European Medicines Agency
Evaluation of Medicines for Human Use

London, 8 May 2009
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ASSESSMENT REPORT

FOR

PANTOZOL Control

International Nonproprietary Name: pantoprazole

Procedure No. EMEA/H/C/001013

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

TABLE OF CONTENTS

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Nycomed GmbH submitted on 28 April 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for PANTOZOL Control, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004. In addition, the applicant proposed the classification for supply of PANTOZOL Control to "medicinal product not subject to medical prescription".

The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 13 December 2007. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level considering the possibility to obtain a pan-European non-prescription status. This took into account that the need for an optimal self-treatment of heartburn is universal and that it is in patients' interest across the community to allow access to a pantoprazole product with harmonised legal status. In addition, it would give Community-wide access and consumer protection, based on harmonised labelling and avoid diverted markets.

The legal basis for this application refers to Article 10(3) of Directive 2001/83/EC, as amended – hybrid application.

The chosen reference product is:

Reference medicinal product which is or has been authorised for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Pantozol 40 mg gastro-resistant tablets
- Marketing authorisation holder: Nycomed GmbH, D-78467 Konstanz
- Date of authorisation: 23-08-1994
- Marketing authorisation granted by: Germany
- Marketing authorisation number: 30308.00.00

Reference medicinal product authorised in the Community/Member State where the application is made:

- Product name, strength, pharmaceutical form: Pantozol 20 mg gastro-resistant tablets
- Marketing authorisation holder: Nycomed GmbH, D-78467 Konstanz
- Date of authorisation: 28-07-1998
- Marketing authorisation granted by: Germany
- Marketing authorisation number: 43404.00.00

Difference(s) compared to the reference medicinal product: change in therapeutic indication.

The applicant applied for the following indication: "Treatment of reflux symptoms (e.g. heartburn, acid regurgitation)".

Scientific Advice:
The applicant did not seek Scientific Advice at the CHMP with relevance for this application.

Licensing status:
It should be noted that the following overview of marketing authorizations concerns the prescription-only medicine with the exception of the approval in Sweden where pack sizes with 7 and 14 tablets of the 20 mg gastro-resistant tablets are approved for non-prescription use since 24-Feb-2000.

Pantoprazole has been given a Marketing Authorisation in the following countries:
Austria (29/01/1999, 19/03/1999), Belgium (21/06/1999, 26/05/2008), Bulgaria (04/08/2004), Cyprus (12/12/2005), Czech Republic (07/12/2000), Denmark (15/01/1999, 09/05/2008), Estonia (04/02/2005), Finland (21/12/1998), France (25/01/1999), Germany (28/07/1998, 15/01/2008), Greece (29/09/2000, 24/01/2003), Hungary (08/04/2005), Ireland (17/12/2002), Italy (29/05/2000,

22/01/2002), Latvia (05/07/2004), Lithuania (30/12/1999), Luxembourg (26/01/2000, 29/09/2008), Netherlands (28/12/1998), Norway (08/10/2001), Poland (03/08/2006), Portugal (21/01/1999), Romania (29/12/2006), Slovak republic (26/04/2004), Slovenia (03/09/2002), Spain (22/06/1999), Sweden (28/01/1999, United Kingdom (17/03/2003), Antilles, Netherlands (25/08/1998), Argentina (04/11/1997, 21/04/1999), Aruba (24/11/1998), Australia (27/03/2000), 07/04/2000, 01/08/2008), Bosnia and Herzegowina (01/08/2001), Brazil (19/05/1998, 02/04/1998), Canada (01/10/2001, 10/03/2000), Chile (06/12/1999), Colombia (01/03/1999), Costa Rica (29/06/1999), Croatia (04/01/2006), Dominican Republic (10/02/1999), Ecuador (08/12/1998), Egypt (14/09/2004), Guatemala (20/04/1999), Honduras (13/08/1999), Hong Kong (24/06/1999), India (09/12/1998), Indonesia (06/10/2003), Iran (06/06/2004), Israel (28/10/1999), Jamaica (08/03/1999), Kazakhstan (14/04/2008), South Korea (08/10/1999), Kuwait (16/08/1999), Kyrgyzstan (09/08/1999), Macedonia (08/05/2007), Malaysia (23/01/2003), Marocco (29/01/2002), Mexico (10/06/1994, 25/11/1994), New Zealand (03/12/1998), Nicaragua (17/06/1999), Panama (09/09/1999), People's Republic of China (10/04/2001), Peru (10/04/1998), Philippines (16/08/2000), Russian Federation (28/04/2008), El Salvador (16/11/1999), Saudi Arabia (13/03/2001), Serbia (25/08/2004), Singapore (07/10/1999), South Africa (13/12/2000, 27/07/2005), Sudan (23/06/2005), Switzerland (26/03/1999), Taiwan (03/08/2000), Thailand (28/08/2000), Trinidad and Tobago (27/05/1999), Tunisia (12/06/2002), Ukraine (29/05/1999), United Arab Emirates (03/04/2000), United States of America (12/06/2001), Venezuela (12/02/2003), Vietnam (29/01/2003)

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Rafe Suvarna
Co-Rapporteur: Gonzalo Calvo Rojas

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 28 April 2008.
- The procedure started on 28 May 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 August 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 August 2008.
- During the meeting on 22-25 September 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 September 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 November 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 January 2009.
- During the CHMP meeting on 19-22 January 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 27 January 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 6 February 2009.
- During the meeting on 16-19 February 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to PANTOZOL Control on 19 February 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 17 February 2009.
- Furthermore, the CHMP adopted an opinion on the significant non-clinical or clinical data in relation to the claimed new indication for PANTOZOL Control on 19 February 2009.
- On 3 April 2009, the European Commission (EC) requested the CHMP to reconsider its opinion adopted on 19 February 2009 on the significance of the data submitted in support of the classification of PANTOZOL Control, 20 mg gastro-resistant capsules as 'medicinal product

not subject to medical prescription', taking into account the provisions of Article 74a of Directive 2001/83/EC, as amended and the EC guideline on '*Changing the classification for the supply of a medicinal product for human use'*.

- During the meeting on 20-23 April 2009, the CHMP adopted a revised opinion on the significant non-clinical or clinical data in relation to the claimed new indication for PANTOZOL Control.
- The CHMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on 12 June 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Gastro-oesophageal reflux disease (GORD) is defined as a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications. Reflux of gastric acid into the oesophagus is mediated by different mechanisms such as transient lower oesophageal sphincter relaxations or reduced pressure, impaired oesophageal clearance and hiatus hernia. Factors such as hormonal and neuronal mechanisms, medication, food and lifestyle can also contribute to the pathophysiology.

Heartburn and acid regurgitation are the most common symptoms associated with GORD and the condition can adversely affect the individual's quality of life. Mild symptoms occurring 2 or more days per week or moderate to severe symptoms occurring more than 1 day per week are often considered troublesome for patients. Heartburn describes a burning feeling, rising from the stomach or lower chest and radiating toward the neck, throat and occasionally the back. It usually occurs after large meals or after eating spicy foods, citrus products, fats, chocolates or drinking alcohol. Night time heartburn may cause sleeping difficulties and impair next-day function. Regurgitation is defined as the perception of flow of refluxed gastric content into the mouth or hypopharynx.

Some tests are available to diagnose GORD patients. However, the presence of frequent heartburn and acid regurgitation are sufficiently accurate to identify the disease. Initial GORD treatment is usually managed by a symptom-based rather than a pathogenesis-based approach. An empiric trial of acid suppression is the simplest method used for GORD diagnosis and to assess its relationship to symptoms. Symptoms responding adequately to an acid suppressant and returning when medication is discontinued allows a diagnosis of GORD. Non-responders to acid suppression could indicate the role of other factors. The majority of patients with reflux symptoms can be controlled at the self-care level or a primary care level. Non-prescription medicines for relief from heartburn include antacids, alginates, histamine2-receptor antagonist and proton pump inhibitors (PPIs). Recent clinical guidelines recommend treatment with PPIs as initial therapy for patients with symptoms impacting on their quality of life, while histamine2-receptor antagonist are recommended for patients whose symptoms are mild or infrequent.

Pantoprazole belongs to the class of proton pump inhibitors. It acts by inhibiting the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells. Pantoprazole-containing products are currently licensed throughout the European community for the treatment of conditions such as gastro-oesophageal reflux disease, Zollinger-Ellison syndrome, acid reflux disease, dyspepsia and duodenal or gastric ulcers. It was first authorised in 1994 and is available as 20 mg and 40 mg tablets and as a lyophilised powder for injection. The supply status in all Member States is "prescription-only medicine" with the exception of Sweden where some pack-sizes of the 20 mg gastro-resistant tablets are supplied as non-prescription medicine.

The objective of the current application for PANTOZOL Control is to seek approval for the short-term use of pantoprazole orally in the strength of 20 mg to treat reflux symptoms as a non-prescription medicine. The application is submitted through the Centralised Procedure as a hybrid application meaning that reference was made to an already approved product but that changes in the therapeutic

indication compared to the reference products were applied for supported by the results of appropriate nonclinical test or clinical trials. The reference product used for this purpose is Pantozol 20 mg gastro-resistant tablets (Germany, MA number 43404.00.00), which is approved for the treatment of mild reflux disease and associated symptoms, long-term management and prevention of relapse in reflux oesophagitis, as well as the prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment.

There is no specific EMEA/CHMP guideline relevant for the proposed therapeutic indication. The EC Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use, in its current version (January 2006), is applicable for this application. EMEA/CHMP scientific advice with relevance for this particular development has not been obtained by the applicant.

PANTOZOL Control is available in film coated tablets containing 20 mg pantoprazole. The recommended dose is 20 mg pantoprazole (one tablet) per day. Overall treatment duration without consultation of a doctor is limited to 4 weeks; if no symptom relief is obtained within 2 weeks of continuous treatment, the patient should be instructed to consult a doctor.

The claimed indication at time of application read as follows: “Treatment of reflux symptoms (e.g. heartburn, acid regurgitation)”

The approved indication is:

> “Short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.”

2.2 Quality aspects

Introduction

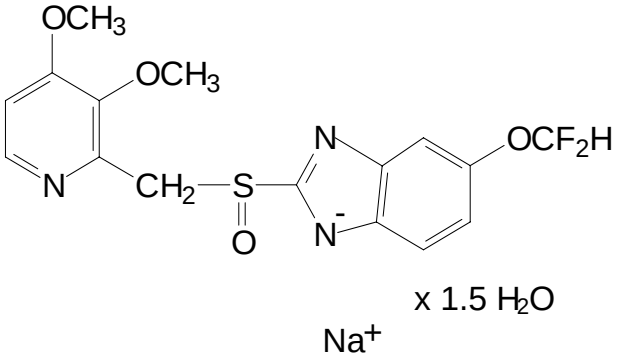
PANTOZOL Control is presented in form of gastro-resistant tablets containing pantoprazole as an active substance. Each gastro-resistant tablet contains 20 mg pantoprazole (equivalent of 22.6 mg of pantoprazole sodium sesquihydrate). Tablets are yellow, oval, biconvex, film-coated and imprinted with “P20” in brown ink on one side.

The excipients used in the formulation of the finished product are well known excipients used for preparation of tablets such as sodium carbonate, mannitol, crospovidone, povidone K90, calcium stearate (present in tablet core), hypromellose, povidone K25, titanium dioxide, yellow iron oxide, methacrylic acid-ethyl acrylate copolymer (1:1), sodium laurilsulfate, polysorbate 80, triethyl citrate (present in film-coating, including enteric coating and undercoating), shellac, red iron oxide, black iron oxide, yellow iron oxide, soya lecithin, titanium dioxide and antifoam DC 1510 (present in printing ink).

