Public Assessment Report
Decentralised Procedure

Pantoprazole 40 mg, powder for solution for injection

PL 15773/0747

ratiopharm GmbH

UK/H/1950/01/DC
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted ratiopharm GmbH a Marketing Authorisation (licence) for the medicinal product Pantoprazole 40 mg, powder for solution for injection (Product Licence numbers 15773/0747). This medicine is available on prescription only.

Pantoprazole is a medicine which reduces the amount of acid produced in your stomach. It is used for treating acid-related diseases of the stomach and intestine such as:

- Reflux oesophagitis, an inflammation of your oesophagus (the tube which connects your throat to your stomach) accompanied by the regurgitation of stomach acid
- Stomach and duodenal ulcers
- Zollinger–Ellison Syndrome and other conditions producing too much acid in your stomach.

The data submitted in support of this application for Pantoprazole 40 mg, powder for solution for injection raised no significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
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## Module 1

### Information about decentralised procedure

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Pantoprazole 40 mg, powder for solution for injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of application (Eudratrack details)</td>
<td>Level 1 Abridged</td>
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<tr>
<td></td>
<td>Level 2 Initial</td>
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<tr>
<td></td>
<td>Level 3 10.1</td>
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<td></td>
<td>Level 4 Chemical substance</td>
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<td>Level 5 Prescription only</td>
</tr>
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<td>Name of the active substance (INN)</td>
<td>Pantoprazole</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>A02BC02</td>
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<td>Pharmaceutical form and strength</td>
<td>Powder for solution for injection</td>
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<tr>
<td>Reference numbers for the decentralised Procedure</td>
<td>UK/H/1950/01/DC</td>
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<td>Reference Member State</td>
<td>United Kingdom</td>
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<tr>
<td>Member States concerned</td>
<td>AT, DK, ES, FI, HU, NL, NO, PL, PT</td>
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<td>Date of start of the procedure</td>
<td>22 July 2008</td>
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<td>End date of decentralised procedure</td>
<td>21 April 2010</td>
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<tr>
<td>Marketing Authorisation Number</td>
<td>PL 15773/0747</td>
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<tr>
<td>Name and address of the authorisation holders</td>
<td>ratiopharm GmbH, Graf-Arco-Str.3, 89079 Ulm, Germany</td>
</tr>
</tbody>
</table>
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Pantoprazole 40 mg, powder for solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 40 mg of pantoprazole (as sodium sesquihydrate)

Excipients
Each vial contains 5.0 mg of sodium citrate dihydrate and sodium hydroxide q.s.
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e.
is essentially “sodium free”.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Powder for solution for injection.
White or almost white, uniform porous cake.
For the solution reconstituted with 10 ml of 0.9% NaCl solution the pH is approximately 10 and the osmolality is approximately 382 mOsm/Kg
For the solution reconstituted with a further 100 ml of 0.9% NaCl solution or 5% glucose solution the pH is approximately 9 and 8.5, respectively

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
- Reflux oesophagitis
- Gastric and duodenal ulcer
- Zollinger – Ellison Syndrome and other pathological hypersecretory conditions.

4.2 Posology and method of administration
This medicine should be administered by a healthcare professional and under appropriate medical supervision.
The intravenous administration of pantoprazole is recommended only if oral application is not appropriate. Data are available on intravenous use for up to 7 days. Therefore as soon as oral therapy is possible, treatment with pantoprazole i.v. should be discontinued and 40 mg pantoprazole p.o. should be administered instead.
Recommended dose:
Gastric and duodenal ulcer, reflux oesophagitis
The recommended intravenous dose is one vial of pantoprazole (40 mg) per day.
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 of pantoprazole i.v. 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.
In case a rapid acid control is required, a starting dose of 2 x 80 mg of pantoprazole i.v. is sufficient to manage a decrease of acid output into the target range (<10 mEq/h) within one hour in the majority of patients.

