CBG MEB

Public Assessment Report

Scientific discussion

Esomeprazol SUN Pharma 40 mg powder for solution for injection/infusion

(esomeprazole sodium)

NL/H/3595/001/DC

Date: 12 July 2017

This module reflects the scientific discussion for the approval of Esomeprazol SUN Pharma 40 mg powder for solution for injection/infusion. The procedure was finalised on 10 January 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Esomeprazol SUN Pharma 40 mg powder for solution for injection/infusion, from Sun Pharmaceutical Industries Europe B.V.

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:
  - 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 SmPC.

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 through mutual recognition procedure 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 through mutual recognition procedure SE/H/0211/001-002. In addition, reference is made to Nexium i.v. authorisations in the individual member states (reference product).

The concerned member states (CMS) involved in this procedure were Germany, France, Italy and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Esomeprazol SUN Pharma is a white or almost white porous and uniform lyophilised powder for solution for injection/infusion.

The product contains as active substance 40 mg of esomeprazole, as 42.50 mg of esomeprazole sodium.

The powder is packed in a 10 ml type-I colorless glass vial with grey chlorobutyl stopper and flip-off aluminum seal.

The solution for injection (8 mg/ml) is prepared by adding 5 ml of 0.9% sodium chloride for intravenous use to the esomeprazole 40 mg vial. A solution for infusion is prepared by dissolving the content of one (40 mg) or two vials (80 mg) in up to 100 ml of 0.9% sodium chloride for intravenous use.

The reconstituted solution for injection/infusion is clear and colourless to very slightly yellow. The solution has a pH of 9.5-11.00.

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

II.2 Drug Substance

The active substance is esomeprazole sodium, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). However, Ph.Eur. monographs are available for (RS)-omeprazole sodium. Esomeprazole sodium is a white to yellowish white solid. The active substance contains one chiral sulphur atom and therefore exhibits stereoisomerism. Hence, there are two enantiomers, R and S. The active substance is the S-enantiomer. The R-enantiomer can be present as an impurity. The drug substance is very hygroscopic and freely soluble in water. Regarding polymorphism, it is shown that amorphous esomeprazole sodium is obtained.

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 consists of three steps. A flow-chart and detailed descriptions of the synthesis steps have been provided. The starting material is accepted.

Quality control of drug substance
The requirements of the Ph.Eur. monograph on esomeprazole magnesium stearate are applied on the final drug substance with stricter limits for two specified impurities and water content. Additionally residual solvents ethanol and dichloromethane are limited in line with the ICH limits. The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Six batches have been stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months). All results comply with specifications. A retest period of three years is accepted when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The development studies of the product have been satisfactorily performed and are sufficiently explained. The excipients and packaging are 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. The sterilisation method for Esomeprazol SUN Pharma 40 mg powder for solution for injection/infusion is an aseptic process, which is a common process to any lyophilised product. Use of overages was not considered necessary. Pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing steps are adequately described. The manufacturing process has been validated according to relevant European/ICH guidelines. The validation includes preparation of the formula, media fills, filtration validation, lyophilisation validation, validation of the production area and personnel and validation of the aseptic filling of the vials. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
The excipients used in the drug product are in accordance with the corresponding Ph.Eur. requirements. These specifications are acceptable.

Microbiological attributes
The vials comply with the sterility and bacterial endotoxin test carried out in accordance with the Ph.Eur. No evidence of microbial growth has been found showing the integrity of the container closure used for the drug product.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, pH, moisture content, air tightness, reconstitution time, clarity and colour of solution, uniformity of dosage units, assay, impurities, bacterial endotoxins, sterility and particles. The release and shelf-life acceptance criteria are identical except for moisture content, colour of solution, assay and impurities. 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 three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three batches that were stored at 25°C/65% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). At long term conditions all data remained within the specification. Results of a formal photostability study showed that the drug product was sensitive to light exposure. The claimed shelf life of 2 years with storage conditions 'Store below 30°C' and 'Store in the outer packaging in order to protect from light' is justified.

Also stability data have been provided for two batches of drug product after reconstitution. Chemical and physical in-use stability has been demonstrated for 12 hours at 30°C. From a microbiological point of view, unless the method of reconstitution precludes the risk of microbiological contamination, the product should be used immediately.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Esomeprazol SUN Pharma has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Esomeprazol SUN Pharma is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Nexium i.v., 40 mg which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate

additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Esomeprazole sodium is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Esomeprazol SUN Pharma 40 mg/ml powder for solution for injection/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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Esomeprazol SUN Pharma 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.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Esomeprazol SUN Pharma.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Agranulocytosis • Hypersensitivity reactions • Hypomagnesaemia • Depression • Hepatic reactions • Severe cutaneous reactions • Interstitial nephritis • Fracture of the hip, wrist or spine • Gastrointestinal infections • Interactions with o Warfarin or other coumarine derivatives o Phenytoin o Atazanavir o Nelfinavir o Digoxin o Methotrexate o Tacrolimus o Clopidogrel
Important potential risks	• Convulsion/seizure • Pneumonia
Missing information	• Use in pregnant and lactating women • Long-term treatment in children • Use in patients with renal impairment

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Nexium i.v., powder for solution for injection/infusion 40 mg. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Esomeprazol SUN Pharma 40 mg/ml powder for solution for injection/infusion has a proven chemical-pharmaceutical quality and is a generic form of Nexium i.v., powder for solution for injection/infusion 40 mg. Nexium i.v. 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 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Esomeprazol SUN Pharma 40 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 January 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/3595/ 001/IA/001	SmPC and PL update	SmPC and PL	7-5-2017	Approval	To update SmPC and PL as a consequence of the PRAC recommendations on signals adopted at the PRAC meeting of 28 November - 1 December 2016 (EMA/PRAC/740369/2016)

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)