Tablets are packed in Alu/Alu blisters without cardboard reinforcement or Alu/Alu blisters with cardboard reinforcement (blister wallet).

Active Substance

Pantoprazole sodium sesquihydrate (recommended International Non-proprietary Name), a substituted benzimidazole, is a substance described in the Ph Eur. The active substance is chemically designated as sodium 5-(difluoromethoxy)-2-[(RS)-[(3,4-dimethoxypyridin- 2-yl)methyl] sulphinyl] benzimidazol-1-ide sesquihydrate (Chemical Name) and has the following structure:



It is a white to off white ampholytic crystalline powder with pKa values of 3.92 and 8.19. Is freely soluble in water and in ethanol (96%), practically insoluble in hexane. Solubility of the active is low at neutral pH, increasing with pH. Stable salts are only formed with bases, due to rapid conversion to the cyclic sulphenamide on pyridyl protonation. Polymorphic forms have not been detected, although other hydrates can be formed. The water content is 5.9 - 6.9 %

The active substance can exist as enantiomers due to the presence of an unsymmetrical substituted sulphoxide group. No difference has been found in the in-vitro or in-vivo activity of the two enantiomers.

- Manufacture

The synthesis of the drug substance is performed without optically active reagents and results in a racemate. It involves conventional chemical operations (alkylation, oxidation, formation of salt), which were transferred from laboratory to production batches during the development.

The manufacturing process of pantoprazole sodium sesquihydrate is a four step synthesis. In the first step 5-(difluoromethoxy)-2-{[(3,4-dimethoxypyridin-2-yl)methyl]thio}-1*H*-benz[*d*]imidazole) (sulphide) is formed by a reaction of "Benzimidazole" and "Chloromethylpyridine" in alkylation reaction. In the step 2 this intermediate is subsequently converted by oxidation to 5-(difluoromethoxy)-2-{[(RS)-(3,4-dimethoxypyridin-2-yl)methyl]sulfin-yl}-1*H*-benz[*d*]imidazole (free acid). Subsequently, in the next steps pantoprazole sodium sesquihydrate is formed and isolated as pure active substance.

The proposed manufacturing process has been adequately described, critical steps and accompanying in-process controls have been defined to ensure quality of the final compound. In-process controls performed during the synthesis are suitable to control the reaction progress. Appropriate specifications for starting materials solvents and reagents have been established.

The synthesis of pantoprazole sodium sesquihydrate for commercial purposes was developed more than ten years ago. Process initially validated at smaller scale has been upscaled and transferred to different manufacturing sites where the process was adopted to the equipment of these sites and validated in several steps. All changes during the development have been well characterised. It has been proven that the drug substance can be reproducibly manufactured.

The chemical structure of pantoprazole sodium sesquihydrate was characterised according to the identification tests described in the Ph Eur monograph. All the relevant characteristics of this substance are included in the monograph.

Potential impurities and degradation products have been well discussed in relation to their origin and potential carry-over into the final drug substance. Solvents and heavy metals coming from a catalyst used in an early step of synthesis are routinely controlled.

- Specification

The drug substance specification complies with the Ph Eur monograph. Additional test for particle size

and residual solvents have been added. The drug substance specification includes tests for identification (IR and sodium), appearance of solution, optical rotation, water content (Karl Fisher), heavy metals, related substances (HPLC), assay (titration), particle size (laser diffraction) and residual solvents (GC).

All analytical methods, except for particle size and residual solvents, are compendial and validation of these methods was not deemed necessary. For two additional methods (residual solvents, particle size distribution) appropriate validations have been performed. The GC method has been adequately validated for selectivity, linearity, repeatability, intermediate precision, accuracy, limit of detection (LOD) and limit of quantitation (LOQ). Validation for the particle size method is also acceptable; repeatability, sensitivity and robustness were examined.

In general analytical methods proposed are suitable to control the quality of the drug substance.

Batch analysis data on 6 batches from the proposed manufacturing sites has been provided. All results are with specifications and show batch-to-batch and site-to-site consistency.

- Stability

Stability batches were stored under different controlled conditions and in three different types of packaging. The following storage conditions and duration have been applied during the studies: 25 °C / 60% RH up to 60 months, 30 °C / 70% RH up to 36 months, 37 °C / 75% RH up to 20 months and 0 °C / 75% RH up to 6 months. The aim of these studies was to show evidence that the bulk drug substance remains stable and that the use of different containers for transport and use in the central weighing system in one of the manufacturing sites has no negative influence on the quality of the drug substance.

In addition photostability tests were performed according to the ICH "Guideline for the photostability testing of new drug substances and products". Recent studies on the photostability of the drug substance in solution and solid state, on stability against oxygen, hydrogen peroxide, HCl and sodium hydroxide and high temperatures were also presented. The main degradation pathway has been established through several stress condition studies in solid state and in solution.

The stability studies confirmed the proposed re-test period, when the drug substance is stored in the proposed containers.

Medicinal Product

- Pharmaceutical Development

Pharmaceutical development of the finished product started in the end of the eighties; the first marketing authorization for an orally administered pantoprazole was granted in 1994. Gastro-resistant tablets have been developed in order to protect the drug substance which is acid labile from acidic effect of gastric fluid. Pantoprazole is a prodrug exerting its activity through the cyclic sulphenamide formed by the action of acid at the site of action. It inhibits basal and stimulated acid secretion in animals and man via the covalent binding H+/K+ ATP-ase, also known as the “gastric proton pump” located in the secretory membrane of the parietal cell.

The drug substance is incompatible with all conventional gastro-resistant coating polymers, which are acidic. It was, therefore, necessary to seal the tablet core with an additional isolating layer of neutral coating material before applying the gastro-resistant coat. Appropriate compatibility studies of the active substance with different excipients have been performed. Mannitol was chosen as a filler for the inner phase of the granulate, polyvidone as a binder, crospovidone as a disintegrant and sodium carbonate as an excipient empirically hindering discolouration of the active ingredient by increasing pH. Calcium stearate acts as a lubricant. Hydroxypropyl methylcellulose serves as a film former for the subcoating. The other excipients are propylene glycol as a plasticizer, polyvidone K25 as an adhesion enhancer to promote the binding of the film to the tablet surface and yellow ferric oxide and

titanium dioxide as colorants. The gastro-resistant coating consists of methacrylic acid - ethyl acrylate copolymer 1:1; triethyl citrate is added as a plasticizer.

- Adventitious Agents

Among excipients used in the drug product only shellac, component of the printing ink is of animal origin but without any TSE/BSE risk. Shellac is obtained by purification of Lac, a secretion of the insect Laccifer Lacca Kerr (*Coccidae*).

- Manufacture of the Product

The manufacturing process has been applied unchanged over the recent years. It is divided into three manufacturing steps (1) manufacturing of the tablet cores, (2) coating and (3) printing and packaging of the gastro-resistant tablets. Tablet cores are produced by wet granulation. In the second phase of the process the first coating suspension is sprayed onto the tablets in two phases. The spraying is continued until the nominal tablet weight has been achieved and the cores are dried in an interim step. Tablets cores covered with subcoating are subsequently covered with the second coating layer – enteric coating. Spraying continues until the nominal tablet weight increase has been achieved and the coated tablets are dried. In the final step the gastro-resistant tablets are printed on one side ["P20"] with brown printing ink using an offset printing machine. The printed tablets are put into the container closure systems.

The manufacturing process is fully validated according to GMP requirements. Extensive experience over the years demonstrates that the manufacturing process is well under control and a drug product of adequate quality within the approved specifications is obtained. A continuously high level of quality can therefore be guaranteed.

- Product Specification

The product specification is standard for tablets (modified release) and contains tests with suitable limits for appearance, mean mass, disintegration time, loss on drying, identification, dissolution (UV determination), content uniformity, assay (HPLC), purity - impurities and degradation products (HPLC), microbial limits.

Analytical methods have been adequately described and validated for the intended use. The assay, identification and related substances are determined by an in-house HPLC method. The dissolution test is the same as the one used during drug development. The other tests are carried out according to the Ph Eur. The HPLC method for assay, identity and purity has been validated with respect to specificity, limit of detection, limit of quantitation, selectivity, linearity, range, precision, accuracy and robustness. The UV method for determination of dissolution percentage has been validated with respect to specificity, linearity, precision and accuracy.

Batch analysis results on commercial scale batches of the drug product indicate satisfactory uniformity and compliance with the agreed specification.

- Stability of the Product

Over the long experience with the drug product significant changes have never been encountered, when testing the dosage form in long-term stability studies as well as under accelerated conditions according to the ICH Q1A. Furthermore bulk stability for the gastro-resistant tablets were submitted to guarantee stability prior to further processing.

Supportive stability studies were performed after approval on three commercial scale batches stored up to 36 months under the following conditions 25 °C / 60 % RH (long term), 30 °C / 70 % RH (intermediate) and 40 °C / 75 % RH (accelerated). The tablets stored in primary packaging materials as described in the dossier were in compliance with the shelf-life specifications at all tested time points.

In addition as per GMP requirements the applicant committed to place on the stability study one commercial scale batch of the drug product per year, chosen irrespective of the primary packaging material, on follow-up stability at 25°C/60 % RH.

Based on the stability data the proposed shelf-life and storage conditions as defined in the SPC are acceptable.

In summary the stability data provided support the proposed shelf-life and storage conditions.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance.

2.3 Non-clinical aspects

The applicant provided an acceptable summary of the pharmacology, pharmacokinetics and toxicology of pantoprazole based on published literature as well as reference books and information from databases. No further non-clinical studies are required and the applicant has justified why no such data were provided.

Since the manufacturing of the product is identical to the reference product, there is no requirement to specifically address the impurity profile of the new product from a nonclinical perspective.

For the environmental risk assessment, the applicant has conducted the following studies: Ready biodegradability (OECD 301 D), Aerobic Transformation in Water (OECD 308), Respiration Inhibition Test (OECD 209), Daphnia immobilisation (OECD 202), Daphnia reproduction Test (OECD 211), Acute Toxicity to Fish (OECD 203), Fish Early Life Stage Toxicity Test (OECD 210) and Algae Growth Inhibition Test (OECD 201). In addition, the applicant has initiated a sediment-water chironomid toxicity test using spiked Sediment (OECD 218). The final report of this study will be provided as post-approval commitment together with a discussion on the impact of this data on the environmental risk assessment.

2.4 Clinical aspects

Introduction

This being a hybrid application refers to the approved product Pantozol 20 mg gastro-resistant tablets and concerns a change in the indication for use as non-prescription medicine. Appropriate clinical data in support of the proposed change is required.

To support the efficacy of PANTOZOL control in the proposed indication and posology, the data from 17 clinical studies was provided in which the treatment of symptoms in patients with GORD was studied as primary or secondary criterion. In these studies the use of pantoprazole 20 mg in the symptomatic treatment of GORD of any stage within the first 14 days of treatment has been investigated. Out of these studies, studies BGSA017 and BGI022 comparing pantoprazole to placebo and ranitidine, respectively, after 2 weeks of treatment were considered as main studies for the claimed indication. Table 1 provides an overview of key design elements of the main studies.