Special populations
Paediatric patients:
The experience in children is limited. Therefore, pantoprazole i.v. is not recommended for use in patients below 18 years of age until further data become available.
Hepatic impairment:
A daily dose of 20 mg pantoprazole (half a vial of 40 mg pantoprazole) should not be exceeded in patients with severe liver impairment (see section 4.4).
Renal impairment:
No dose adjustment is necessary in patients with impaired renal function
Elderly
No dose adjustment is necessary in elderly patients

Method of administration:
A ready-to-use solution is prepared in 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. For instructions for preparation see section 6.6.
The prepared solution may be administered directly or may be administered after mixing it with 100 ml of 9 mg/ml (0.9%) sodium chloride injection, or 50 mg/ml glucose (5%) solution for injection.
After preparation the solution must be used within 12 hours. (See section 6.3).
The medicinal product should be administered intravenously over 2 – 15 minutes.

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

4.4 Special warnings and precautions for use
In presence of alarm symptoms
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.
Hepatic impairment
In patients with severe liver impairment liver enzymes should be monitored during therapy. In case of a rise in the liver enzymes, pantoprazole i.v. should be discontinued. (See also section 4.2)
Co-administration with atazanavir

Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir. A pantoprazole dose of 20 mg per day should not be exceeded.

Gastrointestinal infections caused by bacteria

Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria (e.g. Salmonella and Campylobacter).

Sodium

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. essentially “sodium-free”

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Pantoprazole on the absorption of other medicinal products

Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may reduce the absorption of drugs with a gastric pH dependant bioavailability, e.g. some azole antifungals such as ketoconazole, intraconazole, posaconazole and other medicines such as erlotinib.

HIV medications (atazanavir)

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

Coumarin anticoagulants (phenprocoumon or warfarin)

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

Other interactions studies

Pantoprazole is extensively metabolised in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4. Interaction studies with drugs also metabolised with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine and an oral contraceptive
containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions.

Results from a range of interaction studies demonstrate that Pantoprazole does not effect the metabolism of active substances metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with p-glycoprotein related absorption digoxin.

There were also no interactions with concomitantly administered antacids.

Interaction studies have been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

4.6 Pregnancy and lactation

**Pregnancy:**

There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary.

**Lactation:**

Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore a decision on whether to continue/discontinue breast-feeding or to continue/discontinue treatment with pantoprazole should be made taking into account the benefit of breast-feeding to the child and the benefit of pantoprazole therapy to women.

4.7 Effects on ability to drive and use machines

Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.

4.8 Undesirable effects

Approximately 5% of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhoea and headache, both occurring in approximately 1% of patients.

The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:

- Very common ($\geq 1/10$);
- Common ($\geq 1/100$ to $<1/10$);
- Uncommon ($\geq 1/1,000$ to $<1/100$);
- Rare ($<1/10,000$ to $<1/1,000$);
- Very rare ($1/10,000$);
- Not known (cannot be estimated from the available data).

For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a “not known” frequency. Within each frequency, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions with pantoprazole in clinical trials and post-marketing experience

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known</th>
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<tbody>
<tr>
<td>System organ class</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Blood and lymphatic system disorders</td>
<td>Thrombocytopenia: Leukopenia</td>
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<td>-------------------------------------</td>
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<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (including anaphylactic reactions and anaphylactic shock)</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperlipidaemia and lipid increases (triglycerides, cholesterol); Weight changes Hyponatraemia</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Sleep disorders Depression (an all aggravations) Disorientation (and all aggravations) Hallucination: Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)</td>
<td></td>
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<tr>
<td>Nervous system disorders</td>
<td>Headache; Dizziness</td>
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<td></td>
<td></td>
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<tr>
<td>Eye disorders</td>
<td>Disturbances in vision/blurred vision</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea; Nausea/ vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort.</td>
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</table>

<table>
<thead>
<tr>
<th>Frequency System</th>
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MHRA PAR; PANTOPRAZOLE 40 MG, POWDER FOR SOLUTION FOR INJECTION, PL 15773/0747
<table>
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<tr>
<th>organ class</th>
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<th>Bilirubin increased</th>
<th>Hepato-cellular injury; Jaundice; Hepato-cellular failure</th>
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</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash/ exanthema/ eruption; Pruritus</td>
<td>Urticaria; Angioedema</td>
<td>Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity</td>
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<tr>
<td>Musculo-skeletal and connective tissue disorders</td>
<td>Arthralgia; Myalgia</td>
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<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td>Interstitial nephritis</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
<td>Gynaecomastia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site thrombophlebitis</td>
<td>Asthenia, fatigue and malaise</td>
<td>Body temperature increased; Oedema peripheral</td>
</tr>
</tbody>
</table>

4.9 **Overdose**
There are no known symptoms of overdose in man.
Systemic exposure with up to 240 mg administered intravenously over 2 minutes were well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable.
In case of overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5 **PHARMACOLOGICAL PROPERTIES**

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

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

Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H⁺/K⁺-ATPase enzyme i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved within 2 weeks. As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby 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 upper limit of normal. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (similar to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments (see section 5.3) have not been observed in humans.

