LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Zoxilid
(linezolid)

SE/H/1670/01/DC
2017-0910

This module reflects the scientific discussion for the approval of Zoxilid. The procedure was finalised on 2018-09-27. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Zoxilid, 600 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Medochemie Ltd applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BG, CY, CZ, EE, ES, HR, LT, LV, MT, RO and SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is ZYVOXID, 600 mg, film-coated tablet authorised in SE since 2001, with Pfizer AB as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS SK: ZYVOXID, 600 mg, film-coated tablet authorised in SE since 2001, with Pfizer AB as marketing authorisation holder.

The justification to use this product is based on RMS's own files. The ERP information was circulated during the validation period.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Linezolid has an oral bioavailability of approximately 100 %. Following an oral dose of linezolid maximal plasma concentrations occur at approximately 2 hours. The pharmacokinetics of linezolid is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator. A small degree of non-linearity in clearance is observed with increasing doses of linezolid. This appears to be due to lower renal and non-renal clearance at higher linezolid concentrations. However, the difference in clearance is small and is not reflected in the apparent elimination half-life.

No bioequivalence study has been submitted since the applicant applies for a BCS-based biowaiver. BCS-based biowaivers are possible for highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index.

From a pharmacokinetic point of view, a BCS-class I based biowaiver is acceptable for an immediate release drug product if the drug substance has proven to exhibit complete absorption and the excipients that might affect bioavailability are quantitatively and qualitatively the same.

It can be concluded that linezolid is rapidly and extensively absorbed following oral dosing with an absolute oral bioavailability of approximately 100%. This is evident based on information in the SmPC of the reference product. The submitted reference by Dryden 2011 is not an original article but refers to a publication where an absolute bioavailability of 100% was demonstrated in healthy volunteers (Welshman IR, Stalker DJ, Wajsczuk CP. Assessment of absolute bioavailability and evaluation of the effect of food on oral bioavailability of linezolid. Anti-Infect Drugs Chemother 1998; 16 Suppl 1: 54). The study in patients by Beringer et al 2005 demonstrates an absolute bioavailability of 88%. In conclusion, linezolid can be classified as a BCS class I substance from a pharmacokinetic perspective.

Test and reference product are similar with regards to qualitative and quantitative composition. None of the excipients are known to affect bioavailability. The differences regarding excipients are acceptable for a BCS class I substance.

It is agreed that linezolid is not considered to have a narrow therapeutic index in the sense that the acceptance criteria would need to be tightened in a bioequivalence study.

As discussed in the Quality part, the quality aspects of the BCS-based biowaiver have also been fulfilled. Thus, the justification for BCS (Biopharmaceutics Classification System) based biowaiver CAN be accepted.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan (version 1.1 signed 13 March 2018), 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 Zoxilid.

Safety specification

Summary of safety concerns	
Important identified risks	Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) Pseudomembranous colitis Lactic acidosis Serotonin syndrome Peripheral and optic neuropathy Convulsions Mitochondrial toxicity
Important potential risks	Increased risk of fatal outcome in subsets of patients with catheter related infections, especially those with Gram negative infections)
Missing information	Use in severe hepatic and renal insufficiency Pregnancy and lactation

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures

Bone marrow depression (Myelosuppression)	Proposed text in SPC, section 4.4 and 4.8.	None proposed
Inflammation of intestines causing severe and painful diarrhoea (Pseudomembranous colitis)	Proposed text in SPC, section 4.4 and 4.8.	None proposed
Accumulation of lactic acid in the bloodstream (Lactic acidosis)	Proposed text in SPC, section 4.4 and 4.8	None proposed
Potentially life threatening drug reaction that causes the body to have too much serotonin, a chemical produced by nerve cells (Serotonin syndrome)	Proposed text in SPC, section 4.3, 4.4, 4.5 and 4.8.	None proposed
Nerve damage (Peripheral and optic neuropathy)	Proposed text in SPC, section 4.4, and 4.8.	None proposed
Convulsion	Proposed text in SPC, section 4.4, and 4.8.	None proposed
Mitochondrial toxicity (Damaged or decline significantly of mitochondria of a body's cells)	Proposed text in SPC, section 4.4, and 4.8.	None proposed
Long term use	Proposed text in SPC, section 4.4 and 4.8.	None proposed
Potentially life threatening bloodstream infection (Increased risk of fatal outcome in subsets of patients with CRI, especially those with Gram negative organisms)	Proposed text in SPC, section 4.4.	None proposed
Use with severe kidney failure (Use in severe renal insufficiency)	Proposed text in SPC, section 4.2, 4.4 and 4.8.	None proposed
Use with liver failure (Use in hepatic insufficiency)	Proposed text in SPC, section 4.2, 4.4 and 4.8.	None proposed
Pregnancy and breastfeeding	Proposed text in SPC, section	None proposed
(Pregnancy and lactation)	4.3 and 4.6.	

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

In conclusion the submitted Risk Management Plan, version 1.1 signed 13 March 2018 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Zyvox (linezolid) UK/H/0439/001-004/DC, Linezolid Amneal 600 mg film-coated tablets NL/H/3292/001/DC and Aktiprol (amisulpride) tablets DK/H/2386/001-004/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Zoxilid, is found adequate. There are no objections to approval of Zoxilid, from a non-clinical and clinical point of view. The product information is acceptable.
The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Mutual recognition/Decentralised procedure for Zoxilid, 600 mg, film-coated tablet was positively finalised on 2018-09-27.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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