Table 1 Overview of the design of the main studies

Study	Design	Study Objective	Subjects by arm entered/ completed	Duration	Diagnosis Incl. criteria	Primary Endpoint
BGSA017 245/98	randomized, double-blind, multicenter, parallel group comparison	Comparison of symptom relief and tolerability of 20 mg pantoprazole vs placebo in the treatment of GORD in patients with endoscopically normal oesophagus	219 Pantoprazole: 108 Placebo: 111	2 weeks	Normal oesophagus on endoscopy History of reflux symptoms (heartburn, acid eructation, pain on swallowing)	Relief of heartburn in GORD Stage 0
BGI022 257/2004	randomized, double-blind, parallel group	To compare the efficacy and tolerability of pantoprazole 20 mg and ranitidine 150 mg in patients with mild GORD	344 Pantoprazole: 172 Ranitidine: 172	4 weeks	Heartburn of moderate to severe intensity and endoscopic evidence of either reflux oesophagitis or no oesophagus	Relief of heartburn in GORD Stage 0/I

For the safety evaluation a review derived from the applicant's worldwide clinical trial database and post-marketing surveillance data together with a risk-benefit consideration for non-prescription status have been provided.

The applied for medicinal product and the reference product are from a quality perspective identical in terms of qualitative and quantitative composition, and manufacturing sites and processes are identical. Therefore, no bioequivalence data between the two products were required.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

No new pharmacokinetic studies were conducted in support of this application and full reference was made to the available data for the reference product. This was considered acceptable.

The applicant has reviewed the available literature data on the pharmacokinetic profile of pantoprazole. The absolute bioavailability of pantoprazole in healthy subjects is 77% and does not change at multiple dosing. Unlike other proton pump inhibitors, pantoprazole has linear pharmacokinetics in a dose range of 10 - 80mg. It is extensively metabolised in the liver. The main serum metabolite is formed by demethylation at the 4-position of the pyridine ring, followed by conjugation with sulphate. 80% of the administered dose excretes as metabolites in the urine. The pharmacokinetics is unaltered in patients with renal failure. In patients with severe liver cirrhosis, the half-live, AUC and maximum serum concentration are increased. Since the elimination half-life in these patients is still shorter than the dosing interval of 24 hours, no accumulation of pantoprazole was observed following multiple dosing. Since in patients with liver cirrhosis the elimination half-life, the AUC and the maximum serum concentration is increased compared to healthy subjects, patients with

liver disease should not be supplied with non-prescription pantoprazole without consulting a doctor. This is adequately addressed in section 4.4 of the SPC and section 2 of the package Leaflet.

No dose adjustment is required in the elderly. Concomitant intake of food has no influence on the bioavailability of pantoprazole.

Pantoprazole has a low interaction potential. The results of several pharmacokinetic studies with pantoprazole and different drug combinations do not suggest drug-drug interaction between pantoprazole and the tested drugs. There are potential interactions with anticoagulants and with drugs, which bioavailability is pH dependent such as atanazavir. The co-administration with atazanavir is contra-indicated in the SPC and the Package Leaflet.

Pharmacodynamics

No new pharmacodynamic studies were conducted in support of this application and full reference was made to the available data for the reference product. This was considered acceptable.

The applicant has provided a literature review on pharmacodynamics. Pantoprazole inhibits the gastric H+/K+-ATPase (the proton pump) and thereby inhibits H+ ion transfer into the gastric lumen. Like other compounds in its class, pantoprazole becomes active only after chemical rearrangement in a strongly acidic environment. During the first step of the chemical transformation pantoprazole is protonated, assuming a positive charge. The second step of the activation involves rearrangement of the molecular structure into a cyclic sulphenamide, a highly reactive intermediate of pantoprazole which can form disulphide (S-S) bonds with cysteine-containing proteins (or S-H group containing compounds such as glutathione), and thereby affects their structural and/or functional properties.

Treatment with oral doses of pantoprazole once daily leads to a dose-related increase in the 24 h intragastric pH and in the concentration of serum gastrin. The effects of the 20 mg dose are significantly lower than those observed with the 40 mg dose, but higher doses (80 mg and 120 mg) do not differ much from the 40 mg dose. The effect increases with dose and over time and reaches steady state after a few days. Tablet and i.v. formulations of pantoprazole have equipotent effect on intragastric pH. Compared to ranitidine, pantoprazole is significantly more effective in elevating and maintaining intragastric pH. These pharmacodynamic characteristics are in line with findings from clinical trials submitted by the applicant, which show that pantoprazole 20 mg is effective for the treatment of reflux-like symptoms, but it does not provide instant relief of symptoms.

Clinical efficacy

The proof of efficacy is based on a comprehensive assessment of the data from 17 clinical studies that were identified for this purpose, two of which were considered the main studies.

- Dose response studies

No specific dose finding studies have been conducted for this application. Based on the available clinical study data, the applicant considered a daily dose of pantoprazole 20 mg to be established for the short-term (up to 2/4 weeks) treatment of reflux symptoms. These studies compare pantoprazole 20 mg with placebo, histamine2-receptor antagonist or proton pump inhibitors. No comparison with histamine2-receptor antagonist at doses used for non-prescription treatment of heartburn has been performed.

The CHMP asked the applicant to explore whether doses of pantoprazole below 20 mg (namely 10 mg) can be effective in the proposed indication. One study has been identified by the applicant, which studies the 10 mg pantoprazol dose to investigate healing of erosive esophagitis. This study (WA300) includes the absence of reflux symptoms as a secondary endpoint. Three doses of pantoprazole (10, 20 and 40 mg) were compared to placebo. A detailed analysis of the results of this study shows that the 20 mg dose obtained a more consistent profile of relief at earlier time points. The 10 mg dose achieved statistically significant results compared to placebo in the rates of patients with

persistent absence of daytime and night-time heartburn but a statistically significant result in persistence of acid regurgitation is not obtained with this dose. The efficacy and safety of the 20 mg dose subject to medical prescription in the treatment of mild reflux disease and its symptoms is acknowledged. The CHMP therefore agreed that the selection of this dose for the proposed indication of the non-prescription medicine is justified.

- Main studies

Two studies were considered as the main studies for the claimed indication:

- Study BGSA017 was a randomized, double-blind, multicentre, parallel group comparison conducted at 10 study centres in South Africa;
- Study BGI022 was randomized, double-blind, parallel group conducted at 45 study centres in Italy.

Selection of the main studies was based on the criteria that relief of reflux-related symptoms was defined as the primary efficacy criterion in the study protocol and that the primary efficacy analysis was based on the time point of 14 days of treatment (with or without an additional time point at 7 days of treatment).

Study BGSA017

METHODS

Study Participants

Patients in this study were between 18 and 75 years old and had a normal oesophagus on endoscopy. They had a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study, and at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Patients with conditions for whom a non-prescription use of pantoprazole would not be appropriate, like patients with current erosive lesions of the upper gastrointestinal tract (e.g. reflux esophagitis stage I-V, erosive gastritis, were excluded.

Treatments

One group of patients received 20mg pantoprazole every morning before breakfast. The other group of patients took one tablet containing placebo. At the first visit and at the follow-up visit after 7 days the patients received 10 film coated tablets of 20mg pantoprazole or placebo. The maximum duration of treatment per patient was 2 weeks.

Objectives

The objective of the study was to compare the symptom relief and tolerability of 20mg pantoprazole (once daily dose) with placebo in the treatment of symptomatic GORD in patients with endoscopically normal oesophagus.

Outcomes/endpoints

The primary efficacy parameter was freedom from heartburn after 7 and 14 days defined as being free from heartburn for 2 days prior to the first and second follow-up visits.

Secondary efficacy parameter was time until freedom from key symptoms (heartburn, acid regurgitation, pain on swallowing).

Sample size

The sample size was calculated on the basis that for 100 patients in each group a difference of 26% in time until freedom of symptoms can be detected assuming clinical response rates around 50% (i.e. 37%; 63%). This was calculated for a one sided test at the 2.5% level of significance and a power of 90% (leading to 98 patients per group).

Randomisation

Randomisation was based on a computer-generated list of pseudo random numbers. The random sequence was balanced after every 4 patients (block length).

Blinding (masking)

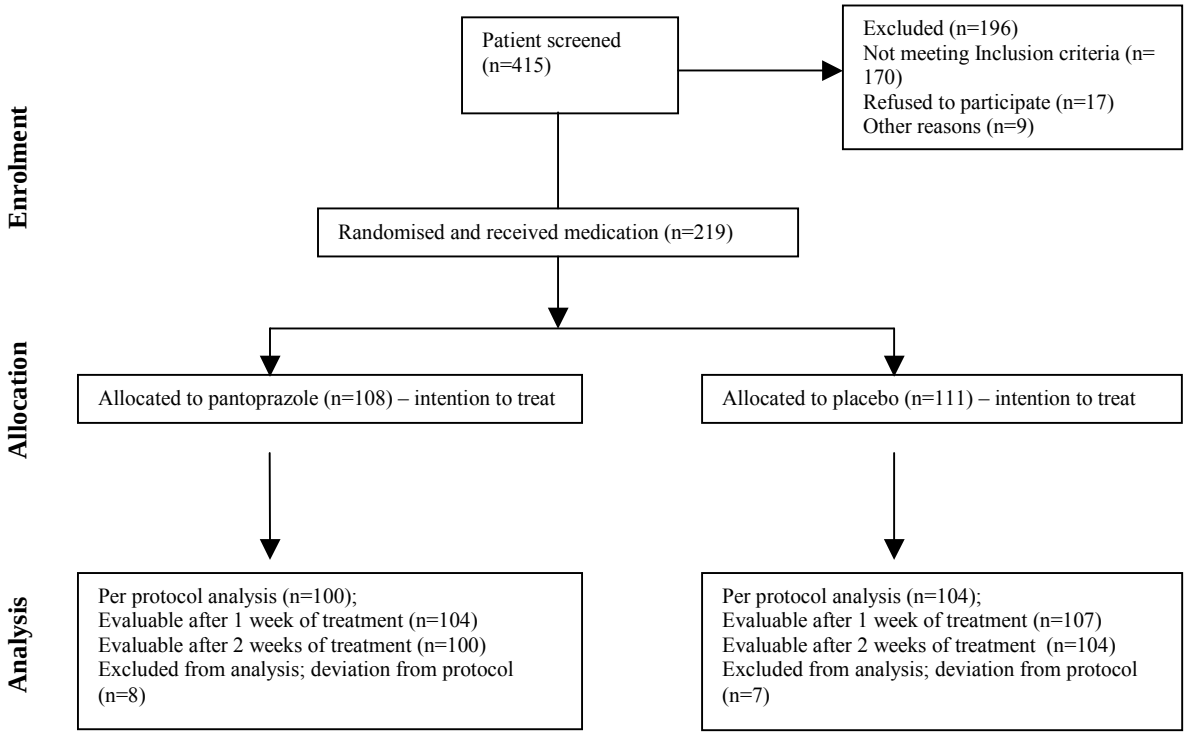
Test product and placebo tablets were of identical appearance, and were packed in identical bottles and cartons.

Statistical methods

With respect to the primary criteria 'freedom from heartburn after 7 days' and freedom from heartburn after 14 days' the two treatment groups were compared by means of Fisher's Exact Test. The null hypothesis that no difference in efficacy exists between the two treatments was tested one-sided versus the alternative that such a difference exists (superiority of pantoprazole). The multiple level of significance was set to 5%, and an appropriate sample size was chosen to achieve a power of 90%.

