CBG MEB

Public Assessment Report

Scientific discussion

Linezolid Sandoz 600 mg, film-coated tablets (linezolid)

NL/H/2965/001/DC

Date: 8 January 2015

This module reflects the scientific discussion for the approval of Linezolid Sandoz 600 mg, film-coated tablets. The procedure was finalised on 25 June 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Linezolid Sandoz 600 mg, film-coated tablets from Sandoz B.V.

The product is indicated for:

- treatment of community acquired pneumonia and nosocomial pneumonia when known or suspected to be caused by susceptible Gram-positive bacteria. In determining whether linezolid 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.

- 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.

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 (NL License RVG 26569) which has been registered in the Netherlands by Pfizer BV since 16 October 2001 (original product) through MRP UK/H/0439/003. 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 Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Ireland, Luxembourg, Lithuania, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Linezolid Sandoz 600 mg is a white to off white colored biconvex oval shaped film-coated tablet with “LZ600” debossed on one side and plain on the other side.

The film-coated tablets are packed in OPA/Al/PVC//Al blister:

The excipients are:
Tablet core - cellulose microcrystalline, silica colloidal anhydrous, sodium starch glycolate type A, hydroxy propyl cellulose, magnesium stearate.
Film coat - hypromellose (E464); titanium dioxide (E171), macrogol (E1521)

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 freely soluble in chloroform and sparingly soluble in methanol.
The substance exhibits at least three polymorphic forms, and one chiral center. Linezolid has the *S*-configuration. the polymorph manufactured is Form-III.

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
Linezolid is manufactured in five steps. The manufacturing process has been described in sufficient detail. Linezolid has been adequately characterized, and acceptable specifications for the starting material and all other solvents and reagents used in the manufacturing process have been adopted.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH, based on the specification of the drug substance manufacturer with additional requirements for microbiological purity. In-house methods and limits are described for the non-compendial tests. 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 pilot-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for six pilot-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The data provided show that no changes or trends occur in the parameters tested when the drug substance is stored under each of these conditions. Therefore, the proposed re-test period of 36 months is acceptable. Although no special storage conditions are required, based on the data, no objection is made to the proposed storage conditions "Preserve in tight containers. Store at 25ºC, excursions permitted between 15°C and 30ºC".

II.3 Medicinal Product

Pharmaceutical development
Linezolid can exist in different polymorphic forms. While in the innovator product polymorphic form II is present, the applied product uses drug substance with polymorphic form III. Since the bioequivalence of the applied product Linezolid 600 mg film-coated tablets (polymorphic form III) versus the reference product (polymorphic form II) has been demonstrated, it can be assumed that polymorphic forms does not affect *in-vivo* performance.
Different methods of granulation were evaluated, and wet granulation was selected for the manufacturing process. By dissolution studies it was shown that Linezolid Sandoz dissolved slightly faster compared to the reference product. The dissolution was similar batch to batch. Furthermore, the test and reference product were found to be bioequivalent, therefore the slight difference in dissolution between the two products can be accepted. The pharmaceutical development of the product has been adequately described, the choice of excipients is justified and their functions explained.

Manufacturing process
The 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 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 the Ph. Eur., except for the coating system. The coating system is a mixture of excipients which are all described in the Ph. Eur. An in-house specification for the coating system is provided. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identity, assay, related substances, dissolution, sterility, endotoxins, water content, and uniformity of dosage units. The shelf-life limits are identical to the release limits, with the exception of water content and total impurities. The proposed specification is acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three production-size batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three full-scale batches, stored in aluminium blisters at 25°C/60% RH (18 months), 30°C/75% RH (18 months), and 40°C/75% RH (6 months). The conditions used in the stability studies are not completely according to the ICH stability guideline, the used relative humidity for the intermediate conditions is higher (75%) than those in the guideline (65%). However, the product remains stable under all storage conditions, no specific up or downward trends are observed. The drug product was demonstrated to be photostable.
The claimed shelf life of 24 months for the film-coated tablets packaged in aluminium blisters is acceptable, without any special storage restrictions.

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 Sandoz 600 mg, film-coated tablets 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 Sandoz 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, 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 Sandoz 600 mg (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Zyvoxid 600 mg tablets (Pharmacia/Pfizer, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 19-42 years. Each subject received a single dose (600 mg) of one of the 2 linezolid formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 9 days.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24 and 36 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 food does not influence the absorption of linezolid.
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
One subject was withdrawn in Period I due to adverse events and one subject did not report to the facility for Period II. Twenty-eight subjects completed the study and were included in the analysis.

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

Treatment N=28	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	122 ± 25	127 ± 30	15.6 ± 2.6	1.25 (0.33 – 3.0)	5.0 ± 1.5
Reference	128 ± 28	133 ± 33	15.5 ± 2.9	1.5 (0.33 – 4.0)	5.4 ± 2.1
***Ratio (90% CI)**	0.95 (0.92 – 0.99)	--	1.01 (0.94 - 1.08)	--	--
CV (%)	9.0	--	14.9	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

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

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 Sandoz.

- Summary table of safety concerns as approved in RMP

Important identified risks	Skin and subcutaneous tissue disorders (bullous disorders such as Stevens-Johnson syndrome and toxic epidermal necrolysis, and angioedema) Use in patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder and acute confusional states Myelosuppression (including anemia, leucopenia, pancytopenia and thrombocytopenia)
	Antibiotic-associated diarrhea and antibiotic-associated colitis, including pseudomembranous colitis and Clostridium difficile-associated diarrhea
	Lactic acidosis
	Mitochondrial toxicity
	Serotonin syndrome during co- administration of serotonergic agents
	Peripheral neuropathy Optic neuropathy
	Convulsions
	Superinfection
Important potential risks	Hypoglycemia Higher mortality in seriously ill patients with intravascular catheter-related infections of gramnegative pathogens and polymicrobial infections
	Monoamine oxidase (MAO) inhibition Altered pharmacokinetics in patients with severe renal insufficiency (special populations) Altered pharmacokinetics in patients with

	severe hepatic insufficiency (special populations) Use in pregnant and lactating women Impairment of fertility
Missing information	Pediatrics and adolescents (<18 years old)
	Administration for periods longer than 28 days
	Administration in patients with diabetic foot lesions, decubitus or ischemic lesions, severe burns or gangrene

The member states agree that none of the important identified or potential risks require additional pharmacovigilance activities other than routine pharmacovigilance.

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

The MAH submitted a bridging user test, referring to the currently approved and successfully user tested package leaflet (PL) for the originator product Zyvox 600 mg film-coated tablets as registered in the UK (same substance, same amount, same pharmaceutical form). The content of the two leaflets is predominantly identical. The bridging report further focusses on the remaining requirements of design and layout issues. The MAH's house style design and layout have been used in many (over 50) successfully user tested package inserts.
The member states agree that the bridging report submitted is acceptable. Separate user testing is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Linezolid Sandoz 600 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Zyvoxid 600 mg. 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 Sandoz 600 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 June 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