Public Assessment Report

Scientific discussion

Linezolid Hetero 2 mg/ml, solution for infusion
(linezolid)

NL/H/2776/002/DC

Date: 8 June 2017

This module reflects the scientific discussion for the approval of Linezolid Hetero 2 mg/ml, solution for infusion. The procedure was finalised on 27 December 2016. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
**List of abbreviations**

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

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Linezolid Hetero 2 mg/ml, solution for infusion from Hetero Europe S.L.

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 Hetero 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 decentralised procedure concerns a generic application claiming essential similarity with the innovator product Zyvox 2 mg/ml, solution for infusion which has been registered in the UK by Pharmacia/Pfizer Limited since 5 January 2001. In the Netherlands, Zyvoxid 2 mg/ml (NL License RVG 26567) was registered by Pfizer B.V. on 16 October 2001 through MRP UK/H/0439/001.

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

Linezolid Hetero 2 mg/ml is an isotonic, clear, colourless to yellow solution with pH 4.4 – 5.0 and osmolarity of 280 – 330 mOsm/kg. One ml of solution for infusion contains 2 mg of linezolid.

The solution is packed in a single use, ready-to-use, multilayered polypropylene bag sealed inside a foil laminate overwrap. The 300 ml infusion bags contain 600 mg linezolid.
The excipients are: glucose monohydrate, sodium citrate (E331), citric acid anhydrous (E330), sodium hydroxide (E524) (for pH adjustment), hydrochloric acid (E507) (for pH adjustment), water for injection.

II.2 Drug Substance

The active substance is linezolid, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to off-white crystalline powder which is sparingly soluble in methanol and soluble in chloroform. The solubility in water is very poor and pH dependent. The product exhibits polymorphism and the polymorph manufactured is Form-II. It is a chiral compound with one stereogenic center, the S-isomer is synthesized.

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 of linezolid (form-II) is a six step process. The structure of the active substance is adequately characterized. The specifications and analytical methods for the control of raw materials and solvents are acceptable.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 6 full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). Data for 2 additional full scaled batches stored at 25°C/60% RH (12 and 24 months) are also provided. Under all storage conditions the drug substance remains stable and complies with the proposed specifications. No specific up- or downward trends are observed. The proposed retest period of 3 years and storage condition "Preserve in tight containers, light-resistant containers. Store at 25°C, excursions permitted between 15°C and 30°C" 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. The main development studies consist of physicochemical characterization of the reference product Zyvoxid 2 mg/ml solution for infusion, and manufacturing and analysis of a prototype formulation. The compatibility and absorption of the filter, silicone tubes and stainless steel were investigated as well as the process hold time, extractable volume, pH suitability, photostability, specific gravity and the terminal sterilization method (i.e. by steam sterilization). A bioequivalence study is not required. The choice of manufacturing process is justified by the adequate validation. The choices of the packaging are justified by the results of the stability studies. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The drug product is manufactured according to a standard process in 5 stages: mixing and dissolution of all ingredients followed by aseptic filtration, bag filling, terminal sterilization and visual inspection. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 minimum scaled commercial
batches. The product is manufactured using conventional manufacturing techniques. Process validation for 3 maximum scaled commercial batches will be performed post authorisation.

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

**Quality control of drug product**
The product specification includes tests for appearance, identification, clarity, color of solution, pH, osmolality, extractable volume, visible and sub-visible particles, assay of dextrose and assay of Linezolid, related substances, uniformity of dosage units, sterility, bacterial endotoxins, enantiomeric purity and water vapour permeability. The proposed release and shelf life parameters and limits are almost identical, except for related substances and total impurities. The proposed limits are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided for 3 minimum scaled commercial batches, demonstrating compliance with the proposed release specification.

