IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Pantoprazole Noridem 40 mg Powder for Solution for Injection
Pantoprazole
PA1122/011/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

The application is in accordance with Article 10 (1) Directive 2001/83/EC as amended. The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements

The active substance pantoprazole, is not considered a new active substance.

I.1 About the product

Pharmacotherapeutic group: Proton Pump Inhibitors
ATC Code: AO2BC02

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 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. As with other proton pump inhibitors and H_2 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.

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.

Pantoprazole was first licensed in 1994.
The current approved indications for the innovator in Ireland are for
- duodenal ulcer
- gastric ulcer
- moderate and severe reflux oesophagitis
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions

II. QUALITY ASPECTS

II.1 Introduction

This application is for a vial containing 40mg of pantoprazole (as pantoprazole sodium sesquihydrate) presented as a sterile lyophilised powder. This powder will be reconstituted to prepare a solution for injection, or can be reconstituted and further diluted to a solution for infusion.

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.

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

No requests for inspection were necessary. The QP at the finished product batch release site has certified the GMP status of the active substance. This is considered adequate.

II.2 Drug Substance

The active substance is pantoprazole sodium sesquihydrate, which is an established active substance described in the European Pharmacopoeia. The active substance manufacturer holds a certificate of suitability from the European Directorate for the Quality of Medicines (EDQM) for pantoprazole sodium sesquihydrate. Therefore the manufacture, characterisation, control, reference standards, container closure system and the stability/retest period have been assessed by the EDQM versus the requirements of the European Pharmacopoeia (Ph.Eur.) monograph for the active substance, and the active substance specification is considered adequate to control the quality. The active substance is tested by the finished product manufacturer according to the Ph.Eur. monograph and batch data shows acceptable results.

II.3 Medicinal Product

The finished product is a powder for solution for injection containing 40mg of the active substance pantoprazole (as pantoprazole sodium sesquihydrate) and the excipients disodium edetate and sodium hydroxide. This is an established pharmaceutical form.

The development of the finished product has been described, the choice of excipients and their functions have been explained adequately in line with relevant European guidelines. The approach taken to formulation, compatibility, manufacturing process development, excipient and bioburden control has been justified. The analytical methods have been described and are supported by validated data. The finished product specification covers appropriate parameters for this type of dosage form according to the European pharmacopoeia monograph for parenteral preparations. Batch analysis has been presented for three batches and data comply with the proposed specification showing that the manufacturer can produce batches of consistent quality. The applicant has registered a batch size for which satisfactory validation according to relevant European/ICH guidelines has been provided. Any future increase in batch size will be by way of Type II variation and further validation will be required. All other ingredients comply with Ph.Eur. requirements. No TSE risk is apparent according to current EU guidelines. The container closure system and test methods have been justified with respect to EU requirements. The stability studies in the proposed packaging are carried out in line with ICH requirements and as24 month stability data has been provided, the final shelf life and storage condition and reconstitution/dilution solutions have been agreed.

The shelf life now proposed is 2 years at 'Do not store above 25^{o}C' when protected from light. In-use stability has been demonstrated on reconstituted and reconstituted and further diluted solution for 12 hours at 25^{o}C.

The applicant has committed to continuing to monitor the stability of the product according to GMP requirements.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The important quality characteristics of the drug product are well defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided assuring consistent quality of Pantoprazole Noridem 40mg powder for solution for injection.

III. 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 pharmacist who also holds a Masters degree in Industrial Pharmacy. The overview cites approximately 9 references from the published literature which are dated up to 2010. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

An environmental risk assessment has also been conducted and concludes that as this is a generic product there will be no increase in overall market consumption and thus no increase in environmental exposure to pantoprazole following marketing authorisation.

