Public Assessment Report

Decentralised Procedure

Pantoprazole 40 mg, powder for solution for injection

Procedure No: UK/H/1953/001/DC

UK Licence No: PL 25975/0077

Cardinal Health UK 434 Limited
LAY SUMMARY

On 17 March 2010, Denmark, France, Finland, Germany, Ireland, Norway, Sweden and the UK agreed to grant a Marketing Authorisation to Cardinal Health UK 434 Limited for the medicinal product Pantoprazole 40mg powder for solution for injection (PL 25975/0077; UK/H/1953/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a Marketing Authorisation was granted in the UK on 26 May 2010.

Pantoprazole belongs to a group of medicine known as 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.

Pantoprazole is used for:

• 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.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Pantoprazole 40mg powder for solution for injection outweigh the risks, hence a Marketing Authorisation has been granted.
# TABLE OF CONTENTS

Module 1: Information about initial procedure .......................... Page 4
Module 2: Summary of Product Characteristics ....................... Page 5
Module 3: Product Information Leaflets ............................... Page 15
Module 4: Labelling ....................................................... Page 16
Module 5: Scientific Discussion ........................................... Page 17
   1 Introduction
   2 Quality aspects
   3 Non-clinical aspects
   4 Clinical aspects
   5 Overall conclusions
Module 6: Steps taken after initial procedure .......................... Page 23
## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Pantoprazole 40mg powder for solution for injection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Pantoprazole.</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Powder for solution for injection</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>40 mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Cardinal Health UK 434 Limited., Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Denmark, France, Finland, Germany, Ireland, Norway, Sweden</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/1953/001/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 17 March 2010</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 (≥1/10);
- Common (≥1/100 to <1/10);
- Uncommon (≥1/1,000 to <1/100);
- Rare (<1/10,000 to <1/1,000), very rare (1/10,000) not known (cannot be estimated from the available data).

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

Within each frequency, 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>System organ class</th>
<th>Frequency</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
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<tr>
<td>Thrombocytopenia: Leukopenia</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity (including anaphylactic reactions and anaphylactic shock)</td>
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<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td>Hyperlipidaemia and lipid increases (triglycerides, cholesterol); Weight changes</td>
<td></td>
<td>Hyponatraemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Sleep disorders</td>
<td></td>
<td></td>
<td>Depression (an all aggravations)</td>
<td>Disorientation (and all aggravations)</td>
<td>Hallucination: Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)</td>
</tr>
<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></td>
<td></td>
<td></td>
<td>Disturbances in vision/blurred vision</td>
<td></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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</tbody>
</table>
Table 1. Adverse reactions with pantoprazole in clinical trials and post-marketing experience

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<th>System organ class</th>
<th>Frequency</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>Liver enzymes</td>
<td>Increased</td>
<td>Bilirubin</td>
<td>Increased</td>
<td>Hepato-cellular injury; Jaundice; Hepato-cellular failure</td>
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<tr>
<td></td>
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<td>(transaminases; (\gamma)-GT)</td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Rash/ exanthema/ eruption; Pruritus</td>
<td></td>
<td>Urticaria; Angioedema</td>
<td></td>
<td>Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity</td>
</tr>
<tr>
<td>Musculo-skeletal and connective tissue disorders</td>
<td></td>
<td>Arthralgia; Myalgia</td>
<td></td>
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<td></td>
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<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Interstitial nephritis</td>
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<tr>
<td>Reproductive system and breast disorders</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td>Injection site thrombophlebitis</td>
<td>Ashtenia, fatigue and malaise</td>
<td>Body temperature increased; Oedema peripheral</td>
<td></td>
<td></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 \(\text{H}^+\text{K}^-\text{ATPase}\) 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 \(\text{H}_2\) 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 C_{\text{max}} 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
Cardinal Health,
Bampton Road,
Harold Hill,
Romford,
Essex,
United Kingdom.
RM3 8UG.

8 MARKETING AUTHORISATION NUMBER(S)
PL 25975/0077

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26/05/2010

10 DATE OF REVISION OF THE TEXT
26/05/2010
Module 3

PAR Pantoprazole 40mg powder for solution for injection

UK/H/1953/001/DC

Read all of this leaflet carefully before you start using this medicinal product. Keep this leaflet. You may need to read it again.

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

If you think this medicinal product is not suited to you, or if you notice any side-effects not listed in this leaflet, please tell your doctor or pharmacist.

Special patient groups

If you have severe liver problems the daily injection should only be 20 mg (half a tablet).

Children (under 16 years). These injections are not recommended for use in children.

If you use more Pantoprazole 40mg powder for solution for injection than you should

Tell your doctor or nurse.

If you use any further questions on the use of this product, speak to your doctor or nurse.

4. Possible side effects

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

The frequency of possible side effects listed below is described using the following conventions:

- Very rare (affects fewer than 1 in 10,000 people)
- Rare (affects from 1 in 100 to 1 in 1,000 people)
- Uncommon (affects from 1 in 1,000 to 1 in 10,000 people)
- Very common (affects more than 1 in 10 people)

If you get any of the side effects listed below, tell your doctor or nurse as soon as possible.

• Severe allergic reaction (rare)

• Miscellaneous side effects

• Very common: dry mouth

• Common: diarrhoea

• Uncommon: constipation

• Rare: flatulence

• Very rare: other gastrointestinal effects

• Very rare: skin rashes (including blisters)

If any of the side effects described above worry you or if you feel that you are becoming unwell, please contact your doctor or nurse immediately.