RESULTS

Participant flow



Baseline data

There were 36 male and 72 female patients in the pantoprazole group at baseline. There were 35 male and 76 female patients in the placebo group. The median age was 39.5 years (range: 19-66 years) in

the pantoprazole group and 40 years (range: 19-73 years) in the placebo group. Median weight was comparable between treatment groups (74.5 kg vs. 75 kg).

The distribution of gender, *H. pylori* status, consumption of nicotine and alcohol was comparable in the two treatment groups.

Numbers analysed

In the intention to treat (ITT) evaluation all patients were included who had taken the study medication at least once. The ITT population included 219 patients. All patients who completed the study according to the protocol were included in the per protocol analysis (PP). Drop outs due to adverse events whose causality to the study medication was assessed as 'likely' or 'definite' by the investigator and failures of treatment were included in the PP analysis. The PP population included 211 patients by the end of week 1 and 204 patients by the end of week 2.

Outcomes and estimation

The results of this study are summarized in the tables below. The differences between pantoprazole and placebo in the relief from heartburn (table 2) were statistically significant at 1 and 2 weeks in both the intent-to-treat and per protocol populations ($p<0.001$, Fisher's Exact Test).

Table 2 Relief rate of heartburn in study BGSA017

Visit		Pantoprazole 20 mg Relief Rate of Heartburn (N/Total N)	Placebo Relief Rate of Heartburn (N/Total N)
Day 7	ITT (N=219)	66.7% (72/108)	32.4% (36/111)
	PP (N=211)	69.2% (72/104)	33.6% (36/107)
Day 14	ITT (N=219)	74.1% (80/108)	43.2% (48/111)
	PP (N=204)	80.0% (80/100)	46.2% (48/104)

82 patients in the pantoprazole group and 76 patients in the placebo group experienced acid regurgitation at baseline. Time until freedom from acid eructation (table 3) was significantly different between the treatment groups ($p < 0.0001$, U-test). The time until freedom from heartburn and "all key GORD symptoms" was also significantly different between the treatment groups ($p < 0.001$, U-test).

Table 3 Relief rate of acid eructation in study BGSA017

Visit		Pantoprazole 20 mg Relief Rate of Acid Eructation (N/Total N)	Placebo Relief Rate of Acid Eructation (N/Total N)
Day 7	PP (N=158)	73.2% (60/82)	35.5% (27/76)
Day 14	PP (N=158)	85.4% (70/82)	54.0% (41/76)

Other GI symptoms (epigastric pain, retrosternal tightness, nausea, vomiting etc.) showed a considerable decrease. After 2 weeks of treatment freedom from all GI symptoms was achieved in 48% of the PP patients in the pantoprazole group and 26% of PP patients in the placebo group. The difference between the treatment groups was statistically significant ($p<0.001$).

No obvious difference in therapeutic response was observed in *H. pylori* negative vs positive patients.

Study BGI022

METHODS

Study Participants

Patients in this study were at least 18 years old and had heartburn of at least moderate intensity for at least the previous 3 months. Patients had to have experienced heartburn of moderate to severe intensity on each of the three days prior to the first visit. Heartburn was defined as burning feeling rising from the stomach or lower chest up towards the neck. An inclusion criterion was also endoscopic evidence of either reflux oesophagitis (stage I according to the Savary-Miller classification) or no oesophagitis. Patients with conditions for whom a non-prescription use of pantoprazole would not be appropriate, like patients with endoscopically diagnosed reflux oesophagitis either of stage II, III or IV according to the Savary/Miller classification, were excluded.

Treatments

Eligible patients were randomized to receive a 4-week treatment with either pantoprazole 20mg once a day (taken in the morning before breakfast) plus one ranitidine placebo tablet in the morning before breakfast and in the evening before bedtime or ranitidine 150mg one tablet in the morning before breakfast and in the evening before bedtime plus one pantoprazole placebo tablet in the morning before breakfast.

Objectives

The study objective was to compare the efficacy and tolerability of pantoprazole and ranitidine in patients with mild GORD (no oesophagitis or stage I oesophagitis according to Savary/Miller).

Outcomes/endpoints

Primary outcome was to demonstrate superiority of pantoprazole over ranitidine in the absence of heartburn during the 3 days prior to the first visit (after 14 +-3 days of treatment).

The secondary outcome was to assess the effects of pantoprazole and ranitidine in the following variables:

- absence of heartburn during the 3 days prior to the second visit (after 28 days ±3 days of treatment)
- safety and tolerability
- influence of H.pylori status on efficacy
- symptomatic improvement after 2 and 4 weeks of treatment, judged by a symptom score

Sample size

In a previous study freedom from the key symptoms were 69% and 48% with pantoprazole and ranitidine, respectively. Assuming similar symptom relief rates, a 0.05 two-sided significance level and using a Fisher's Exact Test as an approximation for the procedure described above, for N=160 patients per group, the power was estimated to be 96%. The plan was to recruit 380 patients in order to have 320 patients eligible for the per protocol evaluation to assess the superiority of pantoprazole over ranitidine.

Randomisation

Allocation of patients to treatment groups occurred on the basis of a computer-generated randomization list. A balanced block randomization was used, so that the total number of patients allocated to the two treatments was balanced.

Blinding (masking)

To make the two treatment schemes indistinguishable the double-dummy technique was adopted.

Statistical methods

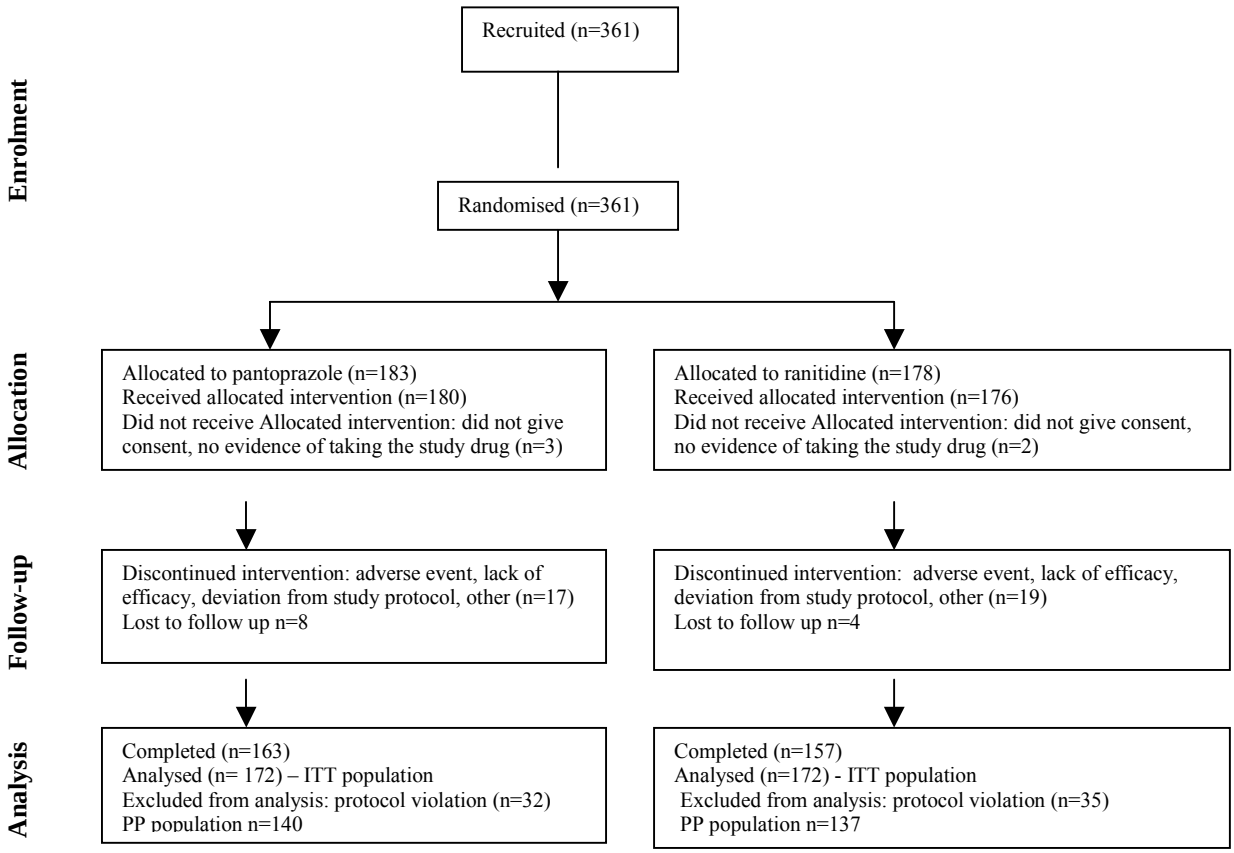
The full analysis set included all patients who were randomized and received trial medication at least once. The per-protocol set included all patients of the full analysis set except those who fulfilled at least one of the major protocol violations. All patients who received at least one study medication dose were included into the safety analysis.

All demographic and baseline variables were described by statistical characteristics. Efficacy analysis was performed both on the intention to treat and per-protocol data sets. Null hypothesis was that the two treatment groups had similar relief rates in the heartburn symptoms. Alternative hypothesis stated that the two rates were statistically different. The level of significance adopted was 0.05 and the test power was 90% for a two-tailed test.

Main variable (absence of heartburn during the three days prior to the first visit) was analysed by means of Cochran-Mantel-Haenszel method including the initial stage of oesophagitis as a covariate. The absence of heartburn during the three days prior to the second visit was analysed by using Cochran-Mantel-Haenszel method, using *H.pylori* at baseline as a covariate. A logistic regression model was performed on the rates of therapeutic success. Descriptive statistics were performed for symptom scores and for adverse events.

RESULTS

Participant flow



Baseline data

There were 159 male and 202 female patients included. There were no important differences between the treatment groups in terms of sex and age. The proportion of patients who were overweight or obese was slightly higher in the pantoprazole group than in the ranitidine group (44.8% vs. 37.64%). The treatment groups were similar in terms of smoking and drinking habits: the majority of patients were non-smokers and non-alcohol users. Endoscopic findings were abnormal in 64.54% in the whole study population. *H. pylori* was found in 31.56% in patients.

Numbers analysed

180 patients were included in the safety analysis in the pantoprazole group and 178 in the ranitidine group. The ITT population included 344 patients (172 in each group) and the PP population included 277 patients (140 in the pantoprazole and 137 in the ranitidine group).

Outcomes and estimation

The rates of complete relief of heartburn at days 14 and 28 are presented in table 4. The differences between the treatment groups in the relief of heartburn were statistically significant in both the intent-to-treat and per-protocol populations at Day 14 ($p < 0.05$). At Day 28 heartburn relief observed with pantoprazole was higher than with ranitidine, but the differences were not significant (p=0.079 ITT, and p=0.088 PP, respectively).

Table 4 Relief rate of heartburn in study BGI022

Visit	Population	Pantoprazole 20 mg Relief Rate of Heartburn (N/Total N)	Ranitidine 150 mg bid Relief Rate of Heartburn (N/Total N)
Day 14	ITT (N=344)	70.4% (121/172)	59.3% (102/172)
	PP (N=277)	73.6% (103/140)	60.6% (83/137)
Day 28	ITT (N=322)	90.2% (148/164)	82.9% (131/158)
	PP (N=268)	91.4% (127/139)	84.5% (109/129)

Heartburn improved in most patients. Worsening of heartburn (from moderate to severe) was observed only in 2 patients in the ITT population. The logistic regression analysis showed that neither the presence of reflux oesophagitis nor the positivity for H. pylori had a significant impact on relief from heartburn at visit one (p=0.813 for reflux oesophagitis and p=0.847 for H. pylori), while at visit 2 positivity for H. pylori (p=0.026) was a significant factor, but reflux oesophagitis is not (p=0.473)

Results for the relief of acid regurgitation are shown in table 5. The success rate was similar in patients treated for more than 17 days and in patients treated between 11 and 17 days in the pantoprazole group, while the success rate was slightly lower with longer treatment in the ranitidine group.

