

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206473Orig1s000

SUMMARY REVIEW

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	206473; Class 2 resubmission
Applicant Name	Hospira, Inc.
Date of Submission	December 19, 2014
PDUFA Goal Date	June 19, 2015
Established (USAN) Name	Linezolid Injection (in 0.9% Sodium Chloride)
Dosage Forms / Strength	Intravenous Solution, 600 mg/300 mL (2 mg/mL)
Proposed Indications	Nosocomial pneumonia Complicated Skin and Skin Structure Infections including diabetic foot infections, without concomitant osteomyelitis Community Acquired Pneumonia Vancomycin resistant <i>Enterococcus faecium</i> infections
Recommended Action:	Approval

1.0 Introduction

NDA 206473, Linezolid Injection (in 0.9% Sodium Chloride), 600 mg/300 mL, submitted by Hospira, Inc., provides for a new formulation of injectable linezolid to be used for the treatment of the same indications as listed in the labeling for Zyvox[®] (linezolid), with the exception of uncomplicated skin and skin structure infections (uSSSI). The uSSSI indication is only for the oral formulation and hence not applicable to this NDA. This NDA was submitted as a 505(b)(2) application and the listed drug is Zyvox[®] (linezolid) Injection, 600 mg/300 mL, held by Pfizer (NDA 21131). Zyvox[®] is also available in other formulations, including 200 mg/100mL and 400 mg/200 mL infusion bags, 100 mg/5mL oral suspension, and as 600 mg tablets. Zyvox[®] (linezolid) is approved for the treatment of the following indications:

- Nosocomial Pneumonia
- Complicated Skin and Skin Structure Infections including diabetic foot infections, without concomitant osteomyelitis
- Uncomplicated Skin and Skin Structure Infections
- Community Acquired Pneumonia
- Vancomycin resistant *Enterococcus faecium* infections

2.0 Background

The proposed drug product, Linezolid Injection (in 0.9% Sodium Chloride), 600 mg/300 mL, is a new formulation of linezolid for injection. The drug product differs from the listed drug in that it is formulated in a different vehicle (i.e., 0.9% sodium chloride instead of 5% dextrose) and the

(b) (4) removing sodium citrate and adjusting the contents of citric acid (b) (4). On September 26, 2014, a tentative approval action was taken as the listed drug, Zyvox® (linezolid) Injection was subject to a period of patent protection.

This review only addresses the issues reviewed with the resubmission. For a detailed discussion of NDA 206473, please refer to discipline specific reviews and the Cross-Discipline Team Leader Review.

3.0 Product Quality

The Chemistry, Manufacturing and Controls (CMC) reviewer for the original submission was Jane Chang, PhD, and the product quality microbiology reviewer was Jessica Cole, PhD. Dorota Matecka, PhD, from the Office of Pharmaceutical Quality has provided a review for this resubmission.

The only change in the resubmission from a CMC perspective was an update to DMF (b) (4) referenced for linezolid drug substance. In a review dated 5/19/2015, Sharon Kelly, Ph.D., noted that the recent amendment to DMF (b) (4) was acceptable and found the DMF to be adequate.

The Office of Process and Facilities has issued an overall recommendation of “Acceptable” for this NDA.

Based on the overall assessment of the CMC information submitted in the NDA, Dr. Matecka concludes that sufficient information to assure the identity, strength, purity, and quality of the drug product has been provided and recommends approval of this NDA.

4.0 Labeling

Aleksander Winiarski, PharmD, from the Division of Medication Error Prevention and Analysis had performed a labeling review in the first review cycle. Dr. Winiarski’s recommendations for labeling revisions have been incorporated. To avoid any potential for overdose, pediatric use language has been added in the Highlights of Prescribing Information, in the Dosage and Administration section and in the Pediatric Use section to state that this product should be used only in pediatric patients who require the entire 600 mg dose and not any fraction thereof. Any reference to the (b) (4) (b) (4). Additional labeling changes were made to be consistent with revised labeling for Zyvox approved on June 06, 2015.¹

¹ http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021130s030,021131s029,021132s034lbl.pdf

5.0 Other Regulatory Issues

At the time of the initial action, the reference listed application, NDA 21131, Zyvox (linezolid) Injection, had 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

With the original submission, the Applicant 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*”.

The Applicant had also 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*”.

On July 24, 2014, the Applicant submitted an amendment 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 Applicant also stated 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 the resubmission, the Applicant confirmed that no litigation was initiated against Hospira by Pharmacia Upjohn Co. for US Patent number 6,559,305 during the 45-day period. US Patent No. 5,688,792 expired on May 18, 2015.

