CBG MEB

Public Assessment Report

Scientific discussion

Lynvox 2 mg/ml, solution for infusion

(linezolid)

NL/H/3443/001/MR

Date: 29 December 2015

This module reflects the scientific discussion for the approval of Lynvox 2 mg/ml, solution for infusion. The procedure was finalised on 11 May 2015. 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
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 Lynvox 2 mg/ml, solution for infusion from Hikma Pharma GmbH.

The product is indicated in adults for:

- Nosocomial pneumonia
- Community acquired pneumonia

Linezolid is indicated for the treatment of community acquired pneumonia and nosocomial pneumonia when known or suspected to be caused by susceptible Gram positive bacteria. In determining whether Linezolid 2 mg/ml is an appropriate treatment, the results of microbiological tests or information on the prevalence of resistance to antibacterial agents among Gram positive bacteria should be taken into consideration. (See section 5.1 of the SmPC for the appropriate organisms).

Linezolid is not active against infections caused by Gram negative pathogens. Specific therapy against Gram negative organisms must be initiated concomitantly if a Gram negative pathogen is documented or suspected.

- Complicated skin and soft tissue infections

Linezolid is indicated for the treatment of complicated skin and soft tissue infections only when microbiological testing has established that the infection is known to be caused by susceptible Gram positive bacteria.

Linezolid is not active against infections caused by Gram negative pathogens. Linezolid should only be used in patients with complicated skin and soft tissue infections with known or possible co-infection with Gram negative organisms if there are no alternative treatment options available. In these circumstances treatment against Gram negative organisms must be initiated concomitantly.

Linezolid should only be initiated in a hospital environment and after consultation with a relevant specialist such as a microbiologist or infectious diseases specialist.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Zyvoxid 2 mg/ml, solution for infusion (NL License RVG 26567) which has been registered in the Netherlands by Pfizer B.V. since 2001 (original product). In addition, reference is made to Zyvoxid authorisation in the concerned member state (reference product).

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

Lynvox 2 mg/ml is an isotonic, clear colourless solution for infusion.
The solution for infusion is packed in single low-density polyethylene infusion bags containing 300 ml (600 mg linezolid) of solution.

The excipients are: citric acid anhydrous (E 330), sodium hydroxide (E 524; for pH-adjustment), glucose monohydrate, sodium citrate (E 331), hydrochloric acid (E 507; for pH-adjustment) and water for injection.

II.2 Drug Substance

The active substance is linezolid, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to off white crystalline powder, witch is freely soluble in chloroform and sparingly soluble in methanol. The product exhibits polymorphism and the polymorphic form manufactured is Form-III. The product is an optically active compound and exhibits isomerism.

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 several stages, such as purification and drying. No class I solvents or heavy metal catalysts are used. The manufacturing process for linezolid is described in detail in the DMF.

Quality control of drug substance
The drug substance specification has been established in-house by the DMF-holder. The specifications are acceptable in line with the Ph.Eur., the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches. In general, the analytical methods are adequately described and validated.

Stability of drug substance
Stability data on the active substance have been provided for six production scaled batches stored at 25°C/60%RH (36 or 6 months) and 40°C/75%RH (6 months). For the tested parameters, no clear trends could be observed under long-term or accelerated conditions. The results remain within the proposed limits. Based on the provided stability data, the proposed retest period of 36 months is justified.
The proposed storage conditions "This medicinal product does not require any special temperature storage conditions; keep the polyethylene container in the outer carton in order to protect from light" are justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. All excipients used are well known and the same as in the reference product. The choices of the packaging and manufacturing process are justified. In accordance with the guideline on bioequivalence the MAH provided adequate justification for not performing bioequivalence studies. Compatibility with 5% glucose, 0.9% sodium chloride and Ringer-lactate solution for a period of 3 hours at 25 – 26 °C has been demonstrated.

Manufacturing process
The adopted manufacturing process for linezolid 2 mg/ml solution for infusion is a non standard process as aseptic filtration is used. The manufacturing process includes dispensing of the raw materials, preparation of the solution, sterile filtration, filling into blow filled seal bags and labelling and packaging.
Adequate in-process controls are laid down. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches.

Control of excipients
The excipients comply with their Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance of solution, clarity of solution, pH, extractable volume, visible and sub-visible particles, identification by HPLC and UV, assay, purity tests, sterility test and bacterial endotoxins.
The release and shelf-life limits for the tests are the same except for impurity at RRT and total impurities. The specification is justified.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 production-scale batches, demonstrating compliance with the release specifications.

Stability of drug product
Stability data on the product has been provided for one full-scale batch and two pilot-scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in polyethylene bags which are placed in an outer carton box. All tested parameters remained within the specifications.
A photostability study on Linezolid 2 mg/ml solution for infusion was conducted according to ICH Q1B guideline. The results showed clear changes in the assay, appearance and impurities for the samples packed in the primary packaging material (PE Bag). The results show that samples packed in the marketing pack (PE bags in cardboard boxes) are stable when irradiated with daylight and UV-light. The proposed shelf-life of 30 months is justified. The proposed storage condition “This medicinal product does not require any special temperature storage conditions; keep the polyethylene container in the outer carton” is justified. Post approval the shelf life was extended to 36 months (variation NL/H/3417/001/IB/004).

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 Lynvox 2 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- The MAH committed to continue the ongoing stability studies. The results at least up to the proposed shelf life will be submitted.
- The MAH committed to perform process validation studies on the first 2 commercial batches.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Lynvox 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 Zyvoxid 2 mg/ml, 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

Linezolid 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

Lynvox 2 mg/ml, solution for 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Lynvox 2 mg/ml 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 Lynvox.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Pseudomembranous colitis • Myelosuppression • Lactic acidosis • Mitochondrial toxicity • Serotonin syndrome • Convulsions • Optic neuropathy; peripheral neuropathy
Important potential risks	• Cardiac events • Increased risk of fatal outcome in subsets of patients with catheter related infections, especially those with Gram negative organisms • Long term use
Missing information	• Use in severe hepatic and renal insufficiency • Pregnant and lactating women • Safety and efficacy in children and adolescents

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 Zyvoxid. 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 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 a pilot test, followed by two rounds with 10 participants each. The questionnaire consisted of 14 questions. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the package leaflet 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

Lynvox 2 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality and <are/is a> generic form of Zyvoxid 2 mg/ml, solution for infusion. Zyvoxid 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 Lynvox with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 11 May 2015.

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
Change in shape or dimensions of the container or closure (immediate packaging).	NL/H/3443/ 001/IB/001	IB	16-9-2015	16-10-2015	Approval	No
Change in the batch size (including batch size ranges) of the finished product.	NL/H/3443/ 001/IB/002	IB	16-9-2015	16-10-2015	Approval	No