CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Previfect 20 mg gastro-resistant tablets Sandoz B.V., the Netherlands

pantoprazole (as sodium sesquihydrate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1808/001/DC
Registration number in the Netherlands: RVG 105877

16 February 2011

Pharmacotherapeutic group:	proton pump inhibitors
ATC code:	A02BC02
Route of administration:	oral
Therapeutic indication:	short-term treatment of reflux symptoms (e. g. heartburn, acid regurgitation) in adults
Prescription status:	Non-prescription
Date of authorisation in NL:	1 February 2011
Concerned Member States:	Decentralised procedure with AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, MT, NO, PL, PT, RO, SE, SI, SK, UK.
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Previfect 20 mg gastro-resistant tablets, from Sandoz B.V. The date of authorisation was on 1 February 2011 in the Netherlands. The product is indicated for short-term treatment of reflux symptoms (e. g. heartburn, acid regurgitation) in adults. A comprehensive description of the indications and posology is given in the SPC.

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

Pantoprazole is converted to its active form, a cyclic sulphenamide, in the acidic environment in the parietal cells where it inhibits the H^+, K^+-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach.
The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from heartburn and acid reflux symptoms is achieved in 1 week. Pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the active substance is given orally or intravenously.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Somac 40 mg gastro-resistant tablets which have been registered in Finland by Altana Pharma since 1994 (original product). In addition, reference is made to Somac, authorisations (other names for the innovator product are amongst others Pantoc, Pantorc, Pantoloc, Pantozol) in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Pantoloc 40 mg, registered in Denmark. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The drug substance, pantoprazole sodium sesquihydrate, is described in the Ph.Eur.*. The active substance is a white or almost white powder, which is freely soluble in water and ethanol, and practically insoluble in hexane. Pantoprazole sodium exists in two polymorphic forms: monohydrate and sesquihydrate. Pantoprazole has a chiral atom, therefore two possible enantiomers exist. Both manufacturers produce a racemic mixture.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product

Manufacture
All three DMF-holders utilize synthesis routes starting with one or two complex starting materials. The provided information on the synthesis scheme of these starting materials is sufficient for all three manufacturers and on the possible carry-over of used reagents, solvents, intermediates and side products.

Quality control of drug substance
The drug substance specification as applied by the MAH and drug product manufacturers is based on the requirements from the Ph. Eur. monograph. Adequate specifications to limit the potential impurities satisfactory data has been provided. APIs from the three sources are controlled on the impurities listed in the Ph.Eur. monograph (Impurities A-F) with the addition of one in-house impurity.

Stability of drug substance
Batch analysis by the drug product manufacturers has shown that drug substance from all three sources meet the requirements from the Ph.Eur. monograph. Different re-test periods and different storage conditions have been laid down for drug substance from the three sources.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Previfect 20 mg – are yellow, oval coated gastro-resistant tablets imprinted *20* in black.

The excipients are:
Tablet core - calcium stearate, microcrystalline cellulose, crospovidone (type A), Hydroxypropylcellulose (type EXF), anhydrous sodium carbonate, colloidal anhydrous silica.
Tablet coating - hypromellose, iron oxide yellow (E 172), macrogol 400, methacrylic acid – ethyl acrylate copolymer (1:1), polysorbate 80, ponceau 4R aluminium lake (E 124), quinoline yellow aluminium lake (E 104), sodium lauryl sulphate, titanium dioxide (E 171), triethyl citrate.

Printing Ink - macrogol 600, shellac, povidone, iron oxide black (E 172), iron oxide red (E 172), iron oxide yellow (E 172).
The tablets are packed into Al-OPA/Al/PVC blister packs or HDPE tablet containers with polypropylene screw caps including a dessicant insert.
The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
Although the application only concerns the 20 mg strength, the dossier was copied from procedures NL/H/727-728-750-751/01-02/DC, containing information of the 20 mg and 40 mg strengths. Only the information on the 20 mg has been assessed for this procedure. The use of the 40 mg strength in the bioequivalence study is deemed acceptable because the 20 mg and 40 mg tablet are dose proportional. Comparing dissolution studies for the proposed product and originator products have been provided

Manufacturing process
Two different manufacturing sites are proposed for the drug product. The MAH demonstrated that the crystalline form of the drug substance did not change during the manufacturing process. The chosen formulation is well explained, also in view of the acid labiality of the drug substance.

Quality control of drug product
Three full-scale batches from both manufacturing sites have been satisfactorily validated, including the as critical step regarded enteric coating step. The validation data show that the quality within full-scale batches and between full-scale batches is well under control. In general, adequate finished product specifications are applied. All batch results regarding the performance of the product (gastroresistance, dissolution, assay, impurities) are satisfactory.
The MAH has committed to improve the assay method as the observed variability is unacceptable. A proposal should be made on how this will be done and the improved method should be submitted within one year from now.

Stability tests on the finished product
With regard to stability no trends or significant changes have been observed. Based on additionally submitted stability data a shelf-life of 3 years in both proposed packaging materials (Al-OPA/Al/PVC blisters as well as HDPE containers) without specific storage temperature can be granted. The MAH placed twelve full-scale batches (six batches, three in blisters and three in containers, manufactured at one specific site) on stability. Additionally, the MAH placed twelve full-scale batches (six batches of each strength, three in blisters and three in containers, manufactured at another specific site) on stability.
To fully support the claimed shelf-life follow-up measures have been imposed. The MAH should submit updated stability data directly when available for both manufacturing sites, provide microbiological quality data at the end of shelf-life (3 years) and submit the results of the in-use stability study with the product at the end of shelf-life.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a generic formulation of Somac, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of pantoprazole sodium sesquihydrate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Pantoprazole sodium sesquihydrate is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Pantoprazole gastroresistant tablets 40 mg (HEXAL A/S, Denmark) compared with the pharmacokinetic profile of the reference product Pantoloc 40 mg gastroresistant tablets (Altana Pharma Denmark).

