atom. Pantoprazole sodium exists in two hydrate forms, monohydrate and sesquihydrate.

Pantoprazole is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance pantoprazole are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

MEDICINAL PRODUCT
Other ingredients
Other ingredients consist of pharmaceutical excipients, namely sodium carbonate, anhydrous, mannitol, sucrose, talc, calcium stearate, silicon dioxide, hypromellose, macrogol, methacrylic acid-ethyl acetate co-polymer, titanium dioxide (E171), triethyl citrate, iron oxide red (E172), iron oxide black (E172) and printing ink (consisting of shellac, iron oxide black (E172), propylene glycol and ammonium hydroxide).

Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monograph with the exception of silicon dioxide which is compliant with National Formulary-US pharmacopoeia (USP) and iron oxide red and iron oxide black, which are controlled to suitable in-house specifications. In addition iron oxide red and iron oxide black are in compliance with current EEC directives concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients.
With the exception of shellac, none of the excipients contain materials of animal or human origin. The supplier of shellac has provided a declaration that the shellac is without risk of TSE/BSE contamination.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical development**
The aim of the development programme was to formulate safe, efficacious, stable tablets that could be considered generic medicinal products of Zurcale 20 mg and 40 mg tablets (Altana Pharma AG, Germany)

Suitable pharmaceutical development data have been provided for these applications.

Comparable *in vitro* dissolution and impurity profiles have been provided for the proposed and originator product.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished product specification**
The finished product specifications are satisfactory. Test methods have been described and have been 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**
All strengths of the finished product are packaged in olefin polyamide/aluminium/polyvinylchloride blister strips and are available in pack sizes of 7, 14, 15, 28, 30, 56, 60, 98 and 100 gastro-resistant tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

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

**Stability**
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with no special storage conditions.
Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PILs and labelling are satisfactory.

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

MAA Form
The MAA forms are satisfactory.

Expert Report
A quality overall summary has been 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.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
No new non-clinical data were submitted, which is acceptable given that the proposed products are generic medicinal products of originator products that have been licensed for over 10 years.

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

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

CONCLUSION
It is recommended that marketing authorisations are granted for these applications.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

The clinical pharmacology of pantoprazole is well-known. With the exception of the bioequivalence studies, no pharmacokinetic or pharmacodynamic data were submitted for these applications, and none were required for applications of this type.

The following bioequivalence studies were submitted:

**Study 1:**
An open label, balanced, randomised, two-treatment, two-sequence, two-period, single dose, two-way crossover study to compare the pharmacokinetics of the test product Pantoprazole 40 mg gastro-resistant tablets versus the reference product Zurcale 40 mg tablets (Altana Pharma AG, Germany) in healthy adult male volunteers under fasted conditions.

All volunteers were dosed in a fasted state in two treatment periods. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 32 hours post dose. The washout period between treatment periods was at least 5 days.

The pharmacokinetic results for pantoprazole, for the test product versus the reference product for the 40 mg strength are presented below as log-transformed values (geometric mean) with ratios of least-square means.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng.h/ml)</th>
<th>AUC_{0-∞} (ng.h/ml)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>8732.725</td>
<td>8854.587</td>
<td>3795.370</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>8798.113</td>
<td>8938.312</td>
<td>3634.267</td>
</tr>
<tr>
<td>Ratio T/R (90% CI*)</td>
<td>99.3%</td>
<td>99.1%</td>
<td>104.4%</td>
</tr>
</tbody>
</table>

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration

**Study 2:**
An open label, balanced, randomised, two-treatment, two-sequence, two-period, single dose, two-way crossover study to compare the pharmacokinetics of the test product Pantoprazole 20 mg gastro-resistant tablets versus the reference product Zurcale 40 mg tablets (Altana Pharma AG, Germany) in healthy adult male volunteers in a fed state.

All volunteers were dosed after a standard high-fat, high-caloric breakfast meal in two treatment periods. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 36 hours post dose. The washout period between treatment periods was at least 4 days.