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

5.2 Pharmacokinetic properties

General Pharmacokinetics

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.

Distribution

Pantoprazole's plasma protein binding is about 98%. Volume of distribution is about 0.15 l/kg.

Elimination

The substance is almost exclusively metabolised in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathways include oxidation by CYP3A4. Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. There were few cases of subjects with delayed elimination. Because of specific binding of pantoprazole to the proton pumps of the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).
Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole; the rest 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 metabolite (about 1.5 hours) is not much longer than that of pantoprazole.

**Characteristics in patients/special groups of subjects:**
Approximately 3% of the European population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of pantoprazole.

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

Although for patients with hepatic cirrhosis (classes A and B according to Child) the half-life 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.

**Children**
Following administration of single intravenous doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 – 16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

### 5.3 Preclinical safety data

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

In the 2-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 treatment. In the two-year rodent studies an increased number of liver tumours was observed in rats and female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg). The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the
breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no side effects to the thyroid glands are expected.
In animal reproduction studies, signs of slight fetotoxicity were observed at does above 5 mg/kg. Investigations revealed no evidence of impaired fertility or teratogenic effects.
Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, the concentration of pantoprazole in the foetus is increased shortly before birth.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mannitol
Sodium citrate dihydrate
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life
As packaged for sale: 2 years
After reconstitution, or reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 12 hours at 25°C.
From a microbiological point of view, the product should be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage
Do not store above 25°C. Keep the vial in the outer carton to protect from light.
For storage conditions of the reconstituted and diluted medicinal product see section 6.3.

6.5 Nature and contents of container
15 ml, type I, colourless glass vial, sealed with a grey chlorobutyl stopper and an aluminium flip-off cap, containing 40 mg powder for solution for injection.
Pack sizes: 1, 5, 10 and 20 vials
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
A ready-to-use intravenous solution is prepared by injecting 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection into the vial containing the lyophilised powder. The reconstituted solution should be clear and colourless. This solution may be administered directly or may be administered after mixing it with 100 ml of sodium chloride 9 mg/ml (0.9%) solution for
injection or glucose 50 mg/ml (5%) solution for injection. Glass or plastic containers should be used for dilution.

Pantoprazole 40 mg, powder for solution for injection should not be prepared or mixed with solvents other than those stated.

This medicine should be administered intravenously over 2-15 minutes.

The content of the vial is for single use only. Any product that has remained in the container or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed) should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
PL 20775/0004:
ratiopharm GmbH,
Graf-Arco-Str.3,
89079 Ulm,
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 15773/0747

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/04/2010

10 DATE OF REVISION OF THE TEXT
21/04/2010
Pantoprazole 40 mg powder for solution for injection

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

Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor or pharmacist.

If any 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 40 mg powder for solution for injection is and what it is used for
2. Before you use Pantoprazole 40 mg powder for solution for injection
3. How to use Pantoprazole 40 mg powder for solution for injection
4. Possible side effects
5. How to store Pantoprazole 40 mg powder for solution for injection
6. Further information

1. WHAT PANTOPRAZOLE 40 MG POWDER FOR SOLUTION FOR INJECTION IS AND WHAT IT IS USED FOR

Pantoprazole 40 mg powder for solution for injection is a selective "proton pump inhibitor", a medicine which reduces the amount of acid produced in your stomach. It is used for treating acid related diseases of the stomach and intestine.

This preparation is injected into a vein and will only be given to you if your doctor thinks pantoprazole injections are more suitable for you at the moment than pantoprazole tablets. Tablets will replace your injections as soon as your doctor sees fit.

Pantoprazole 40 mg powder for solution for injection is used for treating:
- Reflux oesophagitis. An inflammation of your oesophagus (the tube which connects your throat to your stomach) accompanied by the regurgitation of stomach acid.
- Stomach and duodenal ulcers
- Zollinger-Ellison syndrome and other conditions producing too much acid in your stomach.

