PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Omeprazol Sandoz injectie 40,
powder and solvent for solution for injection 40 mg
Sandoz B.V., the Netherlands

omeprazole sodium

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/0688/001/DC
Registration number in the Netherlands: RVG 33290

27 May 2009

Pharmacotherapeutic group: Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), proton pump inhibitors
ATC code: A02BC01
Route of administration: parenteral; intravenous use
Therapeutic indication: As alternative treatment of the oral formulation where fast and pronounced acidity inhibition is required for: Duodenal ulcer, benign gastric ulcer, reflux oesophagitis, Zollinger-Ellison syndrome.

Prescription status: prescription only
Date of authorisation in NL: 19 May 2009
Concerned Member States: Decentralised procedure with DK.
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 Sandoz injectie 40, powder and solvent for solution for injection 40 mg, from Sandoz B.V., the Netherlands. The product is indicated as alternative treatment of the oral formulation where fast and pronounced acidity inhibition is required for: Duodenal ulcer, benign gastric ulcer, reflux oesophagitis, Zollinger-Ellison syndrome.

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

Omeprazole, a substituted benzimidazole, is a gastric proton pump inhibitor, i.e. omeprazole directly and dose-dependently inhibits the enzyme H⁺,K⁺-ATPase, which is responsible for the gastric acid secretion in the gastric parietal cells. Due to this selective intracellular mode of action and the low affinity for other membrane-bound receptors (such as the histamine H₂, muscarine M₁ or gastrinergic receptors), omeprazole has been assigned to a separate class of acid-inhibiting agents, which block the final step of acid production. As a consequence of its mode of action, omeprazole leads to an inhibition of both basal and stimulable acid secretion, irrespective of the stimulus type. Thus, omeprazole increases the pH-value and reduces the volume of gastric acid secretion.

This application concerns a generic application claiming essential similarity with the innovator product Losec, powder and solvent for solution for injection 40 mg (NL License RVG 12439), containing 40 mg omeprazole, which has been registered in the Netherlands by AstraZeneca B.V. since 1988. In addition, reference is made to Losec, powder and solvent for solution for injection 40 mg 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 Sandoz injectie 40 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.

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 sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). 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. The drug substance is a white or almost white hygroscopic powder that is freely soluble in water and in alcohol, soluble in propylene glycol, and very slightly soluble in methylene chloride. Omeprazole has one chiral centre and is produced as a racemate. Omeprazole sodium exists in amorphous and at least five crystalline forms.
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for residual solvents, bacterial endotoxins and microbiological quality. Batch analytical data demonstrating compliance with this specification have been provided for 3 pilot-scale batches for one manufacturer. After marketing authorisation another manufacturer of the active substance was added by a type IA variation (see table Steps taken after finalisation of the initial procedure at Page 8). Batch analytical data demonstrating compliance with this specification have been provided for 1 batch for one manufacturer.

The Active Substance Master File (ASMF) procedure is used for one manufacturer of the active substance omeprazole sodium. 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.

The CEP procedure is used for the other manufacturer of 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 suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, and 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 Ph.Eur.

Stability data on the active substance for one manufacturer have been provided for 3 production batches in accordance with applicable European guidelines demonstrating the stability of the active substance when stored under the stated conditions. Based on the data submitted, a retest period could be granted of 3 year when stored in the original package (in order to protect from humidity and light, see also NL/H/0688/001/IB/003, on Page 8). For the other manufacturer stability data show that the active substance is stable for 9 months when stored under the stated conditions.

Medicinal Product

Composition
Omeprazol Sandoz injectie 40, powder and solvent for solution for injection, contains as active substance 42.56 mg omeprazole sodium, equivalent to 40 mg omeprazole. The powder for solution for injection is a white to almost white powder. The solvent for solution for injection is a clear solution.

The powder for solution for injection is packed in a 10 ml colourless glass vial Type I with a rubber stopper, and an aluminium cramping cap with propylene cap. The solvent for solution for injection is packed in a 10 ml colourless glass ampoule Type I. Before administration each vial is mixed with one ampoule of solvent. The product is intended for single use.

The excipients used are:
Powder for solution for injection: sodium hydroxide
Solvent for solution for injection: Macrogol 400, citric acid monohydrate, water for injections.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The packagings are usual and suitable for the product at issue.

The objective was to develop a product that would be bioequivalent with the innovator product Losec, powder and solvent for solution for injection 40 mg.
The excipients are common in the manufacture of parental formulations. All excipients comply with the requirements laid down in their respective Ph.Eur. monographs.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 consecutive production batches of omeprazole powder for injections and 3 consecutive batches of solvent for powder for injection in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification for the powder includes tests for appearance, particulate matter, water, identification, assay, uniformity of dosage units, related substances and sterility. For the solvent requirements have been adopted for, appearance, particulate matter, sterility, endotoxins, extractable volume and pH.. For the reconstituted solution the specification includes tests for appearance, particulate matter, assay, degradation and pH. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site(s) has been provided for 3 batches of powder and 3 batches of solvent, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches of the powder and 3 batches of the solvent in accordance with applicable European guidelines, demonstrating the stability of the product for 18 months. On basis of the data submitted a shelf life was granted of 24 months. The labelled storage conditions are for the powder and solvent for solution for injections: “Do not store above 25°C. Store in the original package in order to protect from light.” The MAH committed to submit stability data covering the shelf-life period of 24 months. By a type IB variation (NL/H/0688/001/IB/006, see also Page 8), the shelf life of the solvent for solution for injection has been changed from 2 years into 3 years.

Chemical and physical in-use stability data have been provided demonstrating that the reconstituted solution remains stable for 4 hours following reconstitution, when stored below 25°C. The reconstituted solution remains stable when stored for 24 hours at 2-8°C.

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, powder and solvent for solution for injection 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 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.

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Losec, powder and solvent for solution for injection 40 mg marketed by AstraZeneca B.V.

Omeprazol Sandoz injectie 40 mg, powder and solvent for solution for injection 40 mg, is administered as an aqueous solution intended for intravenous injection containing the same active substance in the same concentration as the currently authorised reference medicinal product.

As Omeprazol Sandoz infuus 40 is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). Omeprazol Sandoz infuus 40 is a generic of the reference product Losec, powder and solvent for solution for injection 40 mg, which is already on the market in various European countries. Thus, all data regarding to safety and efficacy available of the reference medicinal product also apply to this application.

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. 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.

Readability test

The 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 two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been adequately performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Omeprazol Sandoz injectie 40, powder and solvent for solution for injection 40 mg, has a proven chemical-pharmaceutical quality and is a generic form of Losec, powder and solvent for solution for injection 40 mg. Losec 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 SPC is consistent with that of the reference product.

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. Braille conditions are met by the MAH.

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 bioequivalence has been demonstrated for Omeprazol Sandoz injectie 40, powder and solvent for solution for injection 40 mg with the reference product, and have therefore granted a marketing authorisation. Omeprazol Sandoz injectie 40 was authorised in the Netherlands on 19 May 2009.

A European harmonised birth date has been allocated (15-04-1987) and subsequently the first data lock point for omeprazole is April 2006. The first PSUR is therefore expected in April 2009, after which a PSUR should be submitted every 3 years.

The date for the first renewal will be: 19 December 2011

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

Quality – Medicinal product
- The MAH committed to submit stability data covering the shelf-life period of 24 months.
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
$C_{\text{max}}$ 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
$t_{\text{1/2}}$ Half-life
$t_{\text{max}}$ Time for maximum concentration
TSE   Transmissible Spongiform Encephalopathy
USP   Pharmacopoeia in the United States
<table>
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<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of procedure</th>
<th>Date of end of procedure</th>
<th>Approval /non approval</th>
<th>Assessment report attached</th>
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<tr>
<td>Submission of a new or updated Ph.Eur. Certificate for an active substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance; from a new manufacturer; other substances.</td>
<td>NL/H/0688/001/IA/001</td>
<td>Type IA</td>
<td>18-9-2007</td>
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<td>Change in batch size of active substance or intermediate, up to 10 fold compared to the original batch size approved at the grant of the marketing authorisation.</td>
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<td>Type IA</td>
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<td>Change in the re-test period of the active substance from 1 to 3 years.</td>
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<td>Type IB</td>
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<td>23-10-2007</td>
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<td>Type IB</td>
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<td>Increase of batch size of solution for powder for solution for injection</td>
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<td>Change in the shelf life of solvent for solution for injection from 2 years into 3 years.</td>
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