The pharmacokinetic results for pantoprazole, for the test product versus the reference product for the 40 mg strength in the fed state are presented below as log-transformed values (geometric mean) with ratios of least-square means.
### Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$ (ng.h/ml)</th>
<th>$\text{AUC}_{0-\infty}$ (ng.h/ml)</th>
<th>$\text{C}_{\text{max}}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>7149.545</td>
<td>7314.741</td>
<td>3053.370</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>7562.868</td>
<td>7684.434.</td>
<td>3461.000</td>
</tr>
<tr>
<td>Ratio T/R (90% CI*)</td>
<td>94.5% (88.58-100.88%)</td>
<td>95.2% (89.21-101.57%)</td>
<td>88.2% (81.07-96.00%)</td>
</tr>
</tbody>
</table>

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

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

$\text{C}_{\text{max}}$ maximum plasma concentration

### Study 3:

An open label, balanced, randomised, two-treatment, two-sequence, two-period, single dose, two-way crossover study to compare the pharmacokinetics of the test product Pantoprazole 20 mg gastro-resistant tablets versus the reference product Zurcalle 20 mg tablets (Altana Pharma AG, Germany) in healthy adult male volunteers under fasted conditions.

All volunteers were dosed in a fasted state in two treatment periods. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 32 hours post dose. The washout period between treatment periods was at least 5 days.

The pharmacokinetic results for pantoprazole, for the test product versus the reference product for the 20 mg strength are presented below as log-transformed values (geometric mean) with ratios of least-square means.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$ (ng.h/ml)</th>
<th>$\text{AUC}_{0-\infty}$ (ng.h/ml)</th>
<th>$\text{C}_{\text{max}}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>3180.769</td>
<td>3206.393</td>
<td>1876.682</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>3281.210</td>
<td>3312.893</td>
<td>1730.008</td>
</tr>
<tr>
<td>Ratio T/R (90% CI*)</td>
<td>96.9% (91.28-102.95%)</td>
<td>96.8% (91.17-102.75%)</td>
<td>108.5% (98.87-119.03%)</td>
</tr>
</tbody>
</table>

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

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

$\text{C}_{\text{max}}$ maximum plasma concentration

For all studies, the 90% confidence intervals for AUC and $\text{C}_{\text{max}}$ were within the predefined acceptance range for pantoprazole. Bioequivalence was therefore demonstrated between all strengths of test product and its respective reference product in fasting and non-fasting conditions.

### Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for these applications.

### Efficacy

No new efficacy data were submitted and none were required for these applications.
Safety
With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were raised by the bioequivalence data.

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

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

Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of these products from a clinical viewpoint.
IV  OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

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

EFFICACY
Bioequivalence has been accepted between the applicant’s Pantoprazole 20 mg and 40 mg gastro-resistant tablets and their respective reference products.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with pantoprazole is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
1 The MHRA received the marketing authorisation applications on 03 April 2008.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 09 September 2008.

3 Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 20 August 2008 and the quality dossier on 08 December 2008, 31 July 2009, 04 April 2010 and 30 September 2010.

4 The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 18 March 2009 and the quality dossier on 18 March 2009, 23 October 2009, 21 May 2010 and 03 February 2011.

5 The applications were determined on 11 August 2011.
## STEPS TAKEN AFTER ASSESSMENT

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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</tbody>
</table>
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 22.6 mg).
Excipient: 8 mg sucrose/gastro-resistant tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant tablet.
A reddish-black coloured, biconvex, oval shaped, coated tablet imprinted with ‘P20’ on one side and plain on the other side.

4 CLINICAL PARTICULARS

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

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

Treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing)
The recommended dosage is 20 mg pantoprazole daily (1 Pantoprazole 20 mg gastro-resistant tablet). 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 (1 Pantoprazole 20 mg gastro-resistant tablet) 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.

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 dosage is 20 mg pantoprazole daily (1 Pantoprazole 20 mg gastro-resistant tablet).

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

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.

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.