2. BEFORE YOU USE PANTOPRAZOLE 40 MG POWDER FOR SOLUTION FOR INJECTION

Do not use Pantoprazole 40-mg powder for solution for injection if:
- You are allergic to pantoprazole or any of the other ingredients of Pantoprazole 40 mg powder for solution for injection (see section 6).
- You are allergic to medicines containing proton pump inhibitors.

Take special care with Pantoprazole 40 mg powder for solution for injection:
- If you have severe liver problems. Please tell your doctor if you ever had problems with your liver in the past. He will check your liver enzymes more frequently. In case of a rise of liver enzymes the treatment should be stopped.
- If you are taking a medicine containing atazanavir (for the treatment of HIV-infection) at the same time as pantoprazole, ask your doctor for specific advice.

Tell your doctor immediately if you notice any of the following symptoms:
- unexplained weight loss
- repeated vomiting
- difficulty in swallowing
- vomiting blood
- you look pale and feel weak (anemia)
- you notice blood in your stools
- severe and/or persistent diarrhoea, as pantoprazole has been associated with a small increase in infectious diarrhoea.

Your doctor may decide that you need some tests to rule out malignant diseases because pantoprazole also alleviates the symptoms of cancer and could cause delay in diagnosing it. If your symptoms continue in spite of your treatment, further investigations will be considered.

Taking other medicines

Pantoprazole injections may influence the effectiveness of other medicines, so tell your doctor if you are taking:
- Medicines such as ketoconazole, rifampicin and posaconazole (used to treat fungal infections) or ethinylestradiol for certain types of cancer because Pantoprazole may stop these and other medicines from working properly.
- Warfarin and phenprocoumon, which affect the thickening or thinning of the blood. You may need further checks.
- Atazanavir used to treat HIV-infections.

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

Pregnancy and breastfeeding

There is no adequate data from the use of pantoprazole in pregnant women. Excretion into human milk has been reported. If you are pregnant or think you may be pregnant, or if you are breastfeeding you should not be given this medicine unless your doctor considers the benefit for you greater than the potential risk for your unborn child or baby.

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

Driving and using machines

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

Important information about some of the ingredients of Pantoprazole 40 mg powder for solution for injection

This medicinal product contains less than 1 mmol of sodium (23 mg) per dose, i.e. essentially "sodium-free."

2. HOW TO USE PANTOPRAZOLE 40 MG POWDER FOR SOLUTION FOR INJECTION

Your doctor or nurse will administer the daily dose to you as an injection into a vein over a period of 2-15 minutes.

The usual dose is:

For gastric ulcer, duodenal ulcers and reflux oesophagitis
One vial (60 mg pantoprazole) a day.

For the long-term treatment of Zollinger-Ellison syndrome and other conditions in which too much stomach acid is produced.
Two vials (120 mg pantoprazole) a day.

Your doctor may later adjust the dose depending on the amount of stomach acid you produce. If you are prescribed more than two vials (120mg) a day, the injections will be in two equal doses. Your doctor may prescribe a temporary dose of more than four vials (160 mg) a day. If your stomach acid level needs to be controlled rapidly, a starting dose of 160 mg (four vials) should be enough to lower the amount of stomach acid sufficiently.

Special patient groups:
- If you have severe liver problems the daily injection should be only 20 mg (half a vial).
- Children (under 18 years). These injections are not recommended for use in children.
- If you use more Pantoprazole 40 mg powder for solution for injection than you should
These doses are carefully checked by your nurse or doctor so an overdose is extremely unlikely.
There are no known symptoms of overdose.
If you have any further questions on the use of this product ask your doctor or nurse.

The following information is intended for medical or healthcare staff only:

A ready-to-use intravenous solution is prepared by injecting 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection into the vial containing the lyophilised powder. The solution may either be administered directly or after mixing it with 50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection. Glass or plastic containers should be used for dilution.

Pantoprazole 40 mg, powder for solution for injection should not be prepared or mixed with solvents other than those stated.

