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APPLICATION NUMBER:

206473Orig1s000

MEDICAL REVIEW(S)

Clinical Review

NDA 206473	505(b)(2)
Date of Class 2 Resubmission	December 19, 2014
New PDUFA Goal Date	June 19, 2015
Applicant	Hospira, Inc
Drug Name	Linezolid Injection in 0.9% Sodium Chloride
Dosage Form/Strength	Injection/ 600 mg in 300 mL
Proposed Indications	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
Clinical Reviewer	Alma C. Davidson, M.D.
Medical Team Leader	Hala Shamsuddin, M.D.

Introduction

Linezolid Injection contains an antibacterial agent of the oxazolidinone class. Hospira, Inc. has submitted a 505(b)(2) New Drug Application (NDA) 206473 for Linezolid Injection in 0.9% Sodium Chloride to the FDA on May 15, 2012, using the Pharmacia & Upjohn Company product, NDA 21131 for Zyvox[®] I.V. (linezolid) injection, as the reference listed drug (RLD). There are no clinical trials conducted by the applicant to support this 505(b)(2) NDA for Linezolid Injection in 0.9% Sodium Chloride. The review for this NDA relies on the prior FDA determination of effectiveness and safety of Zyvox[®] I.V. (linezolid) injection based on studies which were not conducted by or for the applicant.

In that submission, the applicant received a Tentative Approval (TA) on September 26, 2014 because of the reference listed drug upon which this NDA is subject to a period of patent and/or exclusivity protection and therefore final approval of this application under section 505(c) (3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired. The patents expire on May 18, 2015.

On December 19, 2014, the applicant submitted a minor amendment to this NDA for. Linezolid Injection in 0.9% Sodium Chloride. This is in response to the FDA's Tentative Approval Letter dated September 26, 2014.

Recommendation on Regulatory Action

From the clinical standpoint, this application is recommended for approval. The chemistry, manufacturing, and controls (CMC) review is pending. The Linezolid Injection in 0.9% Sodium Chloride label in Physician's Labeling Rule (PLR) format has been reviewed by the respective disciplines.

Review

No new safety information was identified in the recent periodic adverse drug experience report of the RLD that would alter the risk/benefit assessment of linezolid. *(Note to reader: Please see Clinical Review in DARRTS dated August 14, 2014 for the first cycle of this NDA submission.)*

Labeling Recommendations

The clinical reviewer has made labeling changes to Section 14 CLINICAL STUDIES- 14.2 Pediatric Patients and Table 18 subsection of the Linezolid Injection in 0.9% Sodium Chloride label (see below). These labeling changes were added for consistency with the recent labeling changes made to the RLD, Zyvox® I.V. (linezolid) Injection label. (Note: Other minor editorial changes and microbiology labeling changes made to the Linezolid injection in 0.9% Sodium Chloride label are not mentioned in this review.)

- 14 CLINICAL STUDIES

- 14.2 Pediatric Patients: In this subsection, the words [REDACTED] (b) (4)
[REDACTED]
[REDACTED]. Table 18 title and contents were revised including deletion of data pertaining to [REDACTED] (b) (4)
[REDACTED]

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/s/

ALMA C DAVIDSON
06/08/2015

HALA H SHAMSUDDIN
06/08/2015

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Dorota Matecka, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	206473
Applicant	Hospira, Inc.
Date of Submission	November 25, 2013
PDUFA Goal Date	September 26, 2014
Proprietary Name / Established (USAN) names	Linezolid Injection* (linezolid)
Dosage forms/Strength	Intravenous Solution, 600 mg/300 mL (2 mg/mL)
Proposed Indication(s)	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
Recommended:	Tentative Approval (TA)

* 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”.

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 was Jane Chang, Ph.D., and the Product Quality Microbiology Reviewer was Jessica Cole, Ph.D. Their findings are summarized below.