IV. CLINICAL ASPECTS

IV.1 Introduction

The product is a generic medicinal product as defined by article 10(1) of Directive 2001/83/EC, with the reference product being Protium 40mg IV powder for solution for injection (Nycomed GmbH PA 1421/001/001).
In accordance with the current bioequivalence guidelines (Note for guidance on the investigation of bioavailability and bioequivalence CPMP/EWP/QWP/1401/98), the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised product. Therefore Pantoprazole Noridem 40 mg Powder for Solution for Injection is considered bioequivalent with the reference product (Protium 40mg IV powder for solution for injection (Nycomed GmbH PA 1421/001/001) and no bioequivalence study is required for this application.

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.

IV.2 Pharmacokinetics

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 serum protein binding is about 98 %. Volume of distribution is about 0.15 l/kg

Elimination
The substance is almost exclusively metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathway include oxidation by CYP3A4. Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. 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).

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 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 recommended when pantoprazole is administered to patients with impaired renal function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialyzed. Although the main metabolite has a moderately delayed half-life (2-3 h), excretion is still rapid and thus accumulation does not occur.

Although for patients with liver cirrhosis (classes A and B accordingly to Child) the half-life values increased to between 7 and 9 h and the AUC values increased by a factor of 5-7, the maximum serum 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.

IV.3 Pharmacodynamics

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 increases 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, it can inhibit 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 (simple to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments (see section 5.3) 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.

IV.4 Clinical efficacy and Safety

The applicant has satisfactorily described an overview of published literature on clinical efficacy and safety in all accepted indications listed in the SmPC.

Pharmacovigilance System

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided

Risk Management Plan

An EU-RMP was not considered necessary at this time – routine pharmacovigilance was deemed sufficient.

V. OVERALL CONCLUSIONS

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H+,K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H+,K+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested.

Pantoprazole is indicated for the short-term treatment and maintenance therapy of erosive esophagitis associated with gastroesophageal reflux disease (GERD) and for the treatment of Zollinger-Ellison syndrome. It has been shown to be effective in the management of duodenal ulcer or gastric ulcer, including those caused by Helicobacter pylori (H. pylori).

Pantoprazole is 98% bound to plasma proteins. It is extensively metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP2C19, to desmethylpantoprazole; small amounts are also metabolised by CYP3A4, CYP2D6, and CYP2C9. Metabolites are excreted mainly (about 80%) in the urine, with the remainder being excreted in bile. The terminal elimination half-life is about 1 hour, and is prolonged in hepatic impairment; the half-life in patients with cirrhosis was 3 to 6 hours.

Pantoprazole produces extensive and long-lasting inhibition of gastric acid secretion. For some drugs, including ketoconazole, absorption from the gastrointestinal tract is enhanced by the presence of gastric acid. When ketoconazole is co-administered with pantoprazole, reduced acidity may compromise ketoconazole absorption, thus decreasing its bioavailability.

Coadministration of atazanavir and proton pump inhibitors (PPI), such as pantoprazole, may result in substantially decreases serum plasma concentrations of atazanavir. This may result in loss of therapeutic effect and the development of resistance. The absorption of atazanavir is pH dependent. Therefore, PPIs, including pantoprazole, should not be co-administered with it.

Pantoprazole, although metabolized by hepatic cytochrome P 450 systems, does not appear to either inhibit or induce cytochrome P 450 enzyme activity. To date, no clinically significant interactions have been noted for such commonly used drugs as diazepam, phenytoin, nifedipine, theophylline, digoxin, warfarin, or oral contraceptives.

Pantoprazole influences increase of the fasting gastrin value. In short-term usage, in most cases these values do not exceed the normal upper limit. Gastrin levels double in most cases of long-term treatment. Excessive increase in gastrin levels were observed in isolated cases. In consequence, a mild to moderate increase in the number of ECL cells in the stomach (simple to adenomatoid hyperlasia) was observed in some patients during long-term treatment. However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperlasia) or gastric carcinoids as observed in animal testing is highly improbable in humans if pantoprazole is used less than 1 year.

Pharmacodynamic, pharmacokinetic and toxicological literature data about pantoprazole have been summarised and evaluated in the overview.

The Marketing authorisation is granted.

VI. REVISION DATE

September 2011