

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206473Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	(electronic stamp)
<b>From</b>	Dorota Matecka, Ph.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA #</b>	206473
<b>Applicant</b>	Hospira, Inc.
<b>Date of Submission</b>	December 19, 2014 ( <i>Class 2 NDA Resubmission</i> )
<b>PDUFA Goal Date</b>	June 19, 2015
<b>Proprietary Name / Established (USAN) names</b>	Linezolid Injection* (linezolid)
<b>Dosage forms/Strength</b>	Intravenous Solution, 600 mg/300 mL (2 mg/mL)
<b>Proposed Indication(s)</b>	Nosocomial pneumonia; Community-acquired pneumonia; Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; Vancomycin-resistant <i>Enterococcus faecium</i> infections
<b>Recommended:</b>	Approval

\* No proprietary/trade name was proposed for the drug product

## 1. Introduction

This 505(b)(2) NDA submitted by Hospira, Inc. provides for a new injectable formulation of linezolid to be used for the treatment of the same infections as provided in the listed drug labeling except for the uncomplicated skin and skin structure infection. The listed drug for this 505(b)(2) NDA is Zyvox® (linezolid) Injection, 600 mg/300 mL, approved on April 8, 2000 via NDA 21131. The drug product proposed by Hospira, Inc., Linezolid Injection, 600 mg/300 mL, differs from the listed drug in the excipients used in the composition of its formulation; specifically, it is formulated in a different vehicle (i.e., 0.9% sodium chloride instead of 5% dextrose) and (b) (4) removing sodium citrate and adjusting the contents of citric acid (b) (4).

There is no IND associated with the application and no clinical data have been submitted. The applicant is relying on previous findings of efficacy and safety for Zyvox® (linezolid) Injection for approval of this product. The majority of the information submitted in the NDA relates to the chemistry, manufacturing and controls used in the manufacture of the proposed linezolid drug product. In view of the similarities between the proposed and listed drugs, a biowaiver for conducting in-vivo bioequivalence studies was requested by the applicant on the basis of 21 CFR 320.22 (b): “a drug product’s in vivo bioavailability or bioequivalence may be considered self-evident”.

This NDA, originally submitted on November 25, 2013, was issued a tentative approval on September 26, 2014 due to an unexpired patent for the listed drug (Patent Number 5,688,792), which has now expired (on May 18, 2015). Since all of the reviewers found this NDA

acceptable in the first review cycle, for details regarding this application please refer to the original NDA reviews and the first CDTL review dated September 25, 2014.

## 2. Background

Linezolid is a synthetic antibacterial agent of the oxazolidinone class, which has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process. The results of time-kill studies have shown linezolid to be bacteriostatic against enterococci and staphylococci. For streptococci, linezolid was found to be bactericidal for the majority of isolates.

As stated above, Zyvox ® (linezolid) Injection was approved via NDA 21131 in 2000. Linezolid is also available in the United States as tablets and suspension for oral administration. As discussed above, the drug product proposed by Hospira has the same drug substance, dosage form, and concentration, route of administration, (b) (4) as Zyvox ®. Due to the difference in the formulation (i.e., a change in the excipients not permitted per 314.94(a)(9)(iii)), this application was submitted as 505(b)(2) application and not as a 505(j) application.

## 3. CMC/Device

The CMC Reviewer of the original NDA submission was Jane Chang, Ph.D., and the Product Quality Microbiology Reviewer was Jessica Cole, Ph.D.

All CMC issues were resolved during the first review cycle and the NDA was recommended for approval from the product quality perspective. The only change in the NDA resubmission dated December 19, 2014 included an update to DMF (b) (4) referenced for linezolid drug substance. DMF (b) (4) had been previously reviewed and found to be adequate in support of the original NDA. In addition, in support of the current NDA resubmission, a recent amendment to DMF (b) (4) was reviewed and found to be adequate (refer to DMF review by Sharon Kelly, Ph.D., dated 5/19/2015, in DARRTS).

In addition, facilities involved in the manufacture, testing and packaging of the proposed drug substance and the drug product were re-evaluated by the Office of Process and Facilities and found to be acceptable in support of this NDA.

Based on the overall assessment, OPQ recommended this NDA for approval from the product quality perspective (refer to the review by Dorota Matecka dated June 16, 2015 in Panorama).

#### **4. Nonclinical Pharmacology/Toxicology**

Dr. Wendy Schmidt was the Pharmacology/Toxicology Reviewer for this application. No new pharmacology and toxicology information was submitted in this NDA resubmission.