One additional bioequivalence study (single dose, fed conditions) was submitted by the MAH, but this study was rejected beceause of an inadequate sampling schedule. For this study, the absorption phase was not covered in 11 out of 42 evaluable volunteers, which not considered acceptable. Therefore, this study will not be discussed in this PAR.

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study – single-dose, fasted conditions
A randomised, single-dose, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 20-55 years. Each subject received daily a single dose (40 mg) of one of the 2 pantoprazole formulations. The tablet was orally administered with 240 ml water after a 10 hours fast. For each subject there were 2 dosing periods, separated by a washout period of at least 7 days.

Blood-samples were taken pre-dose and at 0.5, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Two subjects witdrew from the study for personal reasons. Thirty-eight volunteers completed the study and were eligible for pharmacokinetic evaluation.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pantoprazole under **fasted** conditions.

Treatment N = 38	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	5561 ± 792	6331 ± 1257	2423 ± 126	2.67 (1.33-5.0)	1.53 ± 0.23
Reference	5619 ± 786	6498 ± 1319	2631 ± 146	2.33 (1.33 4.5)	1.59 ± 0.25
***Ratio (90% CI)**	0.99 (0.95-1.04)	0.99 (0.94-1.03)	0.93 (0.88-0.99)	---	---
CV (%)	11.8	11.3	14.3	---	---

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life

**ln-transformed values*

Two subjects had a residual area above 20%.

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. The statistical analysis of the pharmacokinetic data was adequate. No statistically significant period effect was noted. Based on the pharmacokinetic parameters of pantoprazole under fasting conditions, it can be concluded that test Pantoprazole gastroresistant tablets 40 mg and the reference Pantoloc 40 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study - single-dose study, fed conditions
A randomised, single-dose, 2-way cross-over, bioequivalence study was carried out under fed conditions in 74 healthy male subjects, aged 20-55 years. Each subject received daily a single dose (40 mg) of one of the 2 pantoprazole formulations. The tablet was orally administered with 240 ml water after intake of a high-fat breakfast. For each subject there were 2 dosing periods, separated by a washout period of at least 7 days.

Blood-samples were taken pre-dose and at 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 15, 16, 17, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 23, 24, 26, 28 and 30 hours after administration of the products. The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
There were six withdrawals, i.e. three subjects withdrew for personal reasons and three withdrew due to adverse events. Pharmacokinetic parameters were determined per protocol for the sixty-eight subjects, who completed the study.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pantoprazole under **fed** conditions.

Treatment N = 68	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	5565 ± 4534	5970 ± 5916	2453 ± 751	7.0 (2.0-22)	1.6 ± 1.5
Reference	5977 ± 4853	6327 ± 6137	2768 ± 7712	6.0 (3.0-22)	1.5 ± 1.5
***Ratio (90% CI)**	0.93 (0.91-0.95)	0.93 (0.91-0.96)	0.88 (0.83-0.92)	---	---
CV (%)	61.8	65.2	25.0	---	---

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. The statistical analysis of the pharmacokinetic data was adequate. Based on the pharmacokinetic parameters of both pantoprazole under fed conditions, it can be concluded that test Pantoprazole gastroresistant tablets 40 mg and the reference Pantoloc 40 mg tablets are bioequivalent with respect to rate and extent of absorption after a high-fat breakfast, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results
The 20 mg gastro-resistant tablets are dose proportional with the 40 mg gastro-resistant tablets. The pharmacokinetics of the active substance are linear in the 20-40 mg dose range. Comparable dissolution of the 20 and 40 mg tablets has been sufficiently demonstrated. The results of the bioequivalence studies performed with the 40 mg strength therefore apply to the 20 mg strength.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Pantoprazole was first approved in 1994, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of pantoprazole can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the centrally approved Pantozol Control 20 mg gastro-resistant tablets (EU/1/09/517/001-004).

Readability test
The MAH has submitted a justification and declared that the PIL is prepared in accordance with the European Commission's readability guideline "*A Guideline on the readability of the label and package leaflet of medicinal products for human use*". This new Pantoprazole 20 mg gastro-resistant tablets package insert fulfils the guidelines as the successfully established Pantozol Control text is provided in the clear Sandoz package insert format, layout and design and therefore a further readability test is not necessary.
To conclude, it is not necessary to test the new Pantoprazole 20 mg gastro-resistant tablets package insert, according to the "*Guidance concerning consultations with target patient groups for the package leaflet*" and the CMD(h) Guidance from October 2007.

As a user testing of the package leaflet for "*Pantozol control*" has been performed in accordance with the legislation and also approved during the central procedure, this justification is accepted.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Previfect 20 mg gastro-resistant tablets have a proven chemical-pharmaceutical quality and are a generic form of Somac 20 mg gastro-resistant tablets. Somac is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Previfect 20 mg gastro-resistant tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 16 November 2010. Previfect 20 mg gastro-resistant tablets is authorised in the Netherlands on 1 February 2011. The prescription status is non-prescription.

European harmonised birth date has been allocated 23 August 1994 and subsequently the first data lock point for pantoprazole is August 2012. The first PSUR will cover the period from approval to August 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be 25 May 2013.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH has committed to improve the assay method as the observed variability is unacceptable. A proposal should be made on how this will be done and the improved method should be submitted within one year from now.
- The MAH committed to submit updated stability data directly when available for both manufacturing sites, provide microbiological quality data at the end of shelf-life (3 years) and submit the results of the in-use stability study with the product at the end of shelf-life.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached