CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Omeprazol Sandoz infuus 40, powder for solution for intravenous infusion 40 mg
Sandoz B.V., the Netherlands

omeprazole (as 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/0719/001/DC
Registration number in the Netherlands: RVG 33439

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Pharmacotherapeutic group:	Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), proton pump inhibitors
ATC code:	A02B C01
Route of administration:	intravenous
Therapeutic indication:	As alternative treatment of the oral formulation where 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:	8 October 2008
Concerned Member States:	Decentralised procedure with AT (withdrawn on 9-11-2007), BE, CZ, DK, EL (withdrawn on 25-2-2009), ES, FR, IT, PL, PT, SI and UK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 Omeprazol Sandoz infuus 40, powder for solution for intravenous infusion 40 mg from Sandoz B.V., the Netherlands. The first date of authorisation was on 8 October 2008 in the Netherlands. The product is indicated as alternative treatment of the oral formulation where 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 (PPI), 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 H_2, muscarine M_1 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 Infuus, powder for solution for intravenous infusion 40 mg (NL License RVG 14439), containing 40 mg omeprazole, which has been registered in the Netherlands by AstraZeneca B.V. since 1992. In addition, reference is made to Losec Infuus, powder for solution for intravenous infusion 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 infuus 40 is a product for parenteral use, it is exempted for performing a bioequivalence study (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.). 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 Master File (ASMF) 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, 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.

The CEP procedure is used for the second 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 suitablity 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.

Quality control of drug substance
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 from one manufacturer and 3 production batches from the other manufacturer.

Stability of drug substance
The active substance omeprazole sodium is stable for 18 months. The retest period is indicated on 1 year for one manufacturer and 18 months for the other manufacturer when stored at 2-8°C, without further storage conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** 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
Omeprazol Sandoz infuus 40, powder for solution for intravenous infusion 40 mg contains as active substance 42.56 mg omeprazole sodium, equivalent to 40 mg omeprazole. The powder for solution for infusion is a white to almost white powder.

The powder for solution for infusion is packed in 10 ml colourless glass vials Type I with a red bromobutyl rubber stopper, and an aluminium cramping cap with polypropylene cap.

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

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

The objective was to develop a product that would be equal to the innovator product Losec Infuus, powder for solution for intravenous infusion 40 mg.

Excipients
The used excipients are common in the manufacture of parenteral formulations. All excipients comply with the requirements in the relevant 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 4 consecutive production batches in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications are based on the monograph for parenteral preparations in the Ph.Eur. and in-house specifications. The specification for the powder includes tests for appearance, identity, assay, degradation, particulate matter, sterility, water, related substances and uniformity of dosage units. 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, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the product over 24 months. Based on the data submitted, a shelf life can be granted of 24 months. The labelled storage conditions of the powder for solution for infusion are: *"Do not store above 25°C. Keep vials in the outer carton in order to protect from light."*

Stability data have been provided demonstrating that the reconstituted solution remains stable for 6 hours for 5% glucose injection and 12 hours for 0.9% sodium chloride, when stored below 25°C. Chemical and physical in-use stability has also been demonstrated for 24 hours at 2-8°C when dissolved in both physiological saline solution and 5% glucose. The labeled storage conditions are: *"From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and aseptic conditions."*

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 Infusion, powder for solution for intravenous infusion 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.

Omeprazol Sandoz infuus 40, is administered as an aqueous solution intended for infusion 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 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 product (NfG CPMP/EWP/QWP 1401/98).The quantitative composition of Omeprazol Sandoz infuus 40 is entirely the same as the reference product Losec infuus, which is already on the market in various European countries. 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. Thus, all data regarding to safety and efficacy available of the reference medicinal product also apply to this application.

CMD referral
The following contra-indication was acceptable for all concerned member states: *“Omeprazole is contraindicated in patients with hypersensitivity to omeprazole or to any of the excipients.”* and *“Omeprazole like other proton pump inhibitors should not be administered with atazanavir.”* However during the procedure a concern was raised regarding one proposed contra-indication in the SPC (section 4.3): “*Combination therapy with clarithromycin should not be used with hepatic impairment*.” Therefore, a referral to the CMD(h) was started.

In the CMD meeting of 15, 16 and 17 October 2007 the following was discussed:
A concern was raised regarding the clinical and pharmacokinetic evidence for the contra-indication “*Combination therapy with clarithromycin should not be used with hepatic impairment”.* The contra-indication was raised, as due to an impaired hepatic function, levels of clarithromycin and omeprazole may increase. Omeprazol is metabolised by CYP 3A4 which will be inhibited by clarithromycin, a strong CYP3A4 inhibitor. Due to this interaction between clarithromycin and omeprazole both drug levels may increase, which may in combination with an impaired hepatic function lead to a pronounced increase in drug plasma levels. No other data is available to further support the contraindication. Furthermore, a warning is already included in the SPC of clarithromycin regarding combination therapy with omeprazole, stating that this may lead to increased drug plasma levels.

Consensus was reached prior to the CMD(h) meeting. Agreement was reached that the need for the contra-indication is insufficient and the concerned member states agreed to delete the contra-indication "*Combination therapy with clarithromycin should not be used in patients with hepatic impairment."* from section 4.3, It was also agreed to add the following warning in section 4.4: *"During combination treatment caution should also be exercised in patients with renal or hepatic dysfunction (for dose restriction see section 4.2)"*

No harmonised European SPC text for the intravenous administration for omeprazole is available. The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Losec Infuus, powder for solution for intravenous infusion 40 mg marketed by AstraZeneca B.V.