Table 5 Relief rate of acid eructation in study BGI022

Visit	Population	Pantoprazole 20 mg Relief Rate of Acid Eructation (N/Total N)	Ranitidine 150 mg bid Relief Rate of Acid Eructation (N/Total N)
Day 14	ITT (N=344)	73.8% (127/172)	62.2% (107/172)
Day 28	ITT (N=322)	82.3% (135/164)	75.3% (119/158)

All other GORD symptoms (acid regurgitation, pain on swallowing, epigastric pain etc.) improved in most of the patients.

- Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analysis or meta-analysis was performed in special populations in support of this application.

- Clinical studies in special populations

No clinical studies were performed in special populations in support of this application.

- Supportive studies

The data from 15 supportive studies was provided in support of this application. Table 6 provides an overview of these studies.

Table 6 Overview of the design of the supportive studies

Study ID	Design	Study Objective	Subjects by arm entered/ completed	Duration	Diagnosis Incl. criteria	Primary Endpoint
BF010 298E/99	randomized, double-blind, parallel group	To compare the efficacy and tolerability of pantoprazole 20mg and omeprazole 10mg in patients with symptomatic GORD without oesophagitis	331 Pantoprazole: 162 Omeprazole: 169	4/8 weeks	GORD symptoms with heartburn No oesophagitis at endoscopy	Relief of heartburn in GORD Stage 0
VMG309 323/2004	randomized, double-blind, parallel group	To compare the efficacy and tolerability of pantoprazole 20mg and omeprazole 10mg in patients with reflux oesophagitis Stage I with respect to heartburn	521	2 weeks	Heartburn, Endoscopically confirmed oesophagitis	Relief of heartburn in GORD Stage I
FK3059 93/2001	randomized, double-blind, parallel group	To compare symptom relief and safety of 20mg pantoprazole and 300mg ranitidine in symptomatic patients with GORD	338 Pantoprazole: 167 Ranitidine: 171	4 weeks	Rather severe heartburn, acid regurgitation, pain on swallowing	Relief of key symptoms in GORD

Study ID	Design	Study Objective	Subjects by arm entered/ completed	Duration	Diagnosis Incl. criteria	Primary Endpoint
VMG306 302/98	randomized, double-blind, parallel group	To compare symptom relief and safety of 20mg pantoprazole and 300mg ranitidine in patients with GORD stages 0 or I	356 Pantoprazole: 181 Ranitidine: 175	4 weeks	Endoscopically confirmed GORD and at least one reflux symptom	Relief of symptoms in GORD Stage 0/I
VMG305 301/98	randomized, double-blind, parallel group	To compare efficacy and safety of 20mg pantoprazole and 15mg lansoprazole in patients with GORD stages 0 or I	375 Pantoprazole: 189 Lansoprazole: 186	4 weeks	Endoscopically confirmed GORD and at least one reflux symptom	Relief of symptoms in GORD Stage 0/I
M3-316 152/2003	Open-label, multicenter	Investigation of disease related symptoms over 28 days with pantoprazole 20mg or 40mg; development and initial validation of a comprehensive questionnaire for patients with GORD	421 P20: 222 P40: 199	4 weeks	Endoscopically confirmed reflux oesophagitis	Relief of symptoms in GORD Stage A-D
M3-320 170/2003	Randomized, double-blind, multicenter parallel-group comparison	Evaluation of time to reach symptom relief of GORD-related symptoms during treatment with either pantoprazole 20mg or esomeprazole 20mg	529 Pantoprazole: 263 Esomeprazole: 266	4 weeks	The primary variable was the time interval from first medication to the point of time the symptom score on HiDOS fell below the given cut-off point of 5.04 for the first time.	Relief of symptoms in GORD Stage 0

Study ID	Design	Study Objective	Subjects by arm entered/ completed	Duration	Diagnosis Incl. criteria	Primary Endpoint
FK3034 166/95	Active-controlled, randomized, double blind, multicenter, parallel group comparison	Comparison of efficacy and tolerability of pantoprazole and ranitidine in the therapy of GERD stage I	209	4/8 weeks	GERD stage I according to Savary/Miller	Endoscopic healing of GORD Stage I
BGSA006 208/95	Randomized, double-blind, multicenter parallel-group comparison	To compare efficacy and safety of 20mg pantoprazole and 300mg ranitidine in patients with GORD stage I	201	4/8 weeks	Endoscopically established GORD stage I	Endoscopic healing of GORD Stage I
ESP009 396/2004	Randomized, double-blind, parallel-group comparison	To compare efficacy and safety of 20mg pantoprazole and 300mg ranitidine in patients with GORD	270 Pantoprazole: 134 Ranitidine: 136	4/8 weeks	Endoscopically established GORD stage I	Endoscopic healing of GORD Stage I
MEX020 200/2004	Randomized, double-blind, parallel-group comparison	Comparison of the efficacy of pantoprazole (20mg od) and tolerability with omeprazole (10mg od) in patients with mild reflux oesophagitis stage I	346 Pantoprazole: 173 Omeprazole: 173	4/8 weeks	endoscopically established reflux esophagitis Stage I and at least one of the key reflux symptoms	Endoscopic healing of GORD Stage I
UK005 303/98	Randomized, open-label, parallel-group comparison	Comparison of the efficacy and safety of 20mg pantoprazole and 20mg omeprazole in patients with reflux oesophagitis stage I	327 Pantoprazole: 166 Omeprazole: 161	4/8 weeks	endoscopically established reflux esophagitis Stage I and at least one of the key reflux symptoms	Endoscopic healing of GORD Stage I

Study ID	Design	Study Objective	Subjects by arm entered/ completed	Duration	Diagnosis Incl. criteria	Primary Endpoint
FK3037 105/96	Double-blind, randomised, three parallel group	Comparison of clinical efficacy and safety of three pantoprazole doses in the therapy of GORD in stages II/III	322 Pantprazole 20mg: 108 Pantoprazole 40mg: 108 Pantorazole 80mg: 106	4/8 weeks	GERD stages II and III according to Savary/Miller	Endoscopic healing of GORD Stage II/III
WA300 319E/98	Placebo-controlled, multicenter, randomized, double blind, parallel group comparison	Comparison of QD doses of 10, 20 and 40mg pantoprazole with placebo in the treatment of symptoms of GORD and endoscopically confirmed oesophagitis	603 Pantoprazole 10mg: 174 Pantoprazole 20mg: 174 Pantoprazole 40mg: 173 Placebo: 80	4/8 weeks	Endoscopically confirmed oesophagitis grade II	Endoscopic healing erosive esophagitis
WA301 320E/98	Active-controlled, randomised, double blind, parallel group comparison	Comparison of clinical safety and efficacy of 20mg, 40mg pantoprazole QD and nizatidine 150mg BID in symptomatic erosive oesophagitis	243 Pantoprazole 20mg: 80 Pantoprazole 40mg: 81 Nizatidine: 82	4/8 weeks	Endoscopically confirmed oesophagitis grade II	Endoscopic healing erosive esophagitis

The majority of these studies were performed in mild reflux disease and investigated the efficacy of pantoprazole either in the symptomatic relief or in the endoscopic healing of GORD. The summary of the results obtained in these supportive studies is presented in table 7.

Table 7 Summary of the results in the supportive studies with regard to Complete Relief from Heartburn

Studies	Pantoprazole 20 mg Symptom Relief Rate Min/Max	Comparator	Absolute Difference in Symptom Relief Rate Min/Max	Superiority of Pan (1)	Non-Inferiority of Pan (2)
Day 7					
BGSA017, WA300	60.1% to 69.8%	Placebo	36.5% to 41.1%	2/2	--
VMG306, WA301	54.0% to 55.1%	H2RA (Ranitidine 2x150 mg, Nizatidine 2x150 mg)	12.1% to 20.1%	2/2	--
VMG309, VMG305	69.2% to 80.6%	PPI (Omeprazole 10mg, Lansoprazole 15mg)	-3.1% to 0.1%	--	2/2
Day 14					
BGSA017, WA300	64.7% to 81.6%	Placebo	28.4% to 49.3%	2/2	--
BGI022, BGSA006, ESP009. FK3034, FK3059, VMG306, WA301	62.9% to 83.0%	H2RA (Ranitidine 300mg, Ranitidine 2x150 mg, Nizatidine 2x150 mg)	13.0% to 30.5%	7/7	--
VMG309, UK005, VMG305, M3-320	64.0% to 88.6%	PPI (Omeprazole 10mg, 20mg, Lansoprazole 15mg, Esomeprazole 20mg)	-6.6% to -1.2%	--	4/4
Day 28					
WA300	68.1%	Placebo	30.8%	1/1	--
BGI022, BGSA006, ESP009. FK3034, FK3059, VMG306, WA301	74.3% to 92.3%	H2RA (Ranitidine 300mg, Ranitidine 2x150 mg, Nizatidine 2x150 mg)	7.3% to 44.1%	6/7	--
BF010, UK005, VMG305, M3-320	79.7% to 91.5%	PPI (Omeprazole 10mg, 20mg, Lansoprazole 15mg, Esomeprazole 20mg)	-6.0% to 5.5%	--	4/4

(1) Number of studies with significant superiority of pantoprazole 20 mg vs. comparator/ total number of studies
(2) Number of studies with proven non-inferiority of pantoprazole 20 mg vs. comparator/ total number of studies
Pan = pantoprazole; H2RA = histamine2-receptor antagonist; PPI = proton pump inhibitor

These studies showed that pantoprazole 20mg was superior to placebo and histamine2-receptor antagonist in the complete relief from heartburn and was non-inferior to other proton pump inhibitors. The results also show an early onset of the clinical effect, with rates of complete relief of heartburn between 54.0% and 80.6% achieved after 7 days of treatment with pantoprazole 20 mg. A further improvement in the symptom relief rates was observed after 14 days and 28 days of treatment, respectively.

The evaluation of the symptom acid regurgitation showed similar rates of complete relief as the symptom heartburn at 7, 14, and 28 days.

Daily doses of pantoprazole 40 mg and 80 mg showed higher symptom relief rates than pantoprazole 20 mg, but non-inferiority was concluded in the majority of studies and at most time points. These results support the selection of the 20 mg daily dose of pantoprazole in the treatment of reflux symptoms.

Most patients with reflux symptoms have no or only mild erosive reflux disease. However, in the non-prescription setting the presence of oesophageal erosions cannot be ruled out because treatment will be performed without prior endoscopic examination. Therefore, the efficacy of pantoprazole 20 mg in the relief of reflux symptoms depending on endoscopically determined GORD stages was evaluated in the study set selected for the present application. The results show that symptom relief rates are largely independent of the initial GORD stage of the patients. Only for the symptom heartburn, symptom relief rates were somewhat higher in Group 1 in comparison to Group 0 (NERD) patients and a decrease in the symptom relief rates with higher stages of erosive GORD was observed. Altogether, differences between GORD stage groups were small. These results provide reassurance that patients using pantoprazole in a non-prescription setting will benefit from symptom relief during short-term treatment with pantoprazole without diagnostic endoscopy prior to treatment.