**Stability of drug product**
Stability data on the product has been provided for 3 minimum scaled commercial batches stored at 25°C/40% RH (24 months), 30°C/65% RH (24 months) and 40°C/≤25% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in a polypropylene (PP) and styrene-ethylene-butylene (SEB) block copolymer flexible bag with a twist off port and a medication injection port with off-white elastomer closure. This bag is kept under a 3 layer metalized polymer pouch with transparent window as an overwrap. During the long term and accelerated stability studies all the tested parameters remain within the proposed acceptance limits. The observed trends during the intermediate and long term stability studies are similar to the accelerated study but require a longer time. Under all storage conditions all tested parameters remain within their acceptance limits. The photostability of the drug product is tested per ICH Q1B and the drug product is photo-labile and degraded in the primary packaging material (i.e. naked bag) and stable in the secondary packaging material (i.e. a laminate overwrap with transparent window). Based on the submitted stability data the proposed shelf-life of 24 months is granted, with the storage conditions ‘store in the original package (overwrap and carton) until ready to use in order to protect from light. Store below 25°C. Do not freeze.’.

A compatibility study report has been provided for infusion solutions 5% glucose intravenous infusion, 0.9% sodium chloride intravenous infusion and Ringer-lactate solution for injection. At 25°C an intravenous line is flushed before and after (both for 15 min) infusion of the drug product (for 120 minutes) with a compatibility study solution. Compatible with 5% glucose intravenous infusion, 0.9% sodium chloride intravenous infusion and Ringer-lactate solution for injection has been demonstrated.

**Specific measures for 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 Linezolid Hetero 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. No post-approval commitments were made.

**III. NON-CLINICAL ASPECTS**

**III.1 Ecotoxicity/environmental risk assessment (ERA)**

Since Linezolid Hetero 2 mg/ml 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, solution for infusion, 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

Linezolid Hetero 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 Linezolid Hetero 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 Linezolid Hetero.

- Summary table of safety concerns as approved in RMP

| Important identified risks | • Myelosuppression  
|                           | • Lactic acidosis  
|                           | • Peripheral neuropathy  
|                           | • Optic neuropathy  
|                           | • Serotonin syndrome  
|                           | • Increased risk of fatal outcome in subsets of patients with catheter related infections, especially those with Gram negative organisms  
|                           | • Convulsions  
|                           | • Mitochondrial toxicity  
|                           | • Antibiotic associated diarrhoea and colitis/Pseudomembranous colitis  

| Important potential risks | • Long term use > 28 days  
|                          | • Use in pregnancy and lactation  
|                          | • Impairment of fertility  

Besides routine pharmacovigilance, the MAH will use follow-up questionnaires to further characterise specific safety concerns, *i.e.* serotonin syndrome, lactic acidosis, optic neuropathy, peripheral neuropathy, and death.

Besides the safety concerns included in the RMP, the following issues are under continued monitoring by the innovator MAH:
- Haematological events
- Cardiac disorders
- Hyponatraemia
- Skin disorders
- Serious hepatotoxicity
- Tubulo-interstitial nephritis within the context of renal impairment
- DRESS within the context of severe cutaneous adverse reactions

The MAH has committed to closely monitor the adverse events listed above.

**IV.4 Discussion on the clinical aspects**

For this authorisation, reference is made to the clinical studies and experience with the innovator product Zyvoxid 2 mg/ml, solution for infusion. No new clinical studies were conducted. Similarity with the reference product has been demonstrated on *in-vitro* data. 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 not been evaluated via a user consultation. A bridging report has been submitted. For bridging the content, the MAH provided a rationale that the content and lay-out of the PL for Linezolid Hetero 2 mg/ml, is practically identical to the successfully user tested PL for Linezolid Hetero 600 mg film-coated tablets, with exception of the product specific parts. For bridging the design and lay-out, the MAH has included a comparison between the two PLs, demonstrating that the design (text size, colour) and lay-out of the proposed PL. The linezolid infusion PL is only longer due to the added section for Health Care Professionals. The bridging report has been found acceptable.

**VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

Linezolid Hetero 2 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality and 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 Linezolid Hetero 2 mg/ml, solution for infusion with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 December 2016.
# STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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