CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Omeprazol Polpharma 40 mg, powder for solution for infusion Pharmaceutical Works Polpharma S.A., Poland

omeprazole

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/1361/001/MR
Registration number in the Netherlands: RVG 34322

19 November 2009

Pharmacotherapeutic group:	proton pump inhibitors
ATC code:	A02BC01
Route of administration:	intravenous
Therapeutic indication:	gastric antisecretory treatment in severely ill patients where oral therapy is inappropriate with reflux oesophagitis; duodenal or benign gastric ulcer; Zollinger-Ellison-Syndrome
Prescription status:	prescription only
Date of first authorisation in NL:	12 September 2007
Concerned Member States:	Mutual recognition procedure with PL
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 Omeprazol Polpharma 40 mg, powder for solution for infusion, from Pharmaceutical Works Polpharma S.A. The date of authorisation was on 12 September 2007 in the Netherlands.

The product is indicated for gastric antisecretory treatment in severely ill patients where oral therapy is inappropriate with:

- Reflux oesophagitis
- Duodenal or benign gastric ulcer
- Zollinger-Ellison-Syndrome.

A comprehensive description of the indications and posology is given in the SPC.

Omeprazole reduces gastric acid secretion through a unique mechanism of action. It is a specific inhibitor of the gastric proton pump in the parietal cell. It is rapidly acting and produces reversible control of gastric acid secretion with once daily dosing.
Intravenous administration of omeprazole results in an immediate reduction of intragastric acidity and a mean decrease over 24 hours of approximately 90% in patients with duodenal ulcer disease. A single 40 mg i.v. dose has similar effect on intragastric acidity over a 24 hour period as repeated oral dosing with 20 mg once daily. A higher dose of 60 mg i.v. twice daily has been used in a clinical study in patients with Zollinger-Ellison syndrome.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Losec, pulver til infusionsvaeske, opløsning which has been registered in Denmark by Astra Zeneca since 1989. In the Netherlands, Losec Infuus 40 mg (NL RVG 14439) has been registered since 1992. In addition, reference is made to Losec authorisations 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. As Omeprazol Polpharma 40 mg is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current 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.

No paediatric development programme has been submitted, as this is not required for a generic application.

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 active substance is omeprazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is very slightly soluble in water. It dissolves in dilute solutions of alkali hydroxides.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for four batches stored at 2-8 °C (36 months) and 25°C/60% RH (6 months). The batches were stored in double PE bags.
The proposed retest period and storage condition are justified.

** 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
Each vial of Omeprazol Polpharma 40 mg contains as active substance 42.6 mg omeprazole sodium equivalent to 40 mg omeprazole. The product is a white or almost white dry powder.

The powder for solution for infusion is packed in a colourless, type I glass injection vial with a 15 ml capacity and a protective cap consisting of 2 components: an aluminium frame and a chlorobutyl rubber stopper.

The excipients are: sodium hydroxide (for pH adjustment), disodium edetate.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients and packaging are usual for this type of dosage form. All excipients comply with the requirements in the relevant Ph.Eur. monographs. The amount of sodium hydroxide approximately corresponds to the estequiometric ratio for the ‘in situ’ formation of omeprazole sodium in the solution to be lyophilised. It is also used to stabilise the active substance which is described as being rapidly degraded in acid and even in neutral pH media.

Disodium edetate acts as a chelating agent, preventing any possible degradation of the omeprazole in solution due to its capacity to sequester trace amounts of metal ions which act as catalysts in degradation reactions. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
NaOH, disodium edetate and omeprazole are dissolved in water, the pH is determined. The bulk solution is double filtered under pressure. The solution is filled into pre-sterilised and de-pyrogenized vials (dry heat). The vials are partially stoppered. The vials are lyophilised. The vials are fully stoppered in the lyophiliser under vacuum. All processes are performed in class A and B (GMP) areas to ensure aseptic conditions during the process. Overages are not applied.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches.

Microbiological attributes
The product is sterile. Omeprazole degrades if it is subjected to high temperatures and exposed to radiation of any type. Consequently the product must be sterilized by aseptic filtration followed by aseptic lyophilisation and packaging processes.

Compatibility with standard infusion solutions
The SPC mentions dilution with glucose 5%. A stability study on the reconstituted solution (reconstituted with 5% glucose) is performed. The reconstituted solution (5% glucose) was investigated; the claimed shelf-life of six hours after reconstitution is justified.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, degradation, particulate matter, sterility, endotoxins, water, pH, and uniformity of dosage units The shelf-life specification show higher limits for degradation products. Both specifications are acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three full scaled batches, demonstrating compliance with the release specification.

Stability tests on the finished product
Stability data on the product have been provided on three pilot scaled batches stored at 25°C/60% RH (24 months right side up and upside down), 30°/60% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. The stability results show increase of water and two impurities in all conditions but more pronounced at the accelerated condition. All levels stayed within the proposed limits.
A shelf-life of 2 years was granted, with the storage condition ‘store below 25°C’.
The MAH committed to manufacture and validate three industrial size batches in order to carry out long term and accelerated stability studies. Results will be submitted to the competent authorities.
Stability data have been provided demonstrating that the product remains stable for 6 hours following reconstitution, when stored below 25°C. The MAH committed to perform a stability study on the reconstituted solution on 1 industrial size batch near to the end of shelf-life.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This product is a generic formulation of Losec 40 mg, 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 omeprazole 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

Omeprazole is a well-known active substance with established efficacy and tolerability.

Omeprazol Polpharma 40 mg, powder for aqueous solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Omeprazol Polpharma 40 mg is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Risk management plan

Omeprazole was first approved in 1987, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of omeprazole 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. 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 mutual recognition procedure is in accordance with the recently established SPC for procedure NL/H/1006/001/DC, concerning the product Omeprazol 40 mg PCH.

Readability test

The MAH adapted the proposed package leaflet to the leaflet established during procedure NL/H/1006/001/DC. This package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of three rounds including a pilot test. Overall the results indicate that the package leaflet was comprehensible and well understood. The package leaflet was considered to be of good quality and passed the test. Therefore, it was not deemed necessary to perform an additional test on the PL for this specific product.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Omeprazol Polpharma 40 mg, powder for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Losec 40 mg, powder for solution for infusion. Losec 40 mg is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

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

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other omeprazole containing products.

The Board followed the advice of the assessors. Omeprazol Polpharma 40 mg, powder for solution for infusion was authorised in the Netherlands on 12 September 2007.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Omeprazol Polpharma 40 mg with the reference product, and has therefore granted a marketing authorisation. The mutual recognition procedure was finished on 14 August 2008.

A European harmonised birth date has been allocated (15 April 1987) and subsequently the first data lock point for omeprazole is April 2009. The first PSUR will cover the period from August 2008 to April 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 14 December 2012.

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

Quality - medicinal product

- The MAH committed to manufacture and validate three industrial size batches in order to carry out long term and accelerated stability studies. Results will be submitted to the competent authorities as they become available.
- The MAH committed to perform a stability study on the reconstituted solution on 1 industrial size batch near to 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
PL	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