This application was not presented to the Anti-Infective Drugs Advisory Committee (AIDAC), as there were no issues requiring input from the AIDAC.

6.0 Recommended Regulatory Action

I agree with the recommendations made by the review team that this NDA be approved, under Section 505(b)(2) of the Food Drug and Cosmetic Act, relying on the Agency’s prior findings of safety and effectiveness of the listed drug product, Zyvox® (linezolid) Injection.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUMATHI NAMBIAR
06/18/2015

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	206473
Applicant Name	Hospira, Inc.
Date of Submission	November 25, 2013
PDUFA Goal Date	September 26, 2014
Established (USAN) Name	Linezolid Injection (in 0.9% Sodium Chloride)
Dosage Forms / Strength	Intravenous Solution, 600 mg/300 mL (2 mg/mL)
Proposed Indications	Nosocomial pneumonia Complicated Skin and Skin Structure Infections including diabetic foot infections, without concomitant osteomyelitis Community Acquired Pneumonia Vancomycin resistant <i>Enterococcus faecium</i> infections
Recommended Action:	Tentative Approval

Material Reviewed/Consulted	Names of Discipline Reviewers
Action Package including:	
Pharmacology Toxicology Review	Wendelyn Schmidt PhD
Chemistry Manufacturing and Controls Review	Jane Chang PhD
Quality Biopharmaceutics Review	Elsbeth Chikhale PhD
Cross-Discipline Team Leader Review	Dorota Matecka PhD
Medical Officer Review	Alma Davidson MD
Statistical Review	Christopher Kadoorie PhD
Product Quality Microbiology Review	Jessica Cole PhD
Clinical Microbiology Review	Kerry Snow MS
Clinical Pharmacology Review	Ryan Owen PhD
Division of Medication Error Prevention and Analysis	Aleksander Winiarski Pharm D

1.0 Introduction

NDA 206473, Linezolid Injection (in 0.9% Sodium Chloride), 600 mg/300 mL, submitted by Hospira, Inc., provides for a new formulation of injectable linezolid to be used for the treatment of the same indications as listed in the labeling for Zyvox[®] (linezolid), with the exception of uncomplicated skin and skin structure infections (uSSSI). The uSSSI indication is only for the oral formulation and hence not applicable to this NDA. This NDA was submitted as a 505(b)(2) application and the listed drug is Zyvox[®] (linezolid) Injection, 600 mg/300 mL, held by Pfizer (NDA 21131). Zyvox[®] is also available in other formulations, including 200 mg/100mL and 400 mg/200 mL infusion bags, 100 mg/5mL oral suspension, and as 600 mg tablets. Zyvox[®] (linezolid) is approved for the treatment of the following indications:

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- Vancomycin resistant *Enterococcus faecium* infections

2.0 Background

The proposed drug product, Linezolid Injection (in 0.9% Sodium Chloride), 600 mg/300 mL, is a new formulation of linezolid for injection. The drug product differs from the listed drug in that it is formulated in a different vehicle (i.e., 0.9% sodium chloride instead of 5% dextrose) and the (b)(4) removing sodium citrate and adjusting the contents of citric acid (b)(4). 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. The applicant has requested a biowaiver for conducting in vivo bioequivalence studies on the basis of 21 CFR 320.22 (b).

The review team has completed their reviews of this application. For a detailed discussion of NDA 206473, please refer to discipline specific reviews and the Cross-Discipline Team Leader Review.

3.0 Product Quality

The Chemistry, Manufacturing and Controls (CMC) reviewer for this application is Jane Chang, PhD, and the product quality microbiology reviewer is Jessica Cole, PhD.

For the majority of the information regarding drug substance, the applicant referenced Type II DMF (b)(4) held by (b)(4). This DMF was reviewed and found adequate by Dr. Chang. The drug product is a clear, colorless to slightly yellow sterile aqueous solution for intravenous infusion with a pH range of 4.4 to 5.2 and does not contain any novel excipients. It is

a (b) (4) sterilized product containing no antimicrobial preservatives. The inactive ingredients include citric acid anhydrous USP 1.92 mg/mL, sodium chloride USP 9 mg/mL, and sodium hydroxide NF 0.76 mg/mL, and water for injection USP. Sodium hydroxide NF and/or hydrochloric acid NF are used to adjust the pH.

