CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Esomeprazol SUN 40 mg powder for solution for injection or intravenous infusion Sun Pharmaceutical Industries Europe B.V., the Netherlands

esomeprazole (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/2156/001/DC
Registration number in the Netherlands: RVG 108387

18 March 2012

Pharmacotherapeutic group:	proton pump inhibitors
ATC code:	A02BC05
Route of administration:	intravenous
Therapeutic indication:	gastric antisecretory treatment when the oral route is not possible; prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers (see next page)
Prescription status:	prescription only
Date of authorisation in NL:	23 November 2011
Concerned Member States:	Decentralised procedure with DE, DK, ES, FR, IT, SE, 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 Esomeprazol SUN 40 mg powder for solution for injection or intravenous infusion from SUN Pharmaceutical Industries Europe B.V. The date of authorisation was on 23 November 2011 in the Netherlands.

The product is indicated for:
In adults
- gastric antisecretory treatment when the oral route is not possible, such as
  - gastroesophageal reflux disease (GERD) in patients with oesophagitis and/or severe symptoms of reflux
  - healing of gastric ulcers associated with NSAID therapy
  - prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.
- prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

In children and adolescents aged 1-18 years
- gastric antisecretory treatment when the oral route is not possible, such as:
  - gastroesophageal reflux disease (GERD) in patients with erosive reflux esophagitis and/or severe symptoms of reflux.

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

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.
Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+K^+-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Nexium i.v., powder for solution for injection or infusion 40 mg (NL License RVG 30091) which has been registered in the Netherlands by AstraZeneca B.V. since 23 January 2004 (MRP SE/H/0211/003). This pharmaceutical form was authorised as a line extension to the original Nexium dossier of 20 mg and 40 mg gastroresistent tablets (NL License RVG 25387-25388), registered since 15 August 2000 (MRP SE/H/0211/001-002). In addition, reference is made to Nexium i.v. 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 Esomeprazol SUN 40 mg is a product for parenteral use in aqueous solution, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

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 esomeprazole sodium, i.e. (S)-omeprazole sodium. It is the S-isomer of racemic omeprazole, the chiral center is at the sulphur atom. The drug substance is non-hygroscopic and freely soluble in water.
For esomeprazole sodium there is no monograph in the European Pharmacopoeia (Ph.Eur.*). However, Ph. Eur. Monographs are available for (RS)-omeprazole sodium and esomeprazole magnesium trihydrate, the preceding intermediate of esomeprazole sodium.

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/EMA 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.

Manufacturing process
The manufacturing process has been described and the choice of starting materials was explained. Synthesis schemes, specifications and discussions provided are satisfactory.

Quality control of drug substance
All other drug substance specifications are acceptable. The use of omeprazole RS working standard instead of Esomeprazole sodium working standard was sufficiently justified. The analytical methods have been fully and adequately validated. Batch analysis results have been provided on 3 batches esomeprazole sodium, with results meeting the set requirements.

Stability of drug substance
Stability data have been provided on three batches of drug substance, which were stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). Three more batches were placed on stability in an improved container closure system (9 months normal stability data available for one batch). Based on the data provided, a re-test period of 1 year was granted, when stored in tight, light resistant containers at 20°C to 25°C, excursion permitted between 15°C and 30°C.

** 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
Esomeprazol SUN 40 mg is a white to off white lyophilized powder, the reconstituted solution has a pH between 9.0 and 11.0 and osmolality between 300 and 350 mOsm.

The powder for solution for injection/infusion is packed in 5 ml colorless type-I tubular glass vial with grey rubber stopper and 20 mm grey flip off aluminum seal.

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

Pharmaceutical development
The development studies of the product have been satisfactorily performed and are sufficiently explained. The packaging is usual and suitable for the product at issue. The development of the product is mainly based on literature data and data on the qualitative composition of the reference product. A prototype batch was then prepared to study the compatibility of raw materials and primary packaging material and subjected to various drug product analyses. Potential degrading influences relevant for the product and important during critical manufacturing steps, have been discussed and investigated. Aseptic filtration was selected as a sterilisation method; this has been sufficiently justified.
There were no differences in assay results during the manufacturing process, and therefore use of overages was not considered necessary.

Microbiological attributes
The container closure integrity was evaluated by a microbial challenge and sterility tests. No evidence of microbial growth has been found showing the integrity of the container closure used for the drug product.

Manufacturing process
The manufacturing steps are described in sufficient detail including the applied in-process controls. The validation includes media fills, filtration validation, equipment qualification, container closure integrity tests, hold time studies of the unfiltered and filtered bulk solutions, validation of the washing and depyrogenation processes of the vials, sterilization of the rubber stoppers, filling, freeze drying process, capping process, leak testing, and visual inspections. Process validation has been performed on three batches.

Control of excipients
The excipients comply with the Ph. Eur. requirements. These specifications are acceptable.

Quality control of drug product
The specification includes tests for identification, water content, clarity and completeness of solution, constitution time, pH of constituted solution, osmololity, absorbance of solution, transmittance, particulate matter, bacterial endotoxins, sterility, uniformity of dosage unit, enantiomeric purity, related substances and assay. The provided qualifications, the set release and shelf-life specifications, are acceptable.
Validation data have been provided for the methods used. Batch analysis results were provided on 3 batches, with results are meeting the set requirements.

Stability of drug product
Stability data have been provided on 3 batches stored at 25°C/65% RH (1x 18 months, 2x 15 months) and 30°C/65% RH (all 12 months) and at 40°C/75% RH (6 months).
All intermediate testing and normal testing results meet the currently set specification. Only at accelerated conditions some results do not meet the set specification. Based on the available stability data, the granted shelf-life is 18 months. Based on the provided photostability results the accepted storage condition is “Store below 30°C. Store in the original package in order to protect from light.”

Compatibility/In-use stability
An admixture study of esomeprazole sodium for injection of both Esomeprazol SUN and innovator Nexium was done by reconstituting and diluting one or two vials containing 40 mg esomeprazol with 100 ml 0.9% NaCl leading to 0.4 and 0.8 mg/ml concentrations for a period of 12 hours. Comparable results were obtained at different time points tested.
A vial of Esomeprazol SUN 40 mg was also reconstituted with 5 ml of 0.9% sodium chloride for injection, to give a reconstituted solution concentration of 8 mg/ml. The reconstituted solutions were stored at room temperature at 30°C and samples were withdrawn after 0 hour and 12 hours. The study shows that the product was stable for 12 hours at room temperature at 30°C after reconstitution with 0.9% sodium chloride injection.

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 Nexium i.v., 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 esomeprazole 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

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

Esomeprazol SUN 40 mg powder for solution for injection or intravenous infusion is a aqueous parenteral formulation and 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 qualitative composition of Esomeprazol SUN 40 mg is 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
Esomeprazole was first approved in 2000, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of esomeprazole can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation 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 reference product Nexium i.v.

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 first round did not reveal any problems with the leaflet. In the second round the same leaflet was used and as the majority of the comments given by the interviewees were positive. No revisions have been made to the leaflet.
In conclusion, the readability of the PL meets the success criteria. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Esomeprazole SUN 40 mg powder for solution for injection or intravenous infusion has a proven chemical-pharmaceutical quality and is a generic form of Nexium i.v. 40 mg. Nexium 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 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 Esomeprazole SUN 40 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 19 October 2011. Esomeprazole SUN 40 mg powder for solution for injection or intravenous infusion was authorised in the Netherlands on 23 November 2011.

The date for the first renewal will be: 19 November 2014.

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
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