Out of the 15 supportive studies, the results of study FK3059 are of particular interest for the intended non-prescription use of pantoprazole. In this trial, patients were entered based on the presence of reflux symptoms without endoscopic examination. Therefore, with regard to the inclusion criteria, the patient population in this study closely resembles the intended patient population for non-prescription pantoprazole. The study was a double-blind comparison of pantoprazole 20 mg and ranitidine 300 mg once daily in patients with reflux-related symptoms (heartburn, acid regurgitation or pain on swallowing) of at least ‘rather severe’ intensity on a 7-point Likert Scale. The results of the study are presented in table 8. The differences between the treatment groups were statistically significant.

Table 8 Results with regard to “Free from key GORD symptoms” in study FK3059

	ITT		**PP**	
	n	**Free from key GORD symptoms n (%)**	**n**	**Free from key GORD symptoms n (%)**
Total	338	188 (55.6)	284	169 (59.5)
Pantoprazole	167	114 (68.3)	136	98 (72.1)
Ranitidine	171	74 (43.3)	148	71 (48)

Clinical safety

- Patient exposure

During drug development more than 250 clinical studies on pantoprazole tablets have been carried out in about 80,500 patients. In most studies daily doses ranged from 20 to 80 mg; however, in particular settings higher doses up to 320 mg p.o. and 240 mg i.v. were given. The applicant considers that 94 of these clinical studies involving 26,615 patients are relevant to the safety aspect of this application.

From the first launch of pantoprazole 733,000 pantoprazole treatment courses were documented in Post-Authorisation Safety Studies. These studies, which reflect the use of the product in medical practice as compared to the scientific setting of clinical studies with strict inclusion and exclusion criteria, contributed to the safety profile of pantoprazole.

The worldwide post-marketing patient exposure based on sales data is approximately 665 million patients.

- Adverse events

Table 9 lists adverse drug reactions, number of patients who experienced these adverse drug reactions in the overall data set and the calculated weighted mean of the study-specific frequencies.

Table 9 Overview of adverse drug reactions

Adverse drug reaction	Number of patients with this adverse drug reaction	Calculated weighted mean of frequency (per 1,000 patients)
Diarrhoea	264	10.18
Headache	225	8.63
Nausea / Vomiting	152	5.16
Abdominal distension and bloating	150	5.48
Abdominal pain and discomfort	140	4.87
Constipation	95	3.28
Dizziness	75	2.83
Liver enzymes increased (transaminases, γ-GT)	62	2.56
Rash / Exanthema / Eruption	44	1.85
Pruritus	44	1.68
Sleep disorders	40	1.58
Dry mouth	36	1.35
Asthenia, fatigue and malaise	27	1.14
Hyperlipidaemias and lipid increases	23	0.95
Disturbances in vision / Blurred vision	18	0.62
Hypersensitivity (incl. anaphylactic reaction and anaphylactic shock)	15	0.52
Depression (and all aggravations)	13	0.49
Urticaria	13	0.40
Weight changes	12	0.48
Arthralgia	10	0.37
Myalgia	8	0.25
Bilirubin increased	6	0.25
Oedema peripheral	5	0.17
Body temperature increased	4	0.16
Angioedema	3	0.09
Leukopenia	2	very rare
Disorientation (and all aggravations)	1	very rare
Thrombocytopenia	1	very rare

Adverse drug reactions reported from Post-Authorisation Safety Studies showed similar patterns to adverse drug reactions from clinical studies. No new adverse drug reactions, or an increased frequency of known adverse drug reactions, or any other risk that might affect the safe use of the drug has been detected in Post-Authorisation Safety Studies.

A case-controlled study on Clostridium difficile associated diarrhoea based on the UK GPRD database showed that 12% of the cases had a history of GORD. However, this is not considered representative for the general population.

- Serious adverse event/deaths/other significant events

The most frequently reported serious adverse events with pantoprazole in clinical trials were surgery, chest pain, injury and abdominal pain. With regard to serious adverse events for which causality to pantoprazole was assessed as related by the investigator, 41 events were reported (18 of these from the SOC 'gastrointestinal disorders'). Serious adverse drug reactions have therefore been rare. Among serious adverse events assessed as related to pantoprazole, the most frequently reported events were diarrhoea, abdominal pain, headache, nausea, chest pain, and rash.

Thirteen patients died in the clinical trials among the pantoprazole-treated population. All these cases with fatal outcome were finally assessed by the investigator as 'unrelated' to pantoprazole.

- Safety in special populations

Clinical trials have been performed in special patient populations, such as children, the elderly and renal- or liver-impaired patients. With regard to the latter, no adverse events have been reported in patients with liver cirrhosis, and most adverse events reported among patients with hepatic impairment, including changes in laboratory results or vital signs were considered unrelated to pantoprazole. With regard to elderly or renal-impaired patients, special safety and pharmacokinetic studies showed that pantoprazole was safe, and that no dose adjustment was necessary.

Treatment of children is not intended in the present application in the non-prescription setting. Clinical trial data did not indicate any specific safety issue in this patient population and the oral prescription-only product is approved for adolescent patients.

- Post marketing experience

The applicant has conducted an overall analysis of post-marketing data. Overall, 11,153 case reports have been received with 20,697 associated adverse event terms; 1,599 cases (14.3%) were regarded as serious; the serious reports comprised 3,793 associated terms, of which 2,982 were serious adverse events.

Considering the most frequently reported adverse events and serious adverse events overall, the most affected system organ class was 'gastrointestinal disorders' (30% of all adverse events). Further affected system organ classes included mainly 'nervous system disorders', 'General disorders and administration site conditions', 'skin and subcutaneous tissue disorders', and 'investigations'. The most frequent adverse events (≥5%) included diarrhoea, headache, and nausea. These findings are consistent with the information collected in the clinical trial setting.

During the post-marketing period, 1,314 reports of unlisted serious adverse drug reactions have been received worldwide. The analysis of these serious unlisted adverse drug reaction cases did not point to any new safety concern with regard to pantoprazole treatment.

123 cases of death were recorded during the post-marketing period. Seven deaths were assessed as having a 'possible' relation to the drug. They included six patients who suffered from toxic epidermal necrolysis (TEN), and one patient with Stevens-Johnson syndrome (SJS).

During the post-marketing period 91 cases with drug exposure during pregnancy has been reported. In 43 cases the outcome was a normal baby. Although spontaneous abortions and premature births did not occur with higher frequency, because animal studies have shown reproductive toxicity (signs of slight fetotoxicity were observed at doses above 5 mg/kg), patients are advised not to use pantoprazole during pregnancy. There were five post-marketing reports concerning lactating women, none of which resulted in a safety concern.

No increased risk of the treatment with pantoprazole in patients with renal impairment or impaired liver function has been detected in the post-marketing period.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The CHMP did not require the MAA to submit a risk management plan because of the long safety record in Europe since 1994, its large patient user base as well as the product's wide therapeutic window. The application is based on a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified. The 20-mg strength, which is intended for the non-prescription market, has been widely used in the prescription-only setting and it is considered that the use in the proposed indication without a medical prescription does not mandate a risk management plan.

The PSUR submission schedule for PANTOZOL Control 20 mg gastro-resistant tablets should follow the PSUR submission schedule of the reference medicinal product.

2.6 Legal Status

The applicant requested the supply of the medicinal product to be classified as non prescription medicine meaning that the criteria of Article 71 of Directive 2001/83/EC, as amended, do not apply. For the assessment of this request, the criteria as laid down in the Commission Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use are being applied.

- Direct danger

Pantoprazole has been available on prescription for 14 years and its safety profile is well documented. There are no direct safety issues that preclude pantoprazole being available as a non-prescription medicine. The product information warns against the use of pantoprazole in certain conditions such as pregnancy and with certain other medications such as oral anticoagulants.

Additional information on the available safety data from Sweden where pantoprazole 20mg is available non-prescription were provided. Between 01 February 2000 and 12 December 2007 3 cases concerning the intake of 20 mg pantoprazole and 3 cases with unknown dosage of pantoprazole have been spontaneously reported. Five cases were serious/labelled and recovered without sequelae. One case was serious/unlabelled and recovered without sequelae. Acknowledging a potentially significant under-reporting, there is no evidence that non-prescription supply in Sweden raised any concerns over the issue of incorrect self-assessment. The available evidence provided does not suggest that non-prescription supply of pantoprazole alters the known safety profile of this product.

- Indirect danger

Indirect danger may arise by masking any serious underlying conditions such as an upper gastrointestinal tumour or myocardial infarction if the patient erroneously assesses his or her symptoms (with the help of the pharmacist as appropriate) as caused by gastro-oesophageal reflux. However, patients with alarming symptoms indicative of gastrointestinal malignancy (such as unintentional weight loss, bleeding, dysphagia, abdominal pain etc.) will normally see a physician. Additionally, patients with symptoms related to conditions other than GORD will not experience

improvement after 2 weeks of treatment or they will need longer than 4-week treatment and therefore will see a doctor. Symptoms of myocardial infarction are usually serious and develop suddenly. Patients with new symptoms will be referred to a doctor. Additionally, non-prescription supply of pantoprazole will be indicated for patients with reflux-like symptoms described as heartburn and regurgitation. Patients with chest pain will be excluded from non-prescription supply. Appropriate advice to minimise the risk for an indirect danger will be included in the package leaflet so that patients will be able to follow this guidance without involvement of the pharmacist.

Based on the available information regarding potential serious underlying conditions together with adequate product information it is considered that indirect danger is minimal.

- Self-assessment

It is acknowledged that a patient's first contact with a healthcare professional for GORD symptoms is typically during a visit of the pharmacy. The initial GORD treatment is symptom-based rather than pathogenesis-based. Proton pump inhibitors are often prescribed as first-line treatment for GORD. Products for the treatment of reflux-like symptoms are available over-the-counter in a number of countries worldwide where patients' ability to self-select OTC medicines for GORD is accepted.

Actual use studies showed that around 80% of patients are able to self-select non-prescription medication for reflux-symptoms correctly. The results of a published study conducted in the US showed that a high proportion of patients self-selected omeprazole correctly[1]. Among those who did not meet the non-prescription inclusion criteria, 9.5% had contraindicated symptoms. However, the majority of these patients consulted a doctor and none of them used the study medication longer than 14 days. No further information on the contraindicated symptoms or the consequences of the treatment is available. There were only 2% of patients who took the study medication longer than 4 weeks. The majority of subjects who took the study medication longer contacted a healthcare professional, which is reassuring.

- Risk and consequences of incorrect use

There are no concerns in relation to incorrect use or intentional misuse. Additionally, the proposed small pack size minimises the risk for abuse or misuse.

- Patient information

The package leaflet and the labelling are considered adequate to contribute effectively to the safe and effective use of the medicine including appropriate guarding that the non-prescription medicine is not used where it is contraindicated or unsafe. The written information clearly expresses when the medicinal product should not be used. A user testing of the package leaflet has been performed in accordance with the legislation.

The available experience with pantoprazole 20 mg orally is considered sufficient for assessing the proposed non-prescription status, and the documented use relevant for the proposed indication and age group of PANTOZOL Control. Overall, the CHMP considers that the supply as non-prescription medicine is appropriate. It is noted that specific aspects of the national implementation of a non-prescription status vary amongst Member States.

2.7 Data exclusivity

With reference to Article 74a of Directive 2001/83/EC, as amended, the applicant requested one year data exclusivity for the data submitted for the change of the classification of the medicinal product

[1] FENDRICK AM et al., Self-Selection and Use Patterns of Over-the-Counter Omeprazole for Frequent Heartburn, Clinical Gastroenterology and Hepatology 2004;2:17–21

from prescription to non-prescription. Such exclusivity requires that the change of classification "has been authorised on the basis of significant preclinical tests or clinical trials".

The justification of the applicant was based on 6 'non-published' studies, 5 full and one published by abstract only, which have been provided in support of the application (BY1023/BGI022, BY1023/BF010, BY1023/ESP009, BY1023/MEX020, BY1023/FK3037 and BY1023/VMG309). It was stated that these 6 studies support the proposed new indication and treatment duration by providing at least one symptom recording point of reflux-related symptoms during the first 14 days of treatment with pantoprazole and therefore are considered significant for the application. Study BY1023/BGI022 was particularly emphasised. During the procedure, the applicant further substantiated the justification. The applicant emphasised that these studies demonstrated efficacy in the non-prescription setting regarding the proposed indication and related posology which differs from that of the prescription product. The applicant, in addition to study BGI022 (CSR 257/2004), referred to study MEX020 (CSR 200/2004). The applicant also referred to studies BF010 (CSR 298E/99) and VMG309 (CSR 323/2004) which were considered to provide data for early onset of relief of reflux symptoms. Overall the applicant considered that the new data from the aforementioned studies added significant support to the classification as non-prescription product as they provided both effect and relevance to the assessment.

The CHMP reviewed the clinical data submitted, taking into account the provisions of Article 74a of Directive 2001/83/EC, as amended, in support of the classification of PANTOZOL Control 20 mg gastro-resistant tablets as 'medicinal product not subject to medical prescription'.

Out of the 17 studies submitted in support of the application, the following 11 studies did not form the basis of the applicant's request for data exclusivity:

Study No. ***(CSR No.)***	**Primary Objective**	**Secondary Objective**	**Treatment**	**Duration**	**N (ITT)**	**Results**
BY1023/BGSA017 ***(245/98)***	Relief of heartburn in GORD Stage 0	Time to freedom from key GORD symptoms	Pan 20, Placebo	2 weeks	219	Pantoprazole was superior to placebo
BY1023/FK3059 ***(93/2001)***	Relief of key symptoms in GORD after 28 days	Relief of key symptoms in GORD after 14 days	Pan 20, Ran 300 once daily	4 weeks	338	Pantoprazole was superior to ranitidine
BY1023/VMG306 ***(302/98)***	Relief of symptoms in GORD Stage 0/I after 4 weeks of treatment	Leading symptom relief after 2 weeks of treatment	Pan 20, Ran 150 bid	4 weeks	356	Pantoprazole was superior to ranitidine
BY1023/VMG305 ***(301/98)***	Relief of symptoms in GORD Stage 0/I after 4 weeks of treatment	Relief of GORD symptoms after 2 weeks of treatment	Pan 20, Lan 15	4 weeks	375	Pantoprazole was non-inferior to lansoprazole after 4 weeks of treatment
BY1023/M3-316 ***(152/2003)***	Relief of symptoms in GORD Stage A-D	Assessment of GI symptoms at day 14 and 28	Pan 20, 40	4 weeks	421	Pantoprazole was effective and well tolerated
BY1023/M3-320 ***(170/2003)***	Time to first symptom relief of GORD-related symptoms in GORD Stage 0	Relief of GORD-related symptoms after 14 and 28 days	Pan 20, Eso 20	4 weeks	529	Both PPIs were comparably effective; pantoprazole was non-inferior to esomeprazole
BY1023/FK3034 ***(166/95)***	Endoscopic healing of GORD Stage I	Relief of leading GORD symptoms and other GI symptoms	Pan 20, Ran 300 once daily	4/8 weeks	209	Pantoprazole was significantly more effective than ranitidine

BY1023/BGSA006 ***(208/95)***	Endoscopic healing of GORD Stage I	Relief of leading GORD symptoms and other GI symptoms	Pan 20, Ran 300 once daily	4/8 weeks	201	Pantoprazole was significantly more effective than ranitidine
3001A1-300-US ***(319E/98)***	Endoscopic healing erosive esophagitis	Relief of typical GORD symptoms	Pan 10, 20, 40, Pla	4/8 weeks	603	Pantoprazole was significantly more effective than placebo
3001A1-301-US ***(320E/98)***	Endoscopic healing erosive esophagitis	Relief of typical GORD symptoms	Pan 20, 40, Niz 150 bid	4/8 weeks	243	Pantoprazole was significantly more effective than nizatidine
BY1023/UK005 ***(303/98)***	Endoscopic healing of GORD Stage I after 4 weeks	Endoscopic healing of GORD Stage I after 8 weeks, Improvement of GORD symptoms after 2 and 4 weeks	Pan 20, Ome 20	4/8 weeks	327	Pantoprazole and omeprazole were similarly effective

CSR = Clinical Study Report, N = Number of Patients, Eso = Esomeprazole, Lan = Lansoprazole, Niz = Nizatidine, Ome = Omeprazole, Pan = Pantoprazole, Pla = Placebo, Ran = Ranitidine, bid =twice daily

Based on the above results the CHMP considered the following:

- pantoprazole 20mg is effective in the short-term treatment of GORD symptoms
- the applicant's justification to extrapolate the results of these studies to the proposed non-prescription setting is acceptable
- the safety profile of pantoprazole is well established and acceptable.

Out of the 17 studies provided by the applicant, the following 6 studies formed the basis of the applicant's request for data exclusivity:

Study No. ***(CSR No.)***	**Primary Objective**	**Secondary Objective**	**Treatment**	**Duration**	**N (ITT)**	**Results**	**Comments**
BY1023/BGI022 ***(257/2004)***	Relief of heartburn in GORD Stage 0/I at day 14	Relief of heartburn in GORD Stage 0/I at day 28	Pan 20, Ran 150 bid	4 weeks	344	Pantoprazole was superior to ranitidine in the relief of GORD symptoms	Results are similar to published studies (FK3059, VMG306, FK3034 and BGSA006)
BY1023/BF010 ***(298E/99)***	Relief of heartburn in GORD Stage 0	Quality of life, Time to heartburn relief	Pan 20, Ome 10	4/8 weeks	331	Both medications were similarly effective	Published studies showed non-inferiority of pantoprazole compared to other PPIs (Study VMG305 and M3-320)
BY1023/VMG309 ***(323/2004)***	Relief of heartburn in GORD Stage I after 1 and 2 weeks of treatment	Relief of GORD symptoms, Time to heartburn relief	Pan 20, Ome 10	2 weeks	521	Both PPIs were comparably effective; pantoprazole was non-inferior to omeprazole, non-significant primary endpoint	Published studies suggest non-inferiority of pantoprazole compared to other PPIs (Study VMG305 and M3-320)
BY1023/ESP009 ***(396/2004)***	Endoscopic healing of GORD Stage I after 8 weeks of treatment	Endoscopic healing of GORD Stage I after 4 weeks of treatment	Pan 20, Ran 150 bid	4/8 weeks	270	Pantoprazole was superior to ranitidine	Results are similar to published studies (FK3059, VMG306, FK3034 and BGSA006)
BY1023/MEX020 ***(200/2004)***	Endoscopic healing of GORD Stage I	Relief of GORD symptoms after 7 and 28 days of	Pan 20, Ome 10	4/8 weeks	346	Pantoprazole and omeprazole	Published studies showed non-inferiority of

		treatment				were similarly effective	pantoprazole compared to other PPIs (Study VMG305 and M3-320)
BY1023/FK3037 ***(105/96)***	Endoscopic healing of GORD Stage II/III after 4 and 8 weeks of treatment	Symptom relief at 2 and 4 weeks of treatment	Pan 20, 40, 80	4/8 weeks	322	There was no statistically significant difference between the treatment groups	Similar results were shown in the published study M3-316.

CSR = Clinical Study Report, N = Number of Patients, Eso = Esomeprazole, Lan = Lansoprazole,
Niz = Nizatidine, Ome = Omeprazole, Pan = Pantoprazole, Pla = Placebo, Ran = Ranitidine, bid =twice daily

With reference to the above 6 studies, the CHMP made the following observations (see also comments included in the above table):

- BGI022 (CSR 257/2004)
  In this pivotal study the differences between pantoprazole 20 mg and ranitidine 150 mg results were significant; however the unpublished study conclusion for BGI022 were very similar to those of the published ranitidine 150 mg comparative study VMG306 and overall does not add significant value to the application.

- BF010 (CSR 298E/99)
  This study compared the efficacy of omeprazole 10 mg versus pantoprazole 20 mg at day 28 in patients without oesophagitis established by endoscopy. No day 14 data was available in the study report. In the non-prescription product setting, the patient would be self-referring to their physician if no symptomatic relief was obtained by day 14, making this study of limited value in the non-prescription context. Additionally, the usual starting dose for omeprazole in reflux disease is 20 mg; 10 mg omeprazole is not therapeutically equivalent to 20 mg pantoprazole. The study contained a treatment phase C; days 29-56, but again, this is not relevant to a non-prescription indication of no more than 28 days. Overall this study provides no relevant data analogous to the initial non-prescription medication period of up to 14 days. Additionally, in other studies efficacy of pantoprazole was compared to other PPIs (lansoprazole, esomeprazole) and it was found to be non-inferior to these PPIs in relieving symptoms of heartburn and acid regurgitation (Study VMG305 and M3-320).

- VMG309 (CSR 323/2004)
  This study compared the efficacy of omeprazole 10 mg versus pantoprazole 20 mg after one and two weeks or treatment. Symptomatic relief was comparable between the products though no statistically significant differences could be found between the groups at the end of week 1. No week 2 relief rate analysis was provided. The findings of this study are in line with other published studies (Study VMG305 and M3-320), which showed that the efficacy of pantoprazole is non-inferior to other PPIs (such as lansoprazole and esomeprazole).

- ESP009 (CSR 396/2004)
  This study compared the efficacy of 20 mg pantoprazole once daily with 150 mg twice daily ranitidine in healing of oesophagitis and freedom from GORD symptoms after treatment. Pantoprazole was superior to ranitidine in the treatment of key GORD symptoms. Similar results were shown by study FK3059, VMG306, FK3034, BGSA006, which also showed superiority of 20 mg pantoprazole compared to 300 mg ranitidine in the treatment of reflux symptoms.

- MEX020 (CSR 200/2004)
  In this study the efficacy of 20 mg pantoprazole was compared to 10 mg omeprazole at day 28 in patients with reflux oesophagitis. The study concluded that pantoprazole 20 mg has a trend to have a faster relief of symptoms during the first 7 days of treatment compared with omeprazole 10 mg, but no statistically significant differences were found after 7 days, 4 weeks or 8 weeks treatment between the groups. 14 day data was not provided by this study. The shortcomings of this study are the same as described above for study BF010: lack of day 14 makes this study of limited value in the non-prescription context where the patient would be self-referring to their physician if no

symptomatic relief was obtained by day 14. The usual starting dose for omeprazole in reflux disease is 20 mg; 10 mg omeprazole is not therapeutically equivalent to 20 mg pantoprazole. Additionally, in other studies efficacy of pantoprazole was compared to other PPIs (lansoprazole, esomeprazole) and it was found to be non-inferior to these PPIs in relieving symptoms of heartburn and acid regurgitation (Study VMG305 and M3-320).