The linezolid drug substance is manufactured by (b)(4). This facility and other testing facilities listed for the drug substance for this NDA were found acceptable by the Office of Compliance. For the majority of CMC information for linezolid drug substance, a reference is made to DMF Type II (b)(4) held by (b)(4). This DMF was reviewed and found adequate by Dr. Chang for the purpose of the current NDA (DMF review in DARRTS dated August 8, 2014). In addition, some general information (Section 3.2.S.1), a specification including information on impurities, container closure system, reference standards, and batch analysis have been also provided in the NDA for the linezolid drug substance and found acceptable.

Linezolid Injection, 600 mg/300 mL, is a sterile aqueous solution for intravenous infusion. The drug product is a clear, colorless to slightly yellow solution with a pH range of 4.4 to 5.2. It is a (b)(4) sterilized product containing no antimicrobial preservatives. The proposed formulation of linezolid does not contain any novel excipients. The inactive ingredients in the linezolid drug product 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 manufacturing process of Hospira's Linezolid Injection includes the following units of operation: (b)(4)

(b)(4)

(b) (4)

The commercial container closure system to be used for Linezolid Injection is a (b) (4) mL VisIV flexible container with a 300 mL fill in a foil laminate overwrap. The flex bag will be closed with administration and additive port assemblies. The drug product, Linezolid Injection, 600 mg/300 mL, in (b) (4) mL VisIV™ (b) (4) flexible containers will be packaged in quantity of 10 containers per case. Two Type III DMFs, which were referenced in the current application for the VisIV containers, were previously referenced and found adequate for other injectable drugs approved by CDER. Information on extractable and leachable profiles for the proposed container closure system for Linezolid Injection has been provided and found adequate. This includes information on extractables using a medium relevant to the proposed drug product formulation (e.g., a medium of pH about 4.8), which was submitted in response to the Agency information request via the September 4, 2014 amendment.

The drug product specification includes tests for clarity, volume, color (visual and instrumental), particulate matter, sterility, bacterial endotoxins, assay, osmolality, pH, identification, assay, impurities, total sodium, and (b) (4). The drug product specification, as revised in several subsequent amendments to the original NDA submission, was found acceptable. As mentioned above, the proposed drug product manufacturing process includes a (b) (4) sterilization. These aspects of the manufacturing process, as well as integrity of the container closure system, and the proposed microbiological quality attributes in the drug product specification were evaluated by the Product Quality Microbiology Reviewer, Dr. Jessica Cole who recommended this NDA for approval from the product quality microbiology standpoint (review dated July 11, 2014 in DARRTS).

Stability information submitted in section 3.2.P.8.3 includes 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 Linezolid Injection, 600 mg/300 mL, manufactured at the proposed commercial facility (Hospira). 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. In addition, the compatibility data showed that Linezolid Injection formulated in 0.9% sodium chloride is compatible with 5% Dextrose Injection, USP, Lactated Ringer's Injection, USP, and 0.9% Sodium Chloride Injection, USP, which are listed in the proposed package insert, specifically Section 2.3 Compatibilities (which are the same diluents listed in Zyvox® package insert) .

The drug product is manufactured, packaged, labeled and tested for release and stability at the Hospira facility at Rocky Mount, NC. This site and several other facilities involved in the manufacture, testing, packaging and labeling of the drug substance and the drug product were found acceptable by the Office of Compliance (an Overall Recommendation of "Acceptable" was issued for this NDA on January 14, 2014). Based on the overall assessment of the CMC information submitted in the NDA, Dr. Chang recommended this NDA for approval (for details refer to the CMC review dated September 19, 2014 in DARRTS).

4. Nonclinical Pharmacology/Toxicology

Dr. Wendy Schmidt was the Pharmacology/Toxicology Reviewer for this application.