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.

There is no experience with the use of pantoprazole in children.

Pantoprazole gastro-resistant tablets contain sucrose. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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
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 breast feeding, pantoprazole tablets
should only be used when the benefit to the mother is considered greater than the potential risk to the
foetus 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</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ system</td>
<td></td>
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<tr>
<td>Blood and the</td>
<td>Leucopenia,</td>
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<tr>
<td>lymphatic system</td>
<td>thrombocytopenia</td>
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<tr>
<td>Immune system</td>
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<tr>
<td>disorders</td>
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<tr>
<td>Psychiatric</td>
<td>Depression</td>
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<tr>
<td>Nervous system</td>
<td>Dizziness,</td>
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<td>disorders</td>
<td>disturbances in</td>
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<tr>
<td>Headache</td>
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<td></td>
<td>vision)</td>
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<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting</td>
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</tr>
<tr>
<td>disorders</td>
<td>Dry mouth</td>
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</tr>
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<td>jaundice with or</td>
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<td>Skin and sub-</td>
<td>Allergic reactions</td>
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<td>cutaneous tissue</td>
<td>such as pruritus</td>
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<td>disorders</td>
<td>and skin rash</td>
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<td>Musculoskeletal,</td>
<td>Arthralgia</td>
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<td>connective tissue</td>
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<td>disorders</td>
<td>Myalgia</td>
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<td>Renal and urinary</td>
<td>Interstitial nephritis</td>
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<tr>
<td>disorders</td>
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<tr>
<td>General disorders</td>
<td>Peripheral edema</td>
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</tbody>
</table>
Frequency | Common | Uncommon | Rare | Very rare
---|---|---|---|---
and administration site conditions | | | subsiding after termination of therapy |
Investigations | | | Increased liver enzymes (transaminases, γ-glutamyltransferase), elevated triglycerides, increased body temperature |

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.

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 2−3 μg/ml after 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-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.
A slight increase in AUC and Cmax in elderly volunteers compared with younger counterparts is also not clinically relevant.

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 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 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, concentration of pantoprazole in the foetus is increased shortly before birth.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
The core tablet:
Sodium carbonate, anhydrous
Mannitol
Sucrose
Talc
Calcium stearate
Silicon dioxide

The coating:
Hypermellose
Talc
Macrogol
Methacrylic acid-ethyl acetate co-polymer
Titanium dioxide (E171)
Triethyl citrate
Iron oxide red (E172)
Iron oxide black (E172)

The printing ink:
Shellac
Iron oxide black (E172)
Propylene glycol
Ammonium hydroxide.
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

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

6.5 Nature and contents of container
Blisters (OPA/Aluminium/PVC film and aluminium foil) in an outer cardboard carton. Pack-sizes of 7, 14, 15, 28, 30, 56, 60, 98 and 100 gastro-resistant tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Jubilant Pharmaceuticals nv
Axxes Business Park
Guldensporenpark 22 – Block C
9820 Merelbeke
Belgium

8 MARKETING AUTHORISATION NUMBER(S)
PL 19156/0041

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/08/2011

10 DATE OF REVISION OF THE TEXT
11/08/2011
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 45.2 mg).
Excipient: 16 mg sucrose/gastro-resistant tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant tablet.
A reddish-black coloured, biconvex, oval shaped, coated tablet imprinted with ‘P40’ on one side and plain on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For relieving the symptoms and for 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
Method of administration
Pantoprazole 40 mg tablets should not be chewed or crushed, and should be swallowed whole with water either before or during breakfast.

Duodenal ulcer
The recommended dosage is 40 mg pantoprazole daily (1 Pantoprazole 40 mg gastro-resistant tablet). 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.

Gastric ulcer and moderate and severe reflux oesophagitis
The recommended dosage is 40 mg pantoprazole daily (1 Pantoprazole 40 mg gastro-resistant tablet). 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 (2 Pantoprazole 40 mg gastro-resistant tablets). 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 exceeded.

