CBG MEB

Public Assessment Report

Scientific discussion

Zoligram 600 mg, film-coated tablets (Linezolid)

NL/H/3011/001/DC

Date: 22 December 2014

This module reflects the scientific discussion for the approval of Zoligram 600 mg, film-coated tablets. The procedure was finalised on 20 August, 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 Zoligram 600 mg, film-coated tablets, from Synthon B.V.

The product 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 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.

  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.

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 through MRP UK/H/0439/003. In addition, reference is made to Zyvoxid 600 mg authorisations in the individual member states (reference product).

The concerned member states (CMS) involved in this procedure were Belgium, France, Germany, Italy, Spain, 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

Zoligram 600 mg, film coated tablets is a white to off-white, oblong (approximately 18 mm x 6 mm), biconvex film coated tablet debossed with “L9II 600” on one side.

The tablets are packed in OPA/Al/PVC-Al blisters.

The excipients are:

Tablet core - cellulose, microcrystalline (E460); crospovidone; hydroxypropylcellulose (E463); silica, colloidal anhydrous; magnesium stearate (E572)
Coating - hypromellose (E464); titanium dioxide (E171); macrogol 400

II.2 Drug Substance

The active substance is linezolid, an established active substance not described in the European or British Pharmacopoeia. The active substance is soluble in ethanol and dichloromethane and insoluble in water. It has a potential chiral center leading to 1 potential stereoisomer. In the drug substance the S-enantiomer is used. The polymorphic form of the drug substance is form I.

Two different manufacturers are used for the production of the active substance. For both manufacturers, the Active Substance Master File (ASMF) procedure is used. 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 manufacturing process is given in the ASMF. The manufacturing process has been described in sufficient detail for both suppliers. Acceptable specifications for the starting material, solvents and reagents used in the manufacturing process have been adopted.

Quality control of drug substance
The drug substance specification fixed by both 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. The MAH has adopted the specifications of the ASMF holders, and additionally included an acceptable limit for particle size distribution.
Batch analytical data demonstrating compliance with the proposed drug substance specification has been provided for -production scaled batches of both suppliers.

Stability of drug substance
Stability data on the active substance have been provided by the ASMF holders.
No significant trends were seen and no out of specification results were observed at both accelerated and real time conditions. The approved retest period is 18 months for one manufacturer, and 30 months for the second manufacturer.

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 and choice of packaging material were performed as part of the development.
Development of the *in vitro* dissolution method and comparison of the drug product with the innovator product at three different pHs in order to substantiate bioequivalence has been provided. The designation of the drug substance as BCS class 1 has been adequately substantiated. As it has high solubility, the polymorphic form is not considered critical for the performance of the drug product *in vivo*.

Manufacturing process
The manufacturing process consists of mixing followed by direct compression and film-coating.
In-process controls are applied.
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. The product is manufactured using conventional manufacturing techniques.

Excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, uniformity of dosage units, dissolution, identification, assay and impurities. The proposed drug product specification is acceptable. Batch analytical data from two production-scale batches has been provided. Since the drug product is a

conventional dosage form– and the drug substance is stable, two batches are considered to be acceptable. Both batches comply with the proposed specification.

Stability of drug product
Stability data on the product has been provided for two production-scale batches stored at 25°C/60% RH (12 months) and 40°C/75% (6 months). Furthermore one batch was put on a photostability study. The conditions used in the stability studies and photostability study are according to the ICH stability guideline. The batches were stored in OPA/Al/PVC-Al blister packs.
At long term and accelerated conditions no trends or out-of-specification results were observed.
In the photostability study no changes were observed. The product was demonstrated to be photostable. The proposed shelf-life of 24 months is justified. The proposed storage condition (none) is considered acceptable.

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 Zoligram 600 mg, film-coated tablets 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 all stability studies up to at least 36 months under long-term conditions.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Zoligram 600 mg, film-coated tablets 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.1 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 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.

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

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

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy subjects, 21 males and 3 females, aged 21-39 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 0.25, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 10, 12, 16, and 24 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.

Linezolid is administered as its S-enantiomer. Using a chiral selective assay, the MAH showed that no conversion took plasma from the S- to the R-enantiomer. Bioequivalence is based upon the S-enantiomer, which is acceptable.

Results
23 subjects completed the study and were included in the analysis. One subject dropped out before period II.
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, of S-linezolid under fasted conditions.

Treatment N=23	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	149 ± 26	168 ± 31	16.1 ± 2.7	1.8 ± 0.8	7.3 ± 1.3
Reference	148 ± 27	167 ± 32	15.8 ± 2.6	1.8 ± 1.1	7.5 ± 1.3
***Ratio (90% CI)**	1.01 (0.98 - 1.03)	--	1.02 (0.98 - 1.05)	--	--
CV (%)	5.2	--	6.9	--	--

$AUC_{0-\infty}$ 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

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of S-linezolid under fasted conditions, it can be concluded that Zoligram 600 mg, film-coated tablets and Zyvoxid 600 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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 Zoligram 600 mg, film-coated tablets.

Summary table of safety concerns as approved in RMP

Important identified risks	Antibiotic-associated diarrhoea and colitis Convulsions Lactic acidosis Mitochondrial toxicity Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) Neuropathy peripheral Optic neuropathy Renal failure Serotonin syndrome 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 Use with tyramine-rich foods
Important potential risks	Impairment of fertility Increased fatal outcome in subsets of patients with catheter related infections, esp. those with Gram-negative organisms Use in patients taking any medicinal product which inhibits monoamine oxidases A or B Use in patients with severe hepatic insufficiency Use in patients with severe renal insufficiency 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

The MAH committed to closely monitor 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 600 mg. 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. The contents of the PL are identical to the agreed wording of the innovator product Zyvoxid 600 mg film-coated tablets (UK/H/0439/003), except for the product specific information. Therefore user testing of the contents is not considered necessary. Further, regarding layout reference is made to the successfully user tested PLs for other products of the same MAH. The user tests for these leaflets confirm that the MAH's house style does not affect readability of the PL. The bridging report has been found acceptable. Separate user testing is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Zoligram 600 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms 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 Zoligram 600 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 August 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