- FK3037 (CSR 105/96)
  This study compared the efficacy and tolerability of pantoprazole 20 mg, 40 mg, or 80 mg in healing of oesophagitis and freedom from GORD symptoms. The results showed that all of the above doses are effective and comparable in the treatment of GORD. Similar results were shown in the published study M3-316 which compared the efficacy of 20 and 40 mg pantoprazole in the treatment of GORD symptoms.

Whereas:

- to support clinical efficacy and safety, the application is based on the results of 17 clinical studies. None of the 6 above-mentioned studies provide data to support the proposed indication and treatment duration that could not be derived from the other 11 studies provided in the application. Therefore, the 6 above-mentioned studies do not provide clinical data which has genuine impact on the assessment of the application.

the CHMP concluded that the studies BY1023/BGI022, BY1023/BF010, BY1023/ESP009, BY1023/MEX020, BY1023/FK3037 and BY1023/VMG309 submitted by the applicant for which the claim of one year data exclusivity is sought, were not relevant and necessary to the classification of PANTOZOL Control 20 mg gastro-resistant tablets as 'medicinal product not subject to medical prescription'.

2.8 Overall conclusions, risk/benefit assessment and recommendation

Quality

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance.

Non-clinical pharmacology and toxicology

No additional nonclinical studies were required for this application. Based on the available data it is concluded that pantoprazole has a nonclinical safety profile comparable to that of other proton pump inhibitors. The relevant information is adequately reflected in section 5.3 of the SPC.

Efficacy

The results of clinical studies where symptomatic relief of GORD was investigated show that pantoprazole provides relief of heartburn and acid regurgitation during a short-term treatment course (2-4 weeks). The data from the main studies can be summarised as follows:

- In study BGSA017 the differences between pantoprazole and placebo in the relief from heartburn were statistically significant at 1 and 2 weeks in both the intent-to-treat and per protocol populations ($p<0.001$). Time until freedom from acid eructation was significantly different between the treatment groups ($p < 0.0001$). The time until freedom from heartburn and "all key GORD symptoms" was also significantly different between the treatment groups ($p < 0.001$). Other GI symptoms (epigastric pain, retrosternal tightness, nausea, vomiting etc.) showed a considerable decrease. The difference between the treatment groups was statistically significant ($p<0.001$).

- In study BGI022 the differences between the pantoprazole and ranitidine groups in the relief of heartburn were statistically significant in both the intent-to-treat and per-protocol populations at Day 14 ($p < 0.05$). At Day 28 heartburn relief observed with pantoprazole was higher than with ranitidine, but the differences were not significant (p=0.079 ITT, and p=0.088 PP, respectively). Results for the relief of acid regurgitation showed similar results. All other GORD symptoms (acid regurgitation, pain on swallowing, epigastric pain etc.) improved in most of the patients.

To further substantiate the appropriateness of the selection of main studies the results were compared with other studies where GORD symptoms were the primary efficacy endpoint and data on symptom relief were available for at least the first seven days of treatment. In these studies between 57 and 78% of patients reported relief from heartburn at day 7 and 73-83% at day 14. In terms of the acid regurgitation between 53 and 78% of subjects had freedom from symptoms at day 7 and between 73 and 80% at day 14. The corresponding results from the pivotal study BGSA017 are 67% at day 7 and 74% at day 14 for heartburn (no data from the ITT population is available for acid regurgitation) and from study BGI022 70% at day 14 for heartburn and 73% at day 14 for acid eructation (no data for day 7 available). The data from the additional studies are in line with the main studies, which is reassuring.

The CHMP noted that in the majority of the studies patients were included based on endoscopic examination rather than symptoms alone. Since the use as non-prescription medicine requires selection of the medicine based on symptoms the applicant was requested to explain how the results of the studies can be extrapolated to the proposed non-prescription indication and patient population. The applicant provided the results of a published study, which involved 3000 subjects as a random sample of the adult population of two Swedish municipalities[2]. 1000 of these subjects underwent endoscopic examination and 76.9% of them had macroscopically normal oesophagus. Of the 400 subjects with symptoms of gastro-oesophageal reflux disease, only 24.5% had erosive oesophagitis. In the 17 studies provided by the applicant 66.5% of the patients had normal oesophagus or mild oesophagitis, which is largely in line with the population of the published study. The results of the Swedish study therefore support that the study population of its main studies is applicable to the non-prescription setting where the majority of patients will have normal oesophagus or mild oesophagitis. In addition, the results of study FK3059 were considered highly relevant to the non-prescription setting as patients were enrolled without endoscopic examination. In this study pantoprazole was significantly better than ranitidine in providing symptomatic relief of GORD. Finally an analysis of heartburn response rates stratified by initial GORD stage was performed for the studies where the primary endpoint was freedom from heartburn. The objective was to explore if different GORD stage has an effect on the efficacy of pantoprazole. The differences between patients with GORD stage 0 vs. GORD stage I in the relief from heartburn rates in the pantoprazole group were not statistically different at day 7, 14 and 28. Taking together the available evidence it is considered that the results of the submitted studies can be generalised to the proposed non-prescription population.

It was noted by the CHMP that the maximum effect of proton pump inhibitors is experienced following a few days treatment, while antacids and histamine receptor antagonists exert their effect without delay. However, indirect data on the consumption of antacids during treatment with pantoprazole which was allowed in two studies show that, in spite of the slower effect of pantoprazole, this consumption was low. Information about the onset of pantoprazole's action and clarification that this medicine does not act immediately is included in the SPC and the Package Leaflet.

Safety

The patient exposure with pantoprazole is large and the product has a well established safety profile. In clinical studies the incidence of adverse events with pantoprazole was comparable to placebo (21.5% vs. 24%, respectively). The most frequently reported adverse events were nausea, diarrhoea and headache. The serious adverse event rates were 2.1% vs. 1.4% for pantoprazole and placebo,

[2] RONKAINEN J et al., 1 High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: A Kalixanda study report, Scandinavian Journal of Gastroenterology, 2005; 40: 275- 285

respectively. These included diarrhoea, abdominal pain, headache, nausea, chest pain and rash. Clinical studies in elderly patients and in patients with liver or kidney disease did not identify any concerns.

The most frequently reported adverse events during the post-marketing period included diarrhoea, headache and nausea. This is in line with adverse events reported from clinical studies. With regard to serious adverse events the most common were thrombocytopenia, angioedema, urticaria and hepatitis.

Seven deaths were reported to the applicant during the post-marketing period where there was a possible relation between pantoprazole and death. One of the cases included a patient with Stevens-Johnson syndrome and six cases included patients with toxic epidermal necrolysis. These cases were strongly confounded with all patients taking concomitant medications.

Conditions with special interest (rhabdomyolysis, pancytopenia, respiratory tract infections, hip fracture, cardiovascular events, pancreatitis, and serious skin reactions) identified during the post-marketing period do not raise concerns.

Overall, the low incidence rate of adverse events during the post-marketing period is reassuring. Pantoprazole is indicated for a range of acid-related gastrointestinal disorders. It is noted that the adverse drug reactions reported during the post-marketing period originated from a patient population received pantoprazole for different indications, not only for the proposed non-prescription indication of mild reflux-like symptoms.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

- User consultation

A user consultation has been performed with the proposed package leaflet. Based on the results it is considered that the leaflet is appropriate for its intended target audience.

Risk-benefit assessment

Benefits

As reflux symptoms are common and can affect the quality of life of the majority of sufferers a proton pump inhibitor is usually used as a first-line treatment. Pantoprazole 20mg provides an effective short-term treatment in mild reflux symptoms. Results of 17 randomized controlled clinical studies (i.e. two pivotal and 15 supportive studies), in which pantoprazole 20mg was investigated with regard to relief of reflux symptoms as a primary or secondary endpoint, have been presented. In the first pivotal study BGSA017 a daily dosage of 20mg pantoprazole was shown to be significantly superior to placebo in the complete relief from heartburn and acid regurgitation during a 2-week treatment course in GORD patients without endoscopic lesions. In the second pivotal study BGI022 pantoprazole 20mg was shown to be significantly superior to ranitidine 150mg twice daily in the complete relief of heartburn after 2 weeks of treatment in patients with endoscopically normal oesophagus or mild oesophagitis.

In a retrospective analysis using a standardized methodology, which included the 17 clinical studies selected for this application, pantoprazole 20mg was shown to be significantly superior to placebo and H2-receptor antagonists, and statistically non-inferior to other proton-pump inhibitors in the complete relief from heartburn after 1 and 2 weeks. Already after 1 week of treatment, rates of complete relief from heartburn between 54% and 81% were achieved with pantoprazole 20 mg. A further improvement in the heartburn relief rates was observed after 14 and 28 days of treatment. Analysis of the symptom acid regurgitation showed similar symptom relief rates after 1 week between 62% and 84% with pantoprazole 20 mg. Again a further improvement was observed after 14 and 28 days, respectively. Significant superiority of pantoprazole 20 mg in the complete relief of acid regurgitation over both placebo and ranitidine 150 mg twice daily was observed at day 14 in the pivotal studies BGSA017 and BGI022, respectively, and in six out of seven supportive studies.

The application concerns the supply as non-prescription medicine. Typically a patient with GORD symptoms sees a pharmacist in the first instance. Initiation of treatment of GORD is based on symptoms, and non-prescription products are used for this purpose. Data from actual use studies support the use of proton pump inhibitors in this setting. Given that there are no direct safety issues that preclude pantoprazole being available as a non-prescription medicine this supply classification is considered of benefit to the patients.

Risks

There is a long-standing safety experience with pantoprazole and its safety profile is well characterised and similar to those reported for other proton pump inhibitors. During extensive post-marketing experience, no safety concerns have been identified. The majority of adverse drug reactions were mild and transient in nature. They mostly referred to gastrointestinal and nervous system disorders such as diarrhoea, nausea, and headache.

Indirect danger to human health, even when the product is used correctly, may arise if the symptomatic treatment masks an underlying condition requiring medical attention. The patient information leaflet includes adequate advice that patients should consult a doctor if alarming symptoms are present or if symptoms are not improving within 2 weeks of treatment. Together with the labelling the written information available to the patient is considered adequate to contribute effectively to the safe and effective use of the medicine including appropriate guarding that the non-prescription medicine is not used where it is contraindicated or unsafe.

The proposed small pack sizes (7 and 14 tablet packs) is an additional measure to minimise any potential risk associated with incorrect use or unintentional misuse.

Balance

Reflux symptoms associated with GORD are in principle a suitable condition for treatment with non-prescription medicines. The efficacy of pantoprazole in the proposed indication and posology has been demonstrated. The safety profile of pantoprazole is established and allows the assessment according to the applicable criteria for non-prescription medicines.

Based on the review of data on quality, safety and efficacy the benefits of PANTOZOL Control outweigh the risks for the short-term treatment of reflux symptoms under the classification as medicinal product not subject to medical prescription.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of PANTOZOL Control indicated for “short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults”, as a medicinal product not subject to medical prescription was favourable and therefore recommended the granting of the marketing authorisation.

Furthermore, the CHMP reviewed the nonclinical and clinical data submitted by the applicant taking into account the provisions of Article 74a of Directive 2001/83/EC, as amended, and did not consider that the data submitted in support of the change of classification of the medicinal product were significant.