CBG MEB

Public Assessment Report

Scientific discussion

Linezolid Teva 600 mg, film-coated tablets

(linezolid)

NL/H/2945/001/DC

Date: 2 March 2015

This module reflects the scientific discussion for the approval of Linezolid Teva 600 mg, film-coated tablets. The procedure was finalised on 16 October 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 Teva 600 mg, film-coated tablets, from Teva Nederland 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The concerned member states (CMS) involved in this procedure were Austria, Belgium, Croatia, Denmark, Finland (withdrawn), France, Germany, Iceland (withdrawn), Ireland, Italy, Luxembourg, Malta, Portugal, Spain, Sweden and the United Kingdom.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 Teva 600 mg is a white, film coated modified capsule shaped tablet, debossed with "600" on one side. The other side is scored.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The film-coated tablets are packed in aluminium–aluminium (push and peel) blisters, transparent PVC/PVdC-aluminium blisters or aluminium–aluminium blisters.

The excipients are:
Tablet core - lactose monohydrate, spray dried lactose monohydrate, maize starch, crospovidone (E1202), hydroxypropylcellulose (E463), crosscarmellose sodium (E468), magnesium stearate (E470b)
Film coat – hypromellose 2910 5cP (E464), titanium dioxide (E171), macrogol 400

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 tighter limits for particle size distribution. 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 two production 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
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were formulation trials and dissolution studies.
Bioequivalence studies were performed with the drug product. The batch used in the bioequivalence study has the same composition and is manufactured in the same way as the future commercial batches. The bioequivalence batch is of sufficient size in relation to the intended commercial batch size. Sufficient comparative dissolution profile data have been provided. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is divided into the following steps: dry mixing, wet granulation, lubrication, 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 two batches of the smallest commercial scale. The product is manufactured using conventional manufacturing techniques and is regarded as a standard process. Process validation for maximum scaled batches will be performed post authorisation.

Control of excipients
All excipients used comply with the requirements of their respective Ph.Eur. monographs, except for the ready to use coating material. In-house specification have been provided for the coating material. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification, dissolution, uniformity of dosage units, assay, related substances, disintegration, microbial quality, water content and identification of titanium dioxide. The release and shelf life limits are identical with the exception of water content. The drug product specification is acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on two batches of the smallest production scale, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided two batches of the smallest production size stored at in 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al/Al *peel push* blisters and PVC-PVdC/Al blisters. The forming foil of the Al/Al *push through* blister is identical to the Al/Al *peel push* blister and the lidding foil is similar to the PVC-PVdC/Al blister. Therefore the Al/Al *push through* blister is considered adequately bracketed by the tested blisters.
An increase in water content was observed in the PVC-PVdC/Al blister. Water content remained relatively stable in the Al/Al *peel push* blister. All other parameters tested remained relatively stable throughout the test periods at both test conditions (with the exception of some analytical variance) and within specification limits. Photostability studies, in line with ICH Q1B, were performed. The drug product was exposed unpacked, packed in Al/Al peel push blister and packed in PVC-PVdC/Al blister. No trends were observed. Based on the stability data provided, the proposed shelf life of 30 months without special storage conditions can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The only substance of animal origin used in the manufacture of the drug product is lactose monohydrate. A BSE-statement is provided stating that the lactose monohydrate is produced from milk that has been sourced from healthy cows in the same conditions as milk collected for human consumption.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Linezolid Teva 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 Teva 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 Teva 600 mg (Teva Nederland 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.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy subjects,19 females and 11 males, aged 43-74 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. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.167, 0.250, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24 and 36 hours after administration of the products.

The design of the study is acceptable. 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 vomiting. 29 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=29	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	140 ± 35	143 ± 35	20.0 ± 5.3	0.75 (0.5 – 3.0)	5.6 ± 1.4
Reference	145 ± 46	149 ± 50	18.1 ± 4.8	0.75 (0.5 – 3.0)	5.8 ± 1.7
***Ratio (90% CI)**	0.98 (0.92 – 1.04)	--	1.10 (1.02 - 1.17)	--	--
CV (%)	13.6	--	15.3	--	--

$AUC_{0-\infty}$	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 Teva 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 Teva.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Myelosuppression • Increased risk of fatal outcome in subsets of patients with catheter related infections (CRI), especially those with Gram negative organisms • Lactic acidosis • Mitochondrial toxicity • Serotonin syndrome and potential for increased blood pressure (potential to inhibit monoamine oxidase) • Peripheral neuropathy • Optic neuropathy • Convulsions
Important potential risks	• Cardiac events
Missing information	• Use in paediatric population • Use during pregnancy • Use during breastfeeding • Long-term use

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

Besides the safety concerns included in the RMP, the following issues should be closely monitored and discussed in the future PSURs:

- 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.

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 package leaflet (PL) 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.
In order to test the readability of the PL, a total of 23 persons were questioned: 3 subjects during the pilot test, and 2 groups of each 10 persons during the following 2 test rounds.
A questionnaire of 20 questions on the leaflet content was used, sufficiently addressing the key safety and usage messages, and 3 additional questions to obtain feedback on the general layout, design, text and comprehensibility of the leaflet.
During the two test rounds, the information was easily found and understood. The questions meet criterion of 81% correct answers. Subjects gave positive feedback on the writing style, the patient friendly descriptions, and on the headings. Some volunteers suggested that important information i.e. warnings should be in red, or bigger print or capital letters.
Overall, 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 Teva 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 Teva 600 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 October 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