Public Assessment Report

Scientific discussion

Linezolid Polpharma 2 mg/ml, solution for infusion

(linezolid)

NL/H/2781/001/DC

Date: 8 July 2014

This module reflects the scientific discussion for the approval of Linezolid Polpharma 2 mg/ml, solution for infusion. The procedure was finalised on 13 January 2014. For information on changes after this date please refer to the module 'Update'.

This report includes a summary, on pages 8-10.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Linezolid Polpharma 2 mg/ml, solution for infusion from Zaklady Farmaceutyczne POLPHARMA Joint-Stock Company.

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 Farmaprojects 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 Zyvoxid 2 mg/ml, solution for infusion (NL License RVG 26567) which has been registered in the Netherlands by Pfizer B.V. since 16 October 2001. In addition, reference is made to Zyvoxid authorisations in the individual member states (reference product).

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

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

II. QUALITY ASPECTS

II.1 Introduction

Linezolid Polpharma 2 mg/ml is an isotonic, clear, colourless solution with pH 4.3 – 5.3 and osmolality of 280 – 340 mOsm/kg. One ml of solution for infusion contains 2 mg of linezolid.

The product is supplied in single use, ready-to-use, low density polyethylene (LDPE) infusion bags containing 300 ml of solution. The 300 ml of solution for infusion contains 600 mg of linezolid.

The excipients are: glucose monohydrate, sodium citrate (E331), citric acid anhydrous (E330), hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

II.2 Drug Substance

The active substance is linezolid, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance white to off white crystalline powder, which is freely soluble in chloroform and sparingly soluble in methanol. The product exhibits polymorphism and the polymorph manufactured is Form-I. The product is an optically active compound with one chiral centre and exhibits isomerism. In the drug substance the S enantiomer is used.

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 synthesis of linezolid consists of six synthetic steps. No class I organic solvents are used in the process. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification of the MAH has been established in-house and is in line with the specifications of the DMF-holder with additional tests for particle size and bacterial endotoxins. The specifications are acceptable in view of the route of synthesis and the various European guidelines. The analytical methods are adequately described and validated. Batch analytical data demonstrating compliance with the drug substance specification have been provided by the drug product manufacturer for two batches of the drug substance.

Stability of drug substance
The active substance manufacturer provided stability data on the active substance for three full-scale batches stored at 25°C/60% RH (12 months), 30°C/65% RH (24 months) and 40°C/75% RH (6 months). From the provided stability data no changes or trends are observed at long-term, intermediate and accelerated conditions. Based on the provided stability data, the proposed retest period of 36 months and the proposed storage conditions of "Store in a well closed container at temperature below 30ºC" 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. Due to the formulation instability and the physico-chemical restrictions of the LDPE container (the LDPE used has a melting point of 114ºC), an autoclave cycle for 15 minutes and moist heat were not feasible. A combination of sterile filtration and aseptic processing is a suitable manufacturing method for linezolid solution for infusion. The sterility and bacterial endotoxin tests are carried out as per the requirements of European Pharmacopoeia. The development of the manufacturing has been adequately described.

Manufacturing process
The adopted manufacturing process for Linezolid Polpharma 2 mg/ml solution for infusion is a non-standard process, as aseptic filtration is used. The manufacturing process includes weighting of the starting materials, preparation of the solution, sterile filtration, forming, filling and sealing of the bags, 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 production-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, pH, osmolality, extractable volume, visible and sub-visible particles, identification, assay, related substances, sterility test and bacterial endotoxins. The release and shelf-life limits for all tests are the same except for related substances. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 production scaled batches, demonstrating compliance with the release specifications.

Stability of drug product
Stability data on the product has been provided for three full scale batches stored at 25°C/60% RH (24 months), 30°C/55% RH (12 months) and 40°C/75% RH (6 months). The batches were stored in PE bags containing 300 ml of solution in an individual carton box.
Stability results showed some increases in impurities. However all tested parameters remained within the specifications. For the other tested parameters no significant changes or trends were observed. The proposed shelf-life of 30 months is justified. A photostability study was performed in conformity with ICH topic Q1B. The provided data shows that the product is light sensitive. The proposed storage condition “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” is justified.

