IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Linezolid 2 mg/ml Solution for Infusion
Linezolid
PA2299/042/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/5737/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 21/01/2019 under procedure number IE/H/0870/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA2299/042/001
Marketing Authorisation Holder: Baxter Holding BV

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Linezolid 2 mg/ml solution for infusion (PL 20568/0078; UK/H/5737/001/DC) could be approved.

This is a decentralised abridged application submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the reference product, Zyvox 2mg/ml solution for infusion, which was granted a Marketing Authorisation to Pharmacia Ltd on 5 January 2001 following a national procedure (PL 00032/0259).

Linezolid 2 mg/ml solution for infusion is a 'Prescription-Only Medicine' (legal status "POM") containing the active substance Linezolid which is indicated for:

- Nosocomial pneumonia.
- Community acquired pneumonia.

  Linezolid is indicated in adults 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 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.

- Complicated skin and soft tissue infections.

  Linezolid is indicated in adults 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 (see section 4.4). 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.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Linezolid is a synthetic, antibacterial agent that belongs to a class of anti-microbials, called the oxazolidinones. It has *in vitro* activity against aerobic Gram positive bacteria and some anaerobic micro-organisms. Linezolid selectively inhibits bacterial protein synthesis binding to a site on the bacterial ribosome (23S of the 50S subunit) and preventing the formation of a functional 70S initiation complex which is an essential component of the translation process.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for an application of this type. In line with the CPMP 'guideline on the investigation of bioequivalence' subpoint 5.1.6, parenteral solutions, document reference: CPMP/EWP/1401/98, a bioequivalence study was not necessary to support this application, as both test and reference products are solutions at the time of administration.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with this application, and these are satisfactory.

The United Kingdom acted as RMS, and Austria, Germany, Greece, Spain, France, Ireland, Italy, Netherlands, Portugal were CMSs.

All Member States agreed to grant a Market Authorisation for the above Linezolid 2 mg/ml solution for infusion on 01 May 2017 (Day 209 of the procedure). Following a subsequent national phase, the UK granted a Market Authorisation (PL 20568/0078) for this product on 31 May 2017.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

Linezolid 2 mg/ml solution for infusion contains 2 mg per ml of Linezolid. Each 300 ml infusion bag contains 600 mg Linezolid. Other ingredients consist of the pharmaceutical excipients glucose monohydrate, sodium citrate (E331), citric acid (E330), sodium hydroxide (for pH adjustment) (E524), hydrochloric acid (for pH adjustment) (E507) and water for injections.

The finished product is packaged in a polyolefin infusion bag (Polyvinyl chloride free) containing a twist off port and extra medication port, sealed inside an aluminium over wrap. The bag holds 300 ml of solution containing 600 mg Linezolid and is packaged into a carton. Each carton contains 5, 10 or 30 infusion bags.

Not all pack sizes may be marketed, however, the marketing authorisation holder has agreed to provide mock-ups of any pack size to the relevant regulatory authorities before marketing.

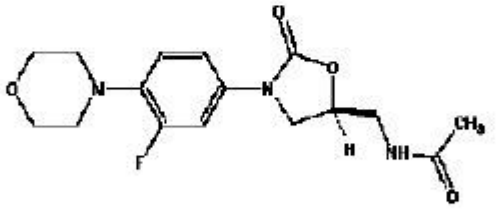
All primary product packaging complies with the current requirements. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 DRUG SUBSTANCES

Linezolid

Chemical Name: N-[[(5S)-3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide or (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide

Structure:



Molecular Formula: $C_{16}H_{20}FN_3O_4$

Molecular Mass: 337.35

Appearance: White to creamish crystalline powder

Solubility: Slightly soluble in acetone, methanol and insoluble in water, ethanol

Synthesis of the active 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 substance. 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 the relevant specification limits.

Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data that comply with the proposed specification are provided.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

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

II.3 DRUG PRODUCT

Pharmaceutical development

The objective of the development programme was to formulate a solution for infusion containing Linezolid 2 mg per ml of solution, which is comparable in performance to the originator product, Zyvox 2mg/ml solution for infusion (Pharmacia Ltd). A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Validation of the manufacturing process at commercial scale has shown satisfactory results.

Finished Product Specification

The finished product specification is acceptable. Test methods have been described that have been adequately validated. Batch data that comply with the release specification have been provided. In-house working standards are used, which are compared to European Pharmacopoeia references, where available. Representative Certificates of Analysis have been provided.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months for the unopened product, with the storage conditions, "Store in the original package (overwrap and carton) until ready to use in order to protect from light" and "Do not freeze".

From a microbiological point of view, the solution for infusion should be used immediately after opening. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Suitable post approval stability commitments to continue stability testing on batches of the finished product have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisation is granted for Linezolid 2 mg/ml solution for infusion.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of the active substance Linezolid are well-known. No new non-clinical data have been submitted for this application and none are required. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

No new pharmacology data were submitted and none are required for an application of this type.

III.3 Pharmacokinetics

No new pharmacokinetic data were submitted and none are required for an application of this type.

III.4 Toxicology

No new toxicology data were submitted and none are required for an application of this type.

III.5 Environmental Risk Assessment

Since this product will be used as a substitute for other products that are currently on the market, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary. The applicant has provided suitable information to verify that no increase in the exposure of the environment to the active ingredient is to be expected.

III.6 Discussion on non-clinical aspects

It is recommended that a Marketing Authorisation is granted for Linezolid 2 mg/ml solution for infusion.

IV. CLINICAL ASPECTS

IV CLINICAL ASPECTS

IV.1 Introduction

No new clinical studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant.

IV.2 Pharmacokinetics

In accordance, with the CPMP guideline "Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 Corr ** - subpoint 5.1.6, parenteral solutions, document reference: CPMP/EWP/1401/98", no bioequivalence data have been submitted with this application and none are required.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy

No new data on efficacy have been submitted and none are required for an application of this type.

IV.5 Clinical Safety

No new data on clinical safety have been submitted and none are required for an application of this type.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder has submitted an RMP, 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 2 mg/ml solution for infusion.

A summary of safety concerns, as approved in the RMP, are listed below:

Summary of safety concerns	
Important identified risks	1-Antibiotic associated colitis and diarrhoea (including pseudomembraneous colitis and Clostridium difficile associated diarrhoea 2-Convulsions 3-Lactic acidosis 4-Optic neuropathy 5-Myelosuppression (including leucopenia, anaemia, pancytopenia, and thrombocytopenia) 6-Mitochondrial toxicity including renal failure 7-Peripheral neuropathy 8-Serotonin syndrome 9- Long term treatment (more than 28 days)
Important potential risks	1-Increased fatal outcome in subset of patients with catheter related infections, especially, those with Gram negative infections.
Important missing information	1-Use in patients with severe hepatic insufficiency 2-Use in patients with severe renal insufficiency 3-Pregnancy and lactation

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Linezolid 2 mg/ml solution for infusion.

V USER CONSULTATION

A user consultation with target patient groups on the package leaflet has been performed and the results submitted in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

V. OVERALL CONCLUSIONS

VI. OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with Linezolid is considered to have demonstrated the therapeutic value of the compound and the product can be regarded as bioequivalent to the authorised reference product. The benefit-risk is, therefore, considered to be positive.

PRODUCT LITERATURE

In accordance with Directive 2010/84/EU the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for the product granted a Marketing Authorisation at a national level is available on the MHRA website.

VI. REVISION DATE

25/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/5737/1/DC to IE/H/0870/1/DC			