After reconstitution, or reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 12 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.
4. POSSIBLE SIDE EFFECTS

Like all medicines, Pantoprazole 40mg powder for solution for injection can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:

- **very common** (affects more than 1 user in 10)
- **common** (affects 1 to 10 users in 100)
- **uncommon** (affects 1 to 10 users in 1,000)
- **rare** (affects 1 to 10 users in 10,000)
- **very rare** (affects less than 1 user in 10,000)
- **not known** (frequency cannot be estimated from the available data).

If you get any of the following side effects, tell your doctor immediately or contact the casualty department at your nearest hospital:

- **Serious allergic reactions (frequency rare):** swelling of the tongue and/or throat, difficulty in swallowing, hives (urticaria), difficulty in breathing, allergic face swelling (Gusmao's edema), anaphylaxis.
- **Severe dizziness with very fast heartbeat and heavy sweating.
- **Serious skin conditions (frequency not known):** blistering of the skin and rapid deterioration of your general condition, eruption (including slight bleeding) of eyes, nose, mouth or genitals (Steven's-Johnson Syndrome, Lyell Syndrome, Erythema multiforme) and sensitivity to sunlight.
- **Other serious conditions (frequency not known):** yellowing of the skin or the whites of your eyes (severe damage to liver cells, jaundice) or fever, rash and enlarged kidneys sometimes with painful urination and lower back pain (serious inflammation of the kidneys).

Other side effects are:

- **Common** (affects 1 to 10 users in 100): inflammation of the wall of the veins and blood clotting (thrombophlebitis) where the medicine is injected.
- **Uncommon** (affects 1 to 10 users in 1,000): headache; dizziness; decreased appetite; feeling sick or vomiting; bloating and flatulence (wind); constipation; dry mouth; abdominal pain and discomfort; skin rash; exanthema; eruption; itching; feeling weak; exhausted or generally unwell; sleep disorders.
- **Rare** (affects 1 to 10 users in 10,000): disturbances in vision such as blurred vision; hives; pain in the joints; muscle pains; weight changes; raised body temperature; swelling of the extremities (peripheral oedema); allergic reactions, depressed blood cell levels in male patients.
- **Very rare** (affects less than 1 user in 10,000): haemorrhage (especially in patients with a history of these symptoms); decreased sodium level in blood.

Side effects identified through blood tests:

- **Uncommon** (affects 1 to 10 users in 1,000): an increase in liver enzymes.
- **Rare** (affects 1 to 10 users in 10,000): an increase in bilirubin; increased fats in the blood.
- **Very rare** (affects less than 1 user in 10,000): a reduction in the number of blood platelets, which may cause you to bleed or bruise more than normal; a reduction in white cells in your blood which may lead to more frequent infections.

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

5. HOW TO STORE PANTOPRAZOLE 40 MG POWDER FOR SOLUTION FOR INJECTION

Keep out of the reach and sight of children.

Do not use Pantoprazole 40 mg powder for solution for injection after the expiry date which is stated on the carton and the vial after EXP.

The expiry date refers to the last day of the month.

Do not store above 25°C.

Keep the vial in the outer carton in order to protect from light.

After reconstitution, or reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 12 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, store at refrigerator temperature and use before the expiration time.

These measures will help to protect the environment.

6. FURTHER INFORMATION

What Pantoprazole 40 mg powder for solution for injection contains:

- The active substance is pantoprazole.
- Each vial contains 40 mg of pantoprazole (as sodium anhydride).
- The other ingredients are:
  - mannitol,
  - sodium citrate dihydrate,
  - sodium hydroxide for pH adjustment.

What Pantoprazole 40 mg powder for solution for injection looks like and contents of the pack

Pantoprazole 40 mg powder for solution for injection is supplied as a white or almost white uniform porous cake.

It comes in packs of 1, 5, 10 and 20 glass vials.

Not all packs may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
ratilpharm GmbH, Gießener Str. 3, 36079 Ulen, Germany.

Manufacturer:
Laboratorios Alcalá Ferrer, S.L, Carretera M-369 Km 29,900, Apartado de correos 27 28802 Alcalá de Henares (Madrid).

This leaflet was revised in: April 2010.
Module 4

Labelling

Label:

Pantoprazole 40 mg powder for solution for injection

For intravenous use.
Read the package leaflet before use.
Each vial contains 40 mg of pantoprazole (as sodium sesquihydrate).

Do not store above 25°C.
Keep vial in outer carton in order to protect from light.