Patients with renal impairment
The daily dose of 40 mg pantoprazole should not be exceeded in patients with impaired renal function.

Patients with hepatic impairment
Patients with severe hepatic impairment should be given 40 mg of pantoprazole every other day (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
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
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).

Pantoprazole 40 mg is not intended for the treatment of mild gastrointestinal complaints, such as functional indigestion.

In combination therapy, the Summaries of Product Characteristics of all respective medicinal products should be observed.

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.

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.

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 with the use of pantoprazole in children.

Pantoprazole gastro-resistant tablets contain sucrose. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Pantoprazole may markedly 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 (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Breast-feeding
There is no information on the excretion of pantoprazole into human breast milk. During breast feeding, pantoprazole tablets should only be used when the benefit to the mother is considered greater than the potential risk to the foetus 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</th>
<th>Uncommon</th>
<th>Rare</th>
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<td>Anaphylactic reactions including anaphylactic shock</td>
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<td>Psychiatric disorders</td>
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<td>Depression</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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<td>Gastrointestinal disorders</td>
<td>Upper abdominal pain, diarrhoea, constipation, flatulence</td>
<td>Nausea, vomiting</td>
<td>Dry mouth</td>
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<tr>
<td>Hepatobiliary disorders</td>
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<td>Severe hepatocellular damage leading to jaundice with or without hepatic failure</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
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<td>Allergic reactions such as pruritus and skin rash</td>
<td>Urticaria, angioedema, severe skin reactions such as Stevens Johnson syndrome, erythema multiforme, Lyell's syndrome, photosensitivity</td>
<td></td>
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<tr>
<td>Frequency</td>
<td>Common</td>
<td>Uncommon</td>
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<td>Musculoskeletal, connective tissue disorders</td>
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<td>Arthralgia</td>
<td>Myalgia</td>
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<td>Renal and urinary disorders</td>
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<td>Interstitial nephritis</td>
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<td>General disorders and administration site conditions</td>
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<td>Peripheral edema subsiding after termination of therapy</td>
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<tr>
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<td></td>
<td>Increased liver enzymes (transaminases, γ-glutamyltransferase), elevated triglycerides, increased body temperature</td>
</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. 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.

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 2–3 μg/ml after 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-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.

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

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 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 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, concentration of pantoprazole in the foetus is increased shortly before birth.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
The core tablet:
Sodium carbonate, anhydrous
Mannitol
Sucrose
Talc
Calcium stearate
Silicon dioxide

The coating:
Hypermellose
Talc
Macrogol
Methacrylic acid-ethyl acetate co-polymer
Titanium dioxide (E171)
Triethyl citrate
Iron oxide red (E172)
Iron oxide black (E172)

The printing ink:
Shellac
Iron oxide black (E172)
Propylene glycol
Ammonium hydroxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

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

6.5 Nature and contents of container
Blisters (OPA/Aluminium/PVC film and aluminium foil) in an outer cardboard carton.
Pack-sizes of 7, 14, 15, 28, 30, 56, 60, 98 and 100 gastro-resistant tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Jubilant Pharmaceuticals nv
Axxes Business Park
Guldensporenpark 22 – Block C
9820 Merelbeke
Belgium

8 MARKETING AUTHORISATION NUMBER(S)
PL 19156/0042

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/08/2011

10 DATE OF REVISION OF THE TEXT
11/08/2011
Module 3
PATIENT INFORMATION LEAFLET

Pantoprazole 20 mg gastro-resistant tablets

The name of your medicine is Pantoprazole 20 mg gastro-resistant tablets, which will be referred to as Pantoprazole throughout the rest of this document.

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you lose it, you can get another copy from your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get 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 tablets belong to a group of medicines called proton pump inhibitors. Proton pump inhibitors reduce the amount of acid that your stomach makes.

You have been given Pantoprazole tablets because you have a condition caused by stomach acid.