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.

Readibility test

Not performed prelicensing.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Omeprazol Sandoz infuus 40, powder for solution for intravenous infusion 40 mg is a generic form of Losec Infuus, powder for solution for intravenous infusion 40 mg. Losec Infuus 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. Braille conditions are met by the MAH.

In the CMD(h) meeting held on the 15, 16 and 17 of October 2007 the following was discussed:
A concern was raised regarding the following contra-indication (section 4.3 SPC): *Combination therapy with clarithromycin should not be used with hepatic impairment.* Consensus was reached prior to the CMD(h) meeting. The SPC was to include in section 4.4 the following warning: *"During combination treatment caution should also be exercised in patients with* severe renal *or hepatic dysfunction (for dose restriction see section 4.2)"*

The SPC is consistent with that of the reference product, except for section 4.4.

The Board followed the advice of the assessors. Omeprazol Sandoz infuus 40, powder for solution for intravenous infusion 40 mg is authorised in the Netherlands on 8 October 2008. The member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Omeprazol Sandoz infuus 40, powder for solution for intravenous infusion 40 mg with the reference product, and have therefore granted a marketing authorisation.

A European harmonised birth date has been allocated (15 April 1987) and subsequently the first data lock point 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: 27 September 2012.

There were no post-approval commitments made during the procedure.

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 procedure	Approval/ non approval	Assessment report attached
Withdrawal of the Marketing Authorisation in Greece.	NL/H/719/ 001/DC	Withdrawal	---	25-2-2009	---	N
Repeat-use procedure with BG.	NL/H/719/ 001/E/001	E	18-9-2009	17-12-2009	Approval	Y, Annex I
Change in the name of the medicinal product in Belgium.	NL/H/719/ 001/IB/001	IB	28-5-2009	30-6-2009	Approval	N
Update dossier with module 1.6, 1.8, 1.9.	NL/H/719/ 001/II/002	II	30-3-2009	2-6-2009	Approval	Y, Annex II
Change in batch size of the active substance or intermediate. Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation. As a consequence of the scale-up, the manufacturing process is slightly amended.	NL/H/0719/ 001/IB/003	IB	8-6-2009	8-7-2009	Approval	N
Administrative changes: A.7 Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier).	NL/H/0719/ 001/IA/004	IA	23-6-2010	23-7-2010	Approval	N

Annex I – Repeat use procedure (NL/H/0719/001/E/001)

The Repeat use procedure started on 18 September 2009. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state (BG), on the basis of the data submitted, agreed that essential similarity has been demonstrated for Omeprazol Sandoz infuus 40, powder for solution for intravenous infusion 40 mg with the reference product, and have therefore granted a marketing authorisation. The repeat use procedure was finished on 17 December 2009.

A European harmonised birth date has been allocated (15 April 1987). The next PSUR will be awaited for April 2009. The PSUR submission cycle is 3 yearly.

The renewal date is 17 July 2012.

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

- The MAH has committed to submit a variation to update the version of the CEP ('R0-CEP 2004-101-Rev 01")
- The MAH has committed to submit a variation to update module 3.2.P.7 with the updated statement associated with TSE/BSE risk and red bromobutyl rubber.
- The MAH has committed to fully update the SPC and PIL to the outcome of the article 30 referral for Losec.

Annex II – Variation NL/H/0719/001/II/002 Update dossier

I. RECOMMENDATION

Based on the review of the data on safety the RMS and concerned member states approved the variation application NL/H/0719/001/II002 and NL/H/720/001/II/003 for Omeprazole Sandoz., indicated as alternative treatment of the oral formulation where pronounced acidity inhibition is required for duodenal ulcer, benign gastric ulcer, reflux oesophagitis, Zollinger-Ellison syndrome, for the following proposed changes or additions of pharmacovigilance system and risk management plan .

II. EXECUTIVE SUMMARY

II.1 Scope of the variation

The MAH submitted a type II variation to update the product information of omeprazol. Omeprazol is authorised through a Decentralised Procedure with The Netherlands acting as RMS. This variation is submitted to update the dossier before a Repeat Use procedure can be submitted. A pharmacovigilance system (PVS) (dated 20 February 2009, signed) was submitted. Furthermore, a statement regarding the need of a Risk Management Plan (RMP) (dated 28 April 2008) was submitted.

In this report, the PVS and RMP statement are assessed.

III. SCIENTIFIC DISCUSSION

III.1 Clinical safety

Pharmacovigilance System

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

Risk Management Plan

The MAH submitted a statement on the absence of a Risk Management Plan, and indicated that the current application concerns a generic product, for which the active ingredient that has been in use for many years, and has a well-established safety profile. Routine pharmacovigilance activities in accordance with EU regulations will be undertaken whilst the product is authorized. As the safety profile of the drug is well-established, a Risk Minimisation Plan is not considered necessary.

IV. OVERALL CONCLUSION

Pharmacovigilance System

The RMS considers that the Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The reasoning of the MAH is accepted. At present, no risk management plan is needed.