Public Assessment Report
Scientific discussion

Linezolid B.Braun 2 mg/ml solution for infusion

Linezolid

ES/H/0348/01/DC

Applicant: B. Braun Medical, S.A.

This module reflects the scientific discussion for the approval of **Linezolid B. Braun 2 mg/mL solution for infusion.** The procedure was finalised on January 2017. For information on changes after this date please refer to the module ôUpdateô

INTRODUCTION

This decentralised application concerns a generic version of linezolid, under Linezolid B. Braun 2 mg/mL solution for infusion trade name.

The originator product is Zyvoxid 2 mg/ml solution for Infusion (Pfizer, Ltd.), first licensed on January 05th, 2001 in the UK.

The legal basis of the application is Article 10(1) of Directive 2001/83/EC.

The Concerned Member States involved in this procedure are DE, FR, IT, PT and UK

Linezolid 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.

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.

Linezolid is indicated 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. 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 product information is given in the SmPC.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for **Linezolid B. Braun 2 mg/mL solution for infusion**.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

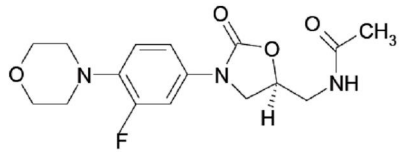
II-1 1 Drug substance

Linezolid

INN: Linezolid

Chemical Name: (S)-N-[{3-[3-Fluoro-4-(morphonyl)phenyl]-oxo-5-oxazolidil} methyl] acetamide

Structure:



Molecular formula: $C_{16}H_20FN_3O_4$
Molecular weight: 337.35
Appearance: White to off-white crystalline powder

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture and control of the active substance linezolid.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.
Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with relevant specifications except for some methods for which commitments have been agreed, so the remaining points will be subjected to variations.

Satisfactory certificate of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used to contain the active substance. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting suitable retest period when stored in the proposed packaging.

II-1 2 Drug product

Pharmaceutical development

The aim was to develop a generic product with the same qualitative and quantitative composition as the UK reference product, Zyvox 2 mg/ml Solution for Infusion and to provide the formulation as a ñready-to-useò single dose preparation for intravenous infusion, which is packaged in a plastic infusion bag.

All the excipients used in the manufacture of the proposed formulation comply with their respective European Pharmacopoeial monographs.

Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

Comparative physico-chemical characteristics have been provided for the proposed product versus the reference product, and pharmaceutical equivalence has been shown.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacture of the products

A satisfactory batch formula has been provided for the manufacturing of the finished product, together with an appropriate account of the manufacturing process. The process has been validated at the proposed industrial scale.

Finished product specifications

The finished product specification is satisfactory. Test methods have been described that have been adequately validated, as appropriate. Batch data from the process validation have been provided for all working standards used.

Stability of the products

Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life for the finished product of 36 months (unopened) with special storage conditions of ñ*Keep the bottle in the original package in order to protect from light*ò. The product should be used immediately after opening.

Suitably post approval stability commitments have been provided to continue the stability studies ongoing.

The grant of a marketing authorisation is recommended for this application provided that the commitments agreed are fulfilled.

II-2 Non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of the active substance has been provided, which is based on up-to-date and adequate scientific literature.
The submitted application concerns film coated tablets with the active substances in the same form as the reference product.
The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and the Member States agreed that no further non-clinical studies are required.

Environmental Risk Assessment (ERA)

No ERA was submitted. The medicinal product has the same quantitative and qualitative composition in active substances and a similar pharmaceutical form to the reference product. The introduction on the market of this medicinal product will not mean an increased exposure to

the environment, since the generic medicinal product is intended to substitute the reference medicinal product as well as other generic products in the market.
In accordance with the Guideline on the Environmental Risk Assessment for medicinal products for human use (CPMP/SWP/4447/00), the absence of this Environmental Risk Assessment is therefore justified.

II.3 Clinical aspects

Introduction

Linezolid is well-known drug with established efficacy and safety.

No new clinical efficacy or safety studies were conducted, which is acceptable for this abridged application. A clinical overview has been provided, which is based on scientific literature. The Member States agreed that no further clinical studies are required.

For this generic application, the MAH has not submitted a bioequivalence study, which is discussed below.

Biowaiver

The Applicant did not conduct any clinical study to support this application. According to the Guideline on the investigation of bioequivalence, if the test product is an aqueous intravenous solution at time of administration and contains an active substance (linezolid) in the same concentration as an approved intravenous solution, bioequivalence studies may be waived.

The Applicant claims that a bioequivalence study is not required since Linezolid B. Braun contains the same active substance in the same quantity as the reference product and has the same indications, route of administration, dosage form and posology.

Clinical bioequivalence studies are not necessary in view that both the reference product and the proposed product are aqueous intravenous solution containing the same active substance as the currently approved product.

In addition, the qualitative differences in excipients (i.e., pH adjuster) and the quantitative differences are not expected to affect the bioavailability of both products.

Bioequivalence

Not Applicable (see above)

Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

Discussion on the clinical aspects

Efficacy and safety of the active substance linezolid is well documented for the reference medicinal product.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the submitted evidence Linezolid B. Braun 2 mg/mL solution for infusion can be considered equivalent to Zyvoxid 2 mg/ml solution for Infusion (Pfizer, Ltd.).

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the reference medicinal product. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in January 2017.