The proposed commercial container closure system is a (b) (4) mL VisIV flexible container with a 300 mL fill in a foil laminate overwrap. Two Type III DMFs, which were referenced in the current application for the VisIV flexible container, were previously referenced and found adequate for other approved injectable drugs. Information on extractable and leachable profiles for the proposed container closure system was found to be adequate. This includes information on extractables using a medium relevant to the proposed drug product formulation (a medium of pH about 4.8), which was submitted on September 4, 2014, in response to an information request from the Agency.

Long-term (25°C/40% RH, 30°C/35% RH, 30°C/75% RH) and accelerated (40°C/<25% RH and 40°C/75% RH) stability data for three representative batches of the drug product manufactured at the proposed commercial facility were submitted. Based on these data, the proposed expiration dating period of 24 months for the commercial drug product stored in the proposed commercial container closure system at 20° – 25°C (68° – 77°F), with excursions permitted to 15° – 30°C (59° – 86°F) was found acceptable by Dr. Chang.

On January 14, 2014, the Office of Compliance issued an overall recommendation of “Acceptable” for this NDA.

Based on the overall assessment of the CMC information submitted in the NDA, Dr. Chang recommends approval of this NDA.

4.0 Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this application is Wendelyn Schmidt, PhD. Dr. Schmidt’s review focused on the toxicology and genotoxicity studies conducted on (b) (4) products in the drug product observed in long-term stability. No toxicology or genotoxicity findings were seen at clinically relevant levels. Dr. Schmidt concluded that degradants can be considered qualified from a pharmacology/toxicology perspective and recommends approval of the NDA.

5.0 Quality Biopharmaceutics

Elsbeth Chikhale, PhD, is the Quality Biopharmaceutics reviewer for this application. The applicant has requested a waiver for conducting in vivo bioequivalence studies based on 21CFR 320.22(b). The applicant had initially proposed a (b) (4)0% overage which was not found to be acceptable. The revised specification proposed by the applicant of (b) (4) mL was found

acceptable. Dr. Chikhale concluded that with the revision of the product specification, the applicant has provided adequate evidence to support the biowaiver request and recommends approval of the NDA.

6.0 Clinical Microbiology

Kerry Snow, MS, is the clinical microbiology reviewer for this application. No new clinical microbiology information was submitted in this application. The labeling recommendations have been incorporated into the Microbiology section.

7.0 Clinical Pharmacology

Ryan Owen, PhD, is the clinical pharmacology reviewer for this application. Dr. Owen notes that the application is acceptable from a clinical pharmacology perspective. No new clinical pharmacology information was submitted in this NDA. Dr. Owen's recommendations for labeling have been incorporated.

8.0 Clinical Efficacy/Safety

Alma Davidson, MD, is the clinical reviewer for this application. No new clinical or statistical information was submitted in this NDA. No new safety issues were identified. Dr. Davidson's recommendations for labeling have been incorporated. Dr. Davidson recommends approval of the NDA.

Christopher Kadoorie, PhD, is the statistics reviewer for this NDA. Dr. Kadoorie stated that as no clinical data were submitted, there are no statistical issues to report and deferred the decision on the NDA to other disciplines.

9.0 Labeling

Aleksander Winiarski, PharmD, from the Division of Medication Error Prevention and Analysis performed a labeling review. Dr. Winiarski's recommendations for labeling revisions have been incorporated. To avoid any potential for overdose, pediatric use language has been added in the Highlights of Prescribing Information and in the Dosage and Administration section to state that this product should be used only in pediatric patients who require the entire 600 mg dose and not any fraction thereof. Any reference to the [REDACTED] (b) (4)

10.0 Pediatrics

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless the requirement is waived, deferred or inapplicable. As none of these criteria are applicable, this NDA is exempt from PREA requirements.

11.0 Other Regulatory Issues

The reference listed application, NDA 21131, 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
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The applicant has 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*".

The applicant has also 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*".

On July 24, 2014, the applicant submitted an amendment 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 applicant also stated 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*".

This application was not presented to the Anti-Infective Drugs Advisory Committee (AIDAC), as there were no issues requiring input from the AIDAC.

12.0 Recommended Regulatory Action

I agree with the recommendations made by the review team that this NDA be approved, under 505(b)(2), relying on the Agency's prior findings of safety and effectiveness of the listed drug product, Zyvox® (linezolid) Injection. However, due to an unexpired patent for Zyvox® Injection (expiration date for patent number 5688792 is 5/18/2015), a Tentative Approval is recommended.

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/s/

SUMATHI NAMBIAR
09/26/2014