Shelf life after reconstitution: 12 hours

Batch No.:
Exp.:
Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the application for Pantoprazole 40 mg, powder for solution for injection in the treatment of gastric and duodenal ulcers and associated conditions is approvable.

EXECUTIVE SUMMARY

About the product
Pantoprazole is one of the proton pump inhibitors. They inhibit gastric acid by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (the ‘proton pump’) of the gastric parietal cell. Proton pump inhibitors are used for the treatment of peptic ulceration and the associated disease conditions.

General comments on the submitted dossier
This is a Decentralised Procedure with the United Kingdom acting as the Reference Member State. These applications are submitted under article 10.1 of Directive 2001/83/EC, as amended, cross-referring to Protium® i.v. Powder for Solution for Injection (PL 31752/0003), licensed to Nycomed GmbH, which was first authorised in the UK on 4 December 1996. The legal basis of this application is, therefore, acceptable.

With the UK as the Reference Member State in this Decentralized Procedure Ratiopharm GmbH is applying for a Marketing Authorisation for this product in AT, DK, ES, FI, HU, NL, NO, PL and PT.

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

No issues regarding GCP or GLP aspects have been identified during the review of this dossier.

SCIENTIFIC OVERVIEW AND DISCUSSION
QUALITY ASPECTS

Drug substance
The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Pantoprazole 40 mg, powder for solution for injection are of sufficient quality in view of the present European regulatory requirements. The drug substance specifications are acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. An adequate re-test period has been defined based on conducted stability studies.

Drug Product
The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validation data supporting the suitability of the analytical methods have been presented. The batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug products are adequately drawn up. The proposed shelf-life of 2 years for unreconstituted drug product stored in the original container is acceptable when the storage precautions ‘do not store above 25°C’ and ‘keep the vial in the outer carton to protect from light’ are applied.

NON CLINICAL ASPECTS
The pharmacological, pharmacokinetic and toxicological properties of pantoprazole are well known. As pantoprazole is a well known active substance, no further studies are required and the applicant has provided none. An overview based on a literature review is thus appropriate.

The non-clinical overview has been written by a physician with suitable experience. It is dated July 2007. The overview cites 34 references from the published literature which are dated from 1990 to 2007. The overview is adequate.

There are no objections to approval of Pantoprazole 40mg powder for solution for injection from a non-clinical point of view.

CLINICAL ASPECTS
The product is a generic medicinal product as defined by Article 10.1 of Directive 2001/83/EC, with the reference product being Pantozol i.v. 40 mg Pulver zur herstellung einer Injektionslosung licensed in Germany in July 1997 to Altana Pharma AG. Pantoprazole 40mg oral solution is considered to be a generic version of the reference medicinal product, Pantozol i.v. 40 mg, which is marketed in many EU countries including the UK where it is marketed as Protium i.v. powder for solution for injection, licensed to Nycomed GmbH. It satisfies the criteria of having the same quantitative and qualitative composition with regards to active ingredients with the same pharmaceutical form.

Clinical study reports
No new efficacy data are presented for this application and none are required. However, the applicant has provided a review of clinical trials published in the literature confirming the efficacy and safety of pantoprazole in the treatment and prevention of relapse of peptic ulceration and the associated disease conditions. No new safety issues have been identified.

Pharmacokinetic studies
Not applicable.

Pharmacokinetic conclusion
Based on the data provided, the applicant’s Pantoprazole 40mg powder for solution for injection is considered to be bioequivalent to Pantozol i.v. 40 mg Pulver zur herstellung einer Injektionslosung.

Pharmacodynamic studies
Not applicable.

Pharmacovigilance system
The RMS considers that 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.

Risk Management Plan
As with the reference medicinal product, no special important risks or potential risks have been identified which require additional risk minimization activities other than the global pharmacovigilance system.

Periodic Safety Update Report (PSUR)
Not applicable.

PRODUCT LITERATURE
All product literature (SPC, PIL and labelling) is satisfactory. The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

BENEFIT RISK ASSESSMENT
Proton pump inhibitors, including pantoprazole, have been used for the treatment and prevention of relapse of peptic ulceration and the associated conditions for much more than ten years within the EU. The use of pantoprazole is well established. It has recognised efficacy and acceptable safety. The risk: benefit ratio is acceptable. Approval is recommended