CBG MEB

Public Assessment Report

Scientific discussion

Linezolid PolPharma 600 mg film-coated tablets

(Linezolid)

NL/H/3124/001/DC

Date: 26 May 2016

This module reflects the scientific discussion for the approval of Linezolid PolPharma 600 mg film-coated tablets. The procedure was finalised on 21 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 Linezolid Polpharma 600 mg, film-coated tablets, from Pharmaceutical Works Polpharma S.A.

The product is indicated for:

- Nosocomial pneumonia

- Community acquired pneumonia

Linezolid is indicated in adults 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 tablets 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 approved 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 (see section 4.4 of the approved SmPC)

Linezolid tablets is indicated in adults 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 (see section 4.4 of the approved SmPC). 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.

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 600 mg film-coated tablets which has been registered in Germany by Pharmacia GmbH since 26 September 2001. In the Netherlands, Zyvoxid 600 mg (NL License RVG 26569) has been registered since 16 October 2001 by the procedure UK/H/0439/003.

The concerned member states (CMS) involved in this procedure were Bulgaria, Czech Republic, Lithuania, Latvia, Poland and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Linezolid Polpharma 600 mg is an off-white, oblong, biconvex, film-coated tablet and contains as active substance 600 mg of linezolid.

The tablets are packed in PVC/PCTFE/Aluminium blisters.

The excipients are:

Tablet core - sodium starch glycolate, microcrystalline cellulose PH 101 and PH 102, povidone, sodium dihydrgen citrate powder type F0100 and magnesium stearate.
Film-coating - Sepifilm® 752 White containing: hypromellose, microcrystalline cellulose, Macrogol stearate 40 and titanium dioxide.

II.2 Drug Substance

The active substance is linezolid, an established active substance not described in the European or British Pharmacopoeia (Ph.Eur., BP). The active substance is freely soluble in chloroform and sparingly soluble in methanol. The substance exhibits polymorphism and the polymorph manufactured is Form-I. The substance 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 synthesis of linezolid consists of six synthetic steps. No class I organic solvents are used in this 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 specification of the ASMF-holder and with an additional test for particle size and microbiological purity. Stability of the drug substance polymorphic form (form I) during storage of the drug substance has been demonstrated. During storage within the drug product, the drug substance form I changes to form II. Form II is also the form in the biobatch. It has been demonstrated that presence of form I or II in the product does not impact product stability or dissolution. 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 three production batches.

Stability of drug substance
Stability data on the active substance have been provided for three full scaled batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months when stored at 25°C/60% RH or 30°C/65% RH and 6 months when stored at 40°C/75% RH. Based on the data submitted, a retest period has been granted of 36 months when stored in a well closed container at a temperature of below 30°C.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described, the choice of excipients is justified and their functions explained in accordance with the relevant European guidelines.
The qualitative composition, size and weight of the innovator/reference product, Zyvoxid 600 mg film-coated tablets, and its physicochemical characteristics were used as prototype in the development of the formulation of the generic product. The dissolution is rapid, and similar to that of the reference product across the physiological pH range (pH=1, pH=4.5, pH=6.8). The discriminating power of the routine dissolution method has been demonstrated. Overall, the pharmaceutical development has been sufficiently elucidated.

Manufacturing process
The linezolid tablets are made by a wet granulation and drying process followed by milling, mixing, lubrication, tableting, compression, film coating and packaging.
The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph. Eur., except for sodium dihydrogen citrate and the film-coating mixture. In-house specifications have been submitted for these excipients. All specifications are acceptable. No novel excipients are used.

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, identity of drug substance and the colouring agent (titanium dioxide), assay, related substances/degradation products, dissolution, microbiological purity, water content, and uniformity of dosage units. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The shelf-life limits are identical to the release limits with the exception of water content, the release limit is tighter than of the shelf-life limits, in view of the results.
Satisfactory validation data for the analytical methods have been provided and adequately described.
Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for four product batches in accordance with applicable European guidelines demonstrating the stability of the product for 24 months (stored at 25°C/60% RH), 12 months (stored at 30°C/75% RH) and 6 months (stored at 40°C/75% RH). The conditions used in the stability studies were according to the ICH stability guideline. The product remained stable under all storage conditions; no specific up or downward trends were observed.
On basis of the data submitted, a shelf life was granted of 36 months in the proposed blister, without special storage conditions. In the photostability study, performed in accordance with the Note for Guidance on the Photostability testing of Medicinal products, no changes were observed. The results showed that the tablets are light resistant.

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 600 mg 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:
- In due time, the MAH's drug substance specification should be updated according to the ASMF-holder's new drug substance specification.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Linezolid Polpharma 600 mg 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 600 mg 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.

For this generic application, the MAH has submitted a bioequivalence study which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Linezolid Polpharma 600 mg (Pharmaceutical Works Polpharma S.A., Poland) is compared with the pharmacokinetic profile of the reference product Zyvoxid 600 mg (Pharmacia/Pfizer, Germany).

The choice of the reference product in the bioequivalence study is accepted.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, open-label, randomised, two-period, crossover, comparative bioequivalence study was carried out under fasted conditions in 26 healthy subjects (10 males/16 females), aged 23-54 years. Each subject received a single dose (600 mg) of one of the 2 linezolid formulations. The tablet was orally administered with 200 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24 and 32 hours after administration of the products.

A single dose, crossover study to assess bioequivalence is considered adequate. Fasting conditions has been applied, which is appropriate as the absorption is not significantly affected by food.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All 26 subjects completed the study and were included in the analysis. There were no withdrawals.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of linezolid under fasted conditions.

Treatment N=26	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	83 ± 26	86 ± 26	12.1 ± 3.3	1.0 (0.33-3.0)	4.3 ± 1.0

Reference	80 ± 22	83 ± 22	11.4 ± 2.6	1.38 (0.50-3.0)	4.3 ± 1.0
***Ratio (90% CI)**	1.03 (0.95 – 1.11)	--	1.06 (0.98 – 1.14)	--	--
CV (%)	15.9	--	15.8	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Linezolid Polpharma 600 mg is considered bioequivalent with Zyvoxid 600 mg.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 600 mg.

Summary table of safety concerns as approved in RMP

Important identified risks	Myelosuppression Lactic acidosis Peripheral and optic neuropathy Serotonin syndrome Convulsions Mitochondrial toxicity
Important potential risks	Increased risk of fatal outcome in subsets of patients with CRI, especially those with Gram negative organisms
Missing information	Long-term use Pregnancy and lactation

Besides the safety concerns included in the RMP, the following issues are under continued monitoring by the innovator MAH:

- haematological events
- hyponatriemia
- 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 and discuss them in the future PSUR.

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. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed, on the basis of a bridging report report and Focus Test & Analysis, making reference to a linezolid injectable product. The visual analysis concluded that both PLs are similar in visual aspects. Second, content analysis was performed between the two leaflets. The PL sections have been compared meticulously, concluding that no significant differences have been identified that could affect readability. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Linezolid Polpharma 600 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Zyvoxid 600 mg film-coated tablets. Zyvoxid is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 600 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 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