Pantoprazole tablets are used:
- in the treatment of non erosive and erosive reflux disease (a condition in which stomach or food contents may rise up to the esophagus and which can be associated with heartburn, acid reflux and heartburn), caused by acid secretion, and the associated symptoms, such as heartburn, acid reflux and heartburn; and pain on swallowing.
- in the treatment of reflux esophagitis (a condition in which the backwash of stomach contents into the esophagus lead to inflammation and pain)
- in the prevention of gastric and duodenal ulcers caused by anti-inflammatory drugs in high-risk patients needing continuous treatment with anti-inflammatory drugs and

2. BEFORE YOU TAKE PANTOPRAZOLE TABLETS

Do not take Pantoprazole tablets if you
- are allergic (hypersensitive) to pantoprazole or any of the other ingredients of Pantoprazole tablets (see Section 6 for a full list).
- are taking alzesine (which is used for the treatment of HIV infection).

Pantoprazole tablets are not recommended for children.

Take special care with Pantoprazole tablets

Please tell the doctor who prescribed this medicine if you:
- have been diagnosed with vitamin B12 malabsorption.
- have been diagnosed with iron deficiency anemia.
- are taking Pantoprazole tablets together with other medicines to treat your pain or discomfort caused by your medical condition, for example, aspirin, ibuprofen or nimesulide.
- are taking Pantoprazole tablets on a long-term basis (longer than 1 year). Your doctor will perform regular check-ups to make sure that you are not at risk of developing other symptoms and circumstances whenever you see your doctor.

Please tell your doctor if you suffer or have recently suffered from any of the following symptoms: unusual weight loss, recurrent vomiting or vomiting of blood, or dark stool.

Your doctor may carry out or have performed an additional investigation called an endoscopy in order to diagnose your condition and/or exclude malignant 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. Remember to tell your doctor about your treatment with Pantoprazole tablets if you are prescribed another medicine while the treatment is still ongoing.

It is especially important to tell your doctor if you’re taking:
- zidovudine (used for the treatment of HIV infection)
- ketoconazole or itraconazole (used for the treatment of fungal infections)
- anticoagulant medicines (e.g. warfarin)

Taking Pantoprazole tablets with food and drink

Take Pantoprazole tablets whole with water either before or during breakfast.

Pregnancy and breast feeding

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

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

Driving and using machines

Pantoprazole tablets may cause dizziness and visual disturbances.

Know how this medicine affects you before driving or using machines.

Important information about some of the ingredients of Pantoprazole tablets

This medicine contains sorbital. If you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

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.

Dose

Treatment of mild reflux disease and the associated symptoms (e.g. heartburn, acid reflux and pain on swallowing): The recommended dose is 1 tablet (20 mg) daily.

Long-term treatment and the prevention of reflux esophagitis: In long-term treatment the recommended dose is 1 tablet (20 mg) daily.

Prevention of gastric and duodenal ulcers caused by anti-inflammatory drugs:

The recommended dose is 1 tablet (20 mg) daily.

Elderly and patients with renal impairment:

Daily dose of 40 mg should not be exceeded.

Patients with hepatic impairment:

Daily dose of 20 mg should not be exceeded.

Children:

Pantoprazole tablets should not be used in children.

Method of administration

Do not chew or crush Pantoprazole tablets but swallow them whole with water either before or during breakfast.

If you take more Pantoprazole tablets than you should

If you or someone you know accidentally takes a lot more than the stated dose (an overdose) you should contact a doctor immediately.

If you forget to take Pantoprazole tablets

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

If you stop taking Pantoprazole tablets

Do not change the dosage or stop the medicine without discussing it with your doctor first.