After dilution with 0.9 % sodium chloride, 5% glucose solution or Lactated Ringer’s solution the product is stable for 2 hours at 25°C.

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

The following post-approval commitments was made:
- The MAH committed to continue the on-going stability studies. The results at least up to the proposed shelf life are awaited as soon as available

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Linezolid Polpharma 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 tot 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 Polpharma 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 Polpharma 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 Polpharma.

Summary table of safety concerns as approved in RMP

Important identified risks	Myelosuppression Lactic acidosis Peripheral neuropathy Optic neuropathy Serotonin syndrome Increased blood pressure (potential to inhibit monoamine oxidase) Convulsions Mitochondrial toxicity
Important potential risks	Increased risk of fatal outcome in subsets of patients with catheter related infections, especially those with Gram negative organisms
Important missing information	None consistently identified at this time

The MAH committed to close monitoring of the following safety concerns identified during worksharing PSUR with procedure number UK/H/PSUR/0037/003:

- haematological events
- cardiac disorders
- hyponatriemia
- skin disorders
- serious hepatotoxicity
- tubulo-interstitial nephritis within the context of renal impairment
- DRESS within the context of severe cutaneous adverse reactions.

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 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 with 2 participants, followed by two rounds with 10 participants each. The questions were formulated to test for the use ability and trace ability of the information. Based on the results of the testing no suggestions for revision of the package leaflet were provided. 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

Linezolid Polpharma 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 Polpharma 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 13 January 2014.

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

Summary Public Assessment Report

Generics

Linezolid Polpharma 2 mg/ml, solution for infusion

(linezolid)

NL/H/2781/001/DC

Date: 8 July 2014

Summary Public Assessment Report

Generics

Linezolid Polpharma 2 mg/ml, solution for infusion

Active substance: linezolid

This is a summary of the public assessment report (PAR) for Linezolid Polpharma 2 mg/ml. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Linezolid Polpharma.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

What is Linezolid Polpharma and what is it used for?
Linezolid Polpharma is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Zyvoxid 2 mg/ml, solution for infusion.

Linezolid is an antibiotic. It is used to treat certain types of pneumonia and some infections in the skin or under the skin in adults.

How is this medicine used?
The medicine can only be obtained with a prescription. This medicine is given through a drip (by an infusion into a vein) by a doctor or healthcare professional. The usual dose for adults (18 years and older) is 300 ml (600 mg linezolid) twice daily which is given directly into the blood stream (intravenously) by a drip over a period of 30 to 120 minutes.
A course of treatment usually lasts 10 to 14 days, but can last up to 28 days. The doctor decides how long you should be treated.
This medicine is not recommended for use in children and adolescents (under 18 years old).

How does this medicine work?
Linezolid Polpharma is an antibiotic that works by stopping the growth of certain bacteria (germs) that cause infections. It prevents bacteria from making proteins. Bacteria cannot develop without proteins.

How has this medicine been studied?
The company provided data from the published literature on the active substance linezolid. No additional studies were needed as Linezolid Polpharma 2 mg/ml is a generic medicine that is given by infusion in an aqueous solution and contains the same active substance in the same concentration as the reference medicine, Zyvoxid 2 mg/ml, solution for infusion.

What are the benefits and risks of this medicine?
Because Linezolid Polpharma is a generic medicine, its benefits and risks are taken as being the same as the reference medicine.

Why is this medicine approved?
It was concluded that, in accordance with EU requirements, Linezolid Polpharma has been shown to be comparable to Zyvoxid. Therefore, the view was that, as for Zyvoxid, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of this medicine?
A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Linezolid Polpharma, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about this medicine
In the Netherlands, the marketing authorisation for Linezolid Polpharma 2 mg/ml, solution for infusion was granted on 5 March 2014.

The full PAR for this medicine can be found on the website http://mri.medagencies.org/Human. For more information about treatment with Linezolid Polpharma, read the package leaflet (http://mri.medagencies.org/download/NL_H_2781_001_FinalPL.pdf) or contact your doctor or pharmacist.

This summary was last updated in July 2014.