5. How to store Panoprazole 40mg powder for solution for injection

Keep out of the reach and sight of children.

Do not use Panoprazole 40mg powder for solution for injection after the expiry date which is stated on the carton and the vial after E39.

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

Do not store above 25°C.

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

After reconstitution, reconstituent and dilution, chemical and physical use stability has been demonstrated for 1 hour at 25°C.

The medical point of view is to store the product should be used immediately. If not used immediately, iv storage times and conditions prior to use are the responsibility of the quack.

Do not use Panoprazole 40mg powder for solution for injection if you notice that the visual appearance has changed (e.g. if solutions on precipitation is observed).

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required - your local council will help to protect the environment.

6. Further Information

What Panoprazole 40mg powder for solution for injection contains

• The active substance is pantoprazole.

• Each vial contains 40mg of pantoprazole (as panoprazole). The other ingredients are:

• Sodium chloride

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

Pantoprazole 40mg powder for solution for injection is a white or almost white无色wax glass vial. It comes in packs of 1, 5, 10 and 20 glass vials. Not all packs may be marketed.

Marketing Authorisation Holder:

Cardinal Health

Bampton Road

Romford

Essex

United Kingdom.

Manufacturer:

Lambertz Alkarma SA

Carouge M 10018 Genève

Apparatus du comte 37

30100 Alkarma (Netherlands) (Europe)

Telephone 0031 (0)69 065 55 05

Fax 0031 (0)69 068 05 00

This leaflet was last amended in April 2010

PL 25757/007

13
Pantoprazole is packaged in 1, 5, 10 and 20 glass vials. Not all pack sizes may be marketed.
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

This application was submitted by the decentralised procedure, with the UK as reference member state (RMS), and Denmark, France, Finland, Germany, Ireland, Norway and Sweden as Concerned Member States (CMS). Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Pantoprazole 40mg powder for solution for injection (PL 25975/0077; UK/H/1953/01/DC) could be approved.

The product is a prescription-only medicine for the treatment of reflux oesophagitis, gastric and duodenal ulcers, Zollinger-Ellison syndrome and other pathological hypersecretory conditions.

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83/EC, as amended, as generic medicinal products of Pantozol i.v. 40 mg Pulver zur herstellung einer Injektionslosung licensed in Germany in July 1997 to Altana Pharma AG.

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. It is well-established for use in the proposed indications.

No new preclinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 210) on 17 March 2010. After a subsequent national phase, the licence was granted in the UK on 26 May 2010.
II. ABOUT THE PRODUCT

<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>Name(s) of the active substance(s) (INN)</td>
<td>Pantoprazole</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Proton pump inhibitors: ATC code: A02BC02</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Powder for solution for injection, 40 mg</td>
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<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/1953/01/DC</td>
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<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Denmark, France, Finland, Germany, Ireland, Norway, Sweden</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 25975/0077</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Cardinal Health UK 434 Limited., Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Pantoprazole
Pharmacopeial name: Pantoprazole sodium sesquihydrate
Chemical name: 5-(Difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfanyl]-1H-benzimidazole sodium sesquihydrate

Structure:

![Chemical Structure](image)

Molecular formula: $\text{C}_{16}\text{H}_{14}\text{F}_{2}\text{N}_{3}\text{NaO}_{4}\text{S} \times 1.5\ \text{H}_{2}\text{O}$
Molecular weight: 432.4
Appearance: A white or almost white powder. Freely soluble in water and in anhydrous ethanol, practically insoluble in hexane.

Pantoprazole is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate data has been supplied to characterise the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

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

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients mannitol, sodium citrate dihydrate and sodium hydroxide (for pH adjustment).

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.
None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**
A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of 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 specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-Closure System**
The finished product is contained in Type I glass vials (15ml), with a grey chlorobutyl stopper and a yellow aluminium flip-off cap. These are packed into boxes in pack sizes of 1, 5, 10 and 20 glass vials.

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 parenteral products.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with the storage conditions, “Do not store above 25°C. Keep the vial in the outer carton to protect from light.”

From a microbiological point of view, the product should be used immediately after opening. After reconstitution, or reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 12 hours at 25°C.
Bioequivalence/bioavailability
A bioequivalence study is not necessary to support this application for a parenteral product.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, 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 forms
The MAA form is pharmaceutically satisfactory.

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

Conclusion
The grant of a marketing authorisation is recommended.

III.2  PRE-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of pantoprazole are well-known, no further preclinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

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

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

III.3  CLINICAL ASPECTS
Pharmacokinetics
No new pharmacokinetic data were submitted with this application and none were required. A bioequivalence study is not necessary to support this application for a parenteral product.

Efficacy
No new efficacy data were submitted with this application and none were required.

Safety
No new safety data were submitted with this application and none were required

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.

**SPC, PIL, Labels**
The SPC, PIL and labels are medically acceptable. The SPC is consistent with the originator product.

**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.

**Conclusion**
The grant of a marketing authorisation is recommended.

**IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT**

**QUALITY**
The important quality characteristics of Pantoprazole 40mg powder for solution for injection 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 risk-benefit balance.

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

**EFFICACY**
No bioequivalence study was submitted or required for this application. As this is a product for injection, bioequivalence can be confirmed from the quantitative and qualitative composition of the product.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product.

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

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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