#### **5. Clinical Pharmacology/Biopharmaceutics**

Elsbeth Chikhale, Ph.D., was the Biopharmaceutics Reviewer and Ryan Owen, Ph.D., was the Clinical Pharmacology Reviewer for this application. No new biopharmaceutics or clinical pharmacology information was submitted in this NDA resubmission.

#### **6. Clinical Microbiology**

Kerry Snow, MS, was the Clinical Microbiology Reviewer for this application. No new clinical microbiology information was submitted in this NDA resubmission.

#### **7. Clinical/Statistical – Efficacy and Safety**

Alma Davidson, MD, was the Clinical Reviewer, and Christopher Kadoorie, Ph.D., was the Statistical Reviewer for this NDA. No new clinical or statistical information was submitted in this NDA resubmission. Recommendations for edits to the labeling have been incorporated. Dr. Davidson recommends approval of the NDA.

#### **8. Safety**

No new safety information was submitted in this NDA resubmission. Dr. Davidson recommends approval of the NDA.

#### **9. Advisory Committee Meeting**

There was no Advisory Committee Meeting for this application (the product is not an NME).

#### **10. Pediatrics**

The drug product proposed via this 505(b)(2) NDA does not contain a new active ingredient and is not a new dosage form. No new indication is proposed and no new dosing regimen is proposed. There is no new route of administration associated with the new product. For these

reasons, the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), does not apply to this application. No pediatric studies will be required as a condition of approval.

## 11. Other Relevant Regulatory Issues

No clinical studies/trials were conducted in support of this NDA. Therefore, no inspection request was sent to the Office of Scientific Investigations (OSI).

The reference listed application, NDA 21131 for Zyvox® (linezolid) Injection, has the following unexpired patents listed in the Orange Book:

- US Patent No. 5,688,792 - Expiry Date: November 14, 2014
- US Patent No. 5,688,792\*PED - Expiry Date: May 18, 2015
- US Patent No. 6,559,305 - Expiry Date: January 29, 2021
- US Patent No. 6,559,305\*PED - Expiry Date: July 29, 2021

In the original NDA submission, Hospira submitted Paragraph III Certification for patent number 5,688,792 stating that “*Hospira certifies that it will **not** market the Linezolid Injection for which this application is submitted until after the expiry of U.S. Patent No 5,688,792, including any pediatric extension thereof*”. This patent is now expired (as of May 18, 2015).

In addition, Hospira submitted Paragraph IV Certification for patent number 6,559,305 stating that “*Hospira certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 6,559,305 is either invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Hospira's Linezolid Injection for which this application is submitted*”. Subsequently, the applicant submitted an NDA amendment (dated July 24, 2014) to certify that “*the holder of the application for the Reference Listed Drug (RLD) and the owner of the patents identified in our Paragraph IV certification have been notified and have acknowledged receipt of said notification*”. The cover letter of the same NDA amendment included also a statement that “*no litigation was initiated against Hospira, Inc. by the holder of the RLD application or patent, Pharmacia Upjohn Co. during the 45-day period*”. In addition, the cover letter of the current NDA resubmission includes a confirmation that no litigation was initiated against Hospira by Pharmacia Upjohn Co. during the 45-day period.

## 12. Labeling

The proposed labeling for Linezolid Injection, 600 mg/300 mL, was submitted in Physician’s Labeling Rule (PLR) format. No trade name was proposed for the drug product. The recommendations from the Division were incorporated by the applicant in the proposed labeling for the proposed Hospira’s product.

All recommended changes were agreed to and incorporated by the applicant in the package insert, and the respective carton and container labels.

### 13. Recommendations/Risk Benefit Assessment

An injectable formulation (intravenous solution) of linezolid has been marketed in the United States since 2000 under the trade name Zyvox® Injection. The currently proposed product by Hospira, Linezolid Injection, 600 mg/300 mL, would provide an alternative product that contains the same amount of the active ingredient, i.e., 2 mg/mL, for the proposed product versus Zyvox® Injection, however, in a different vehicle (i.e., 0.9% saline versus 5% dextrose for the listed drug); therefore, potentially meeting an unmet need for the patient population on sugar restrictions. The risk-benefit profile of the proposed by Hospira linezolid formulation is expected to be similar to the listed drug.

There are no unresolved issues or deficiencies that need to be conveyed to the sponsor. No PMRs, PMCs, or pediatric studies need to be requested.

The overall recommendation for this NDA should be approval. This conclusion is based on recommendations from all Disciplines involved in the review of this application.

Dorota M. Matecka

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Digitally signed by Dorota M. Matecka -S  
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ou=People, 0.9.2342.19200300.100.1.1=1300123291,  
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