Public Assessment Report

Scientific discussion

Pneumolid 2 mg/ml, solution for infusion

(linezolid)

NL/H/2869/001/DC

Date: 9 July 2014

This module reflects the scientific discussion for the approval of Pneumolid 2 mg/ml, solution for infusion. The procedure was finalised on 22 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 Pneumolid 2 mg/ml, solution for infusion from Alvogen IPCo S.ar.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 Pneumolid 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, with has been registered in the UK by Pharmacia Limited since 5 January 2001. In the Netherlands, Zyvoxid 2 mg/ml, solution for infusion (NL License RVG 26567) was registered by Pfizer B.V. on 16 October 2001. In addition, reference is made to Zyvoxid authorisations in the individual member states (reference product).

The concerned member states (CMS) involved in this procedure were Bulgaria, Croatia, Hungary, Poland and Romania.

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

II. QUALITY ASPECTS

II.1 Introduction

Pneumolid 2 mg/ml is an isotonic, clear, colourless to yellow solution. with pH 4.5 – 5.0 and osmolality of 270 – 330 mOsm/kg. One ml of solution for infusion contains 2 mg of linezolid.

The product is supplied in a clear colourless or yellowish polypropylene infusion bag with one port or two ports in a transparent foil laminate overwrap bag, 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 (E507) (as 10% solution; for pH-adjustment), sodium hydroxide (E524) (as 10% solution; 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 is a white to off-white powder, which is soluble in acetone, methanol and 10% HCl. It is partially soluble in water. 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 both manufacturers of 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
A description of the process has been given. No class I organic solvents are present. 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 ASMF holders has been established in-house. The specifications for both suppliers are acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the proposed drug substance specification has been provided for production-scale batches of both suppliers.

Stability of drug substance
Stability data on the active substance have been provided by the ASMF holders. The drug substance was stored at 25°C/60% RH and 40°C/75% RH. No significant trends were seen and no out-of-specification results were observed at both accelerated and real time conditions. A re-test period of 36 months has been granted for both suppliers.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Studies such as pharmaceutical equivalence testing (in terms of comparisons of the innovator product with the proposed product), impurity studies, choice of packaging material and choice of sterilisation method (terminal sterilisation), were performed as part of the development. Equivalence with respect to chemical-pharmaceutical properties has been demonstrated. The pharmaceutical development of the proposed product has been adequately performed. Linezolid cannot be treated by a standard autoclave sterilization process. The conditions of the terminal sterilisation method have been adequately justified The sterility and bacterial endotoxin tests are carried out as per the requirements of European Pharmacopoeia.

Manufacturing process
During the manufacturing process, the excipients and active substance are mixed and dissolved in water for injection, and the pH is adjusted if necessary. Prior to filling, the solution is filtered and filled into the container closure system (infusion bag). The overwrapped infusion bags are autoclaved.
The manufacturing process is controlled in-process. The MAH has set additional tests for in-process control of pre-terminal sterilisation bioburden as well as a test for integrity of the container closure.
Process validation data has been presented for three production-scale batches, according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

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, particulate contamination, pH, extractable volume, identification, assay, impurities, enantiomeric purity, sterility and bacterial endotoxins. The drug product specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from three production-scale batches has been provided. All batches comply with the specification.

Stability of drug product
Stability data on the product has been provided for three production-scale batch stored at 25°C/60% RH (long term) for 12 months and 40°C/75% RH (accelerated) for 6 months. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in polypropylene infusion bags. The results provided justify a shelf-life of 30 months with no storage temperature restriction.
From the photostability study provided it can be seen that the product is sensitive to light, hence the following statement related to light sensitivity is applicable: “Store in the original package, in order to protect from light”. Protection from light during administration is not deemed necessary.

Studies demonstrating compatibility have been performed between the proposed drug product and the solutions indicated in the SmPC: 0.9% sodium chloride, 5% glucose solution or Lactated Ringer’s solution.

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 Pneumolid 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 commitment was made:

- The MAH committed to continue the stability studies post approval in order to confirm the shelf life

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Pneumolid 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

Pneumolid 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 Pneumolid 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 Pneumolid.

Summary of safety concerns	
Important identified risk	Antibiotic-associated diarrhoea and colitis (including pseudomembranous colitis and *Clostridium difficile* associated diarrhoea)
	Convulsions
	Food interaction: tyramine-rich foods
	Lactic acidosis
	Mitochondrial toxicity
	Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia)
	Optic neuropathy
	Peripheral neuropathy
	Renal failure
	Serotonin syndrome associated with the co-administration of linezolid and serotonergic agents (*e.g.* serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants and serotonin 5-HT1 receptor agonists)
	Skin and subcutaneous tissue disorders (bullous disorders such as Stevens-Johnson syndrome and toxic epidermal necrolysis, and angioedema)
	Superinfection (candidiasis and fungal infections)
	Use in patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder and acute confusional states
Important potential risks	Hypoglycemia
	Impairment of fertility
	Increased fatal outcome in subsets of patients with catheter related infections, especially, those with Gram-negative organisms
	Use in patients with severe hepatic insufficiency
	Use in patients with severe renal insufficiency
	Use in patients taking any medicinal product which inhibits monoamine oxidases A or B
	Use in pregnant and lactating women
Important missing information	Long-term treatment (more than 28 days)
	Overdose
	Use in children and adolescents (below 18 years of age)
	Use in patients with diabetic foot lesions, decubitus or ischaemic lesions and severe burns or gangrene

At present, no additional pharmacovigilance activities beyond routine measures are proposed. However, the MAH committed to closely monitor and review the following topics should be: lactic acidosis, peripheral neuropathy, optic neuropathy, haematological events, cardiac disorders, hypernatremia, renal failure, skin disorders and hepatobiliary events.

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 study. Instead, the MAH submitted a bridging report making reference to the PL for Zyvoxid 2 mg/ml solution for infusion.
A comparison between this PL and the one for Pneumolid 2 mg/ml solution for infusion has been made to present and evaluate the differences between the two leaflets. The conclusion in the bridging report was that only few minor content-related differences between the proposed daughter and parent PIL exist and that the writing style is identical.
In addition, the MAH has previously performed a successful user test on a PL for Eplerenone 25 mg and 50 mg film-coated tablets. This PL has the same design and lay-out as the one for Pneumolid. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pneumolid 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 Pneumolid 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 22 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

Pneumolid 2 mg/ml, solution for infusion

(linezolid)

NL/H/2869/001/DC

Date: 9 July 2014

Summary Public Assessment Report

Generics

Pneumolid 2 mg/ml, solution for infusion

Active substance: linezolid

This is a summary of the public assessment report (PAR) for Pneumolid 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 Pneumolid.

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

What is Pneumolid and what is it used for?
Pneumolid 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?
The active substance linezolid 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 Pneumolid 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 Pneumolid 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, Pneumolid 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 Pneumolid, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about this medicine
In the Netherlands, the marketing authorisation for Pneumolid 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 Pneumolid, read the package leaflet (http://mri.medagencies.org/download/NL_H_2869_001_FinalPL.pdf) or contact your doctor or pharmacist.

This summary was last updated in July 2014.