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

MHRA PAR – Pantoprazole 20 mg and 40 mg gastro-resistant tablets (PL 19156/0041-2)
4. POSSIBLE SIDE EFFECTS

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

You should stop taking Pantoprazole tablets and see your doctor immediately if you experience symptoms of angioedema, such as:
- Swollen face, tongue or throat
- Difficulty to swallow
- Hives and difficulties to breath

The frequencies of other side effects are defined as:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Less than 1 in 10, but not more than 1 in 100 people</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Less than 1 in 100, but more than 1 in 1000 people</td>
</tr>
<tr>
<td>Rare</td>
<td>Less than 1 in 1000, but more than 1 in 10,000 people</td>
</tr>
<tr>
<td>Very rare</td>
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</tr>
</tbody>
</table>

Common:
- Upper abdominal pain
- Diarrhea
- Constipation
- Flatulence
- Headache

Uncommon:
- Nausea
- Vomiting
- Dizziness
- Blurred vision
- Allergic reactions such as itching and rash

Rare:
- Dry mouth
- Joint pain

Very rare:
- White blood cell deficiency (leucopenia)
- Platelet deficiency (thrombocytopenia)
- Swelling of hands and feet
- Severe liver cell damage and associated jaundice with potential liver failure
- Severe allergic reaction manifested as acute general symptoms with potential acute and substantial drop in blood pressure
- Elevated liver enzyme and triglyceride levels
- Elevated body temperature
- Muscle pain
- Depression
- Kidney inflammation
- Hives
- Hypersensitivity attacks of local skin and mucous membrane swelling in the face, limbs, lips, tongue, larynx and/or vocal cords (angioedema, see special warning above)
- Photosensitivity reactions and severe skin reactions such as Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis (Lyell’s syndrome)

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

5. HOW TO STORE PANTOPRAZOLE TABLETS

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Expiry date

Do not use Pantoprazole tablets after the expiry date which is stated on the packaging. 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

- Each gastro-resistant tablet contains 20 mg Pantoprazole (as pantoprazole sodium sesquihydrate 22.6 mg).
- The other ingredients are:
  - The core tablet:
    - Sodium carbonate, anhydrous – Mannitol – Sucrose – Talc – Calcium stearate – Silicon dioxide
  - The coating:

The printing ink:
  - Shellac - Iron oxide black (E172) - Propylene glycol - Ammonium hydroxide.

What Pantoprazole tablets look like and contents of the pack

The 20 mg gastro-resistant tablets are reddish-black coloured, biconvex, oval shaped, coated tablets imprinted with “P20” on one side and plain on the other side.

Pack sizes

Boxes of 7, 14, 15, 28, 30, 56, 60, 98 and 100 gastro-resistant tablets in blister packs.

Not all pack sizes may be marketed.

Marketing Authorisation holder and manufacturer

Marketing Authorisation Holder

Jubilant Pharmaceuticals nv
Axces Business Park
Oudenhofspark 22 - Block C
9820 Marelbeke
Belgium

Manufacturer

PSI supply nv
Axces Business Park
Oudenhofspark 22 - Block C
9820 Marelbeke
Belgium

This leaflet was last approved in 11/2010
PACKAGE LEAFLET INFORMATION FOR THE USER

Pantoprazole 40 mg gastro-resistant tablets

Pantoprazole

The name of your medicine is Pantoprazole 40 mg gastro-resistant tablets, which will be referred to as Pantoprazole tablets throughout the rest of this document.

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 your 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 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 tablets belong to a group of medicines called proton pump inhibitors. Proton pump inhibitors reduce the amount of acid that your stomach makes.

You have been given Pantoprazole tablets because you have a condition caused by stomach acid.

Pantoprazole tablets are used in the treatment and to relieve the symptoms of:
- duodenal ulcer
- gastric ulcer
- esophagitis (inflammation of esophagus) caused by acid secretion

Additionally, the preparation is used:
- in the long-term treatment of conditions where gastric acid is constantly being secreted too much (e.g. Zollinger-Ellison syndrome)

Pantoprazole which is contained in Pantoprazole tablets is also 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 of Pantoprazole tablets (see Sections 4 for a full list).
- are taking atazanavir (which is used for the treatment of HIV infection).
- have any relevant liver or kidney problems.

Pantoprazole tablets are not recommended for children.

