COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Esomeprazol Adoh 40 mg, powder for injection or infusion
(esomeprazole sodium)

NL/H/5323/001/DC

Date: 4 April 2022

This module reflects the scientific discussion for the approval of Esomeprazol Adoh 40 mg, powder for injection or infusion. The procedure was finalised at 2 February 2022. 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
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
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
NSAID	Non Steroid Anti-Inflammatory Drug
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 Adoh 40 mg, powder for injection or infusion, from Adoh B.V.

The product is indicated in adults for:

- Gastric antisecretory treatment when the oral route is not possible, such as:
  - gastroesophageal reflux disease (GERD) in patients with esophagitis and/or severe symptoms of reflux
  - healing of gastric ulcers associated with Non Steroid Anti-Inflammatory Drug (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.

The product is also indicated in children and adolescents aged 1 to 18 years for:

- 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 SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Nexium i.v. 40 mg powder for solution for injection or infusion, by Grunenthal B.V. In the Netherlands, Nexium i.v. has been registered since 23 January 2004 by a mutual recognition procedure (SE/H/0211/003).

The concerned member state (CMS) involved in this procedure was Germany.

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

II. QUALITY ASPECTS

II.1 Introduction

Esomeprazol Adoh is a powder for solution for injection/infusion. Each vial contains as active substance 42.5 mg of esomeprazole sodium, equivalent to 40 mg of esomeprazole. The product is packed in clear glass vials with a bromobutyl rubber stopper and an aluminium-

plastic overseal. The excipients are disodium edetate (E385) and sodium hydroxide (E524). Excipients and packaging are usual for this type of dosage form.

II.2 Drug Substance

The active substance is esomeprazole sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a powder and is freely soluble in water. It has one chiral centre. Esomeprazole sodium has eight polymorphic forms. The drug substance used for this product is Form J.

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 synthesis reaction steps followed by several washing and purification steps. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

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 limits. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three production scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scaled batches stored at 25°C/60% RH (6 months), 30°C/75% (6 months) and 40°C/75% RH (6 months). Based on the data submitted, a retest period could be granted of 24 months.

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 choice of an overfill for the drug product has been justified. The main development studies performed were the characterisation of the reference product and the performance of compatibility studies.

Experimental data confirmed the concentration of the reconstituted drug product being 8 mg/ml when diluted with 5.2 ml 0.9% sodium chloride.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The main steps of the manufacturing process are the mixing of the esomeprazole sodium with disodium edetate water for injections and sodium hydroxide. This bulk solution is then filtered aseptically in pre-sterilised vials and lyophilised. Finally the vials are stoppered and capped. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients

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

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, identification, clarity and colour of reconstituted solution, reconstitution time, pH, water content, uniformity of dosage units, particulate contamination (visible and sub-visible particles), bacterial endotoxins, sterility, R-omeprazole, impurities and assay. 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 full scale 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 production scaled batches stored at 25ºC/60% RH (12 months) and 40ºC/75% RH (6 months). The batches were stored in 5 mL glass vials with a bromobutyl rubber stopper and aluminium-plastic overseal. The conditions used in the stability studies are according to the ICH stability guideline. On basis of the data submitted, a shelf life was granted of nine months. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. The labelled storage conditions are “Store at temperature below 25°C in the original package, in order to protect from light.”

The shelf life after reconstitution in terms of chemical and physical stability has been demonstrated for twelve hours at 30°C. However, from a microbiological point of view, 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 Adoh 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 Adoh 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. 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. Also, since the product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference product, there was no need to submit a bioequivalence study.

IV.2 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 Adoh.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

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

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Nexium i.v. No new clinical studies were conducted. 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 language used for the purpose of user testing the PL was Dutch.
The test consisted of two rounds with 10 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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Esomeprazol Adoh 40 mg, powder for injection or infusion has a proven chemical-pharmaceutical quality and is a generic form of Nexium i.v. 40 mg powder for solution for injection or infusion. 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 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 Esomeprazol Adoh with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 February 2022.

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