Take special care with Pantoprazole tablets
Please tell the doctor who prescribed this medicine if you:
- have severe liver problems. In case of a severe liver disorder your doctor should monitor your liver function while you use Pantoprazole tablets.
- have been diagnosed with vitamin B12 malabsorption.

Please tell your doctor if you suffer or have recently suffered from any of the following symptoms: unintentional weight loss, recurrent vomiting or vomiting of blood, or dark stool. Your doctor may perform or have performed an additional investigation called an endoscopy in order to diagnose your condition and/or exclude malignant 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. Remember to tell your doctor about your treatment with Pantoprazole tablets if you are prescribed another medicine while the treatment is still ongoing.

It is especially important to tell your doctor if you’re taking:
- atazanavir (used for the treatment of HIV infection)
- ketoconazole or itraconazole (used for the treatment of fungal infections)
- anticoagulant medicines (e.g. warfarin)

Taking Pantoprazole tablets with food and drink
Take Pantoprazole tablets whole with water either before or during breakfast.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. If you are pregnant or if you are breast-feeding, you should use this medicine only if your doctor considers the benefit for you greater than the potential risk for your unborn child or baby.

Driving and using machines
Pantoprazole tablets may cause dizziness and visual disturbances.

Know how this medicine affects you before driving or using machines.

Important information about some of the ingredients of Pantoprazole tablets
This medicine contains sorbent. If you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

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.

Dosage

- Dosage slider:
  - The recommended dose is 1 tablet (40 mg) daily.
  - Gastric ulcer and esophagitis (inflammation of esophagus) caused by acid secretion:
    - The recommended dose is 1 tablet (40 mg) daily.
  - Long-term treatment of conditions where gastric acid is constantly being secreted too much (e.g. Zollinger-Ellison syndrome):
    - Initial dose is 2 tablets (2 x 40 mg) daily. With doses above 80 mg daily, the dose should be divided and given twice daily.

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

Patients with hepatic impairment
Dose of 1 tablet (40 mg) should be given every second day.

Children
Pantoprazole tablets should not be used in children.

Method of administration
Do not chew or crush Pantoprazole tablets but swallow them whole with water either before or during breakfast.

If you take more Pantoprazole tablets than you should
If you or someone you know accidentally takes a lot more than the stated dose (an overdose) you should contact a doctor immediately.

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You should stop taking Pantoprazole tablets and see your doctor immediately if you experience symptoms of angioedema, such as
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• difficulty to swallow
• hives and difficulties to breath
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Common:
• upper abdominal pain
• diarrhoea
• constipation
• flatulence
• headache

Uncommon:
• jaundice
• vomiting
• dizziness
• blurred vision
• allergic reactions such as itching and rash

Rare:
• dry mouth
• joint pain

Very rare:
• white blood cell deficiency (leucopenia)
• platelet deficiency (thrombocytopenia)
• swelling of hands and feet
• severe liver cell damage and associated jaundice with potential liver failure
• severe allergic reaction manifested as acute general symptoms with potential acute and substantial drop in blood pressure
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• muscle pain
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• hypersensitivity/attacks of local skin and mucous membrane swelling in the face, limbs, lips, tongue, larynx and/or vocal cords (angioedema, see special warning above)
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6. FURTHER INFORMATION
What Pantoprazole tablets contain
• Each gastro-resistant tablet contains 40 mg Pantoprazole (as pantoprazole sodium sesquihydrate 45.2 mg).
• The other ingredients are: The core tablet: Sodium carbonate, anhydrous – Mannitol – Sucrose – Talc – Calcium stearate – Silicon dioxide
The printing ink: Shellac - Iron oxide black (E172) - Propylene glycol - Ammonium hydroxide.

What Pantoprazole tablets look like and contents of the pack
The 40 mg gastroresistant tablets are red/Mish-black coloured, biconvex, oval shaped, coated tablets imprinted with ‘P40’ on one side and phim on the other side.

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Belgium

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PNI supply nv
Axxes Business Park
Onhaleuropark 22 • Block C
9820 Merelbeke
Belgium

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Carton:

Blister