The pharmacology and toxicology review of this 505(b)(2) application, focused on reports from toxicology and genotoxicity studies conducted on a series of degradation products in the drug product observed in long term stability. In 28 day toxicology studies of (b) (4) 1, 2 and 3 (b) (4), no significant toxicities were found at levels up to 10X the clinical level (the highest dose tested). There was no evidence of mutagenicity or clastogenicity for (b) (4) and (b) (4) in the Ames and human chromosomal aberrations assays either. (b) (4) did not appear to be positive for genotoxic damage in an in silico survey. Therefore, Dr. Schmidt concluded that degradants can be considered qualified and further concluded that this NDA can be approved from the nonclinical pharmacology standpoint (for details refer to the review dated April 15, 2014 in DARRTS).

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. Their findings and recommendations are summarized below.

This NDA includes a bioequivalence (BE) waiver request for the proposed drug product (referring to the listed drug, Zyvox® (linezolid) Injection approved under NDA 21131). The focus of the biopharmaceutics review was on the evaluation and acceptability of the data supporting the approval of the BE waiver request. In Dr. Chikhale's assessment, the Applicant provided adequate information demonstrating that the differences in the proposed formulation versus the listed drug such as changes in the inactive ingredients (substitution of 5% dextrose by 0.9% sodium chloride, removal of sodium citrate and adjusting the contents of citric acid (b) (4)) are not expected to affect the distribution or elimination of the active drug substance, linezolid. In addition, in response to the CMC Reviewer's recommendation, the Applicant revised the bag fill volume from originally proposed range (b) (4) ml to the range of (b) (4) mL (target (b) (4) mL) thus ensuring that the proposed product has the (b) (4). Based on the overall information, Dr. Chikhale concluded that the Applicant's request for a biowaiver for their proposed Linezolid Injection, 600 mg/300 mL (2 mg/mL) is acceptable and the biowaiver is granted. Subsequently, this NDA is recommended for approval from the biopharmaceutics perspective (review dated July 15, 2014 in DARRTS).

The Clinical Pharmacology Reviewer, Dr. Ryan Owen, stated that application is acceptable from a clinical pharmacology perspective as no new clinical pharmacology information was submitted by the applicant in this NDA. The clinical pharmacology review focused on the labeling proposed by Hospira for their drug product, which resulted in several recommendations as described in detail in the review document dated June 20, 2014 in DARRTS.

6. Clinical Microbiology

Kerry Snow, MS, was the Clinical Microbiology Reviewer for this application.

No new clinical microbiology information was submitted with this application. The clinical microbiology reviewer provided several recommended changes in the proposed drug product package insert (refer to the review dated September 22, 2014 in DARRTS).

7. Clinical/Statistical - Efficacy

Alma Davidson, MD, was the Clinical Reviewer, and Christopher Kadoorie, Ph.D., was the Statistical Reviewer for this NDA.

The Clinical Reviewer stated that this 505(b)(2) NDA, which provides for a new intravenous formulation of linezolid, does not contain any nonclinical or clinical studies as the applicant of the current 505(b)(2) NDA is relying on the previous findings of safety for the listed drug, Zyvox® (linezolid) Injection. The Clinical Reviewer stated that the proposed active ingredient, concentration, dosage form and strength for the proposed drug product are the same as the listed drug. The proposed inactive ingredients (b) (4) the vehicle (b) (4). The currently proposed drug product has the same proposed indications except for the uncomplicated skin and skin structure infection; Hospira's drug product has also the same dosing regimens and the same intended populations as the listed drug (Zyvox®) Injection). Dr. Davidson concluded that the risk-benefit assessment for this product has been demonstrated and supported by prior evidence and experience with the listed drug (Zyvox® Injection). In addition, no new safety information has been identified that would significantly alter the risk/benefit assessment of linezolid in the treatment of the labeled indications (review dated August 14, 2014 in DARRTS).

Dr. Kadoorie stated that since this application is relying on the listed drug and there are no clinical studies included, there are no issues to report and subsequently no recommended edits to the proposed labeling from a statistical perspective (refer to the review dated August 20, 2014 in DARRTS).

8. Safety

The applicant of the current 505(b)(2) NDA is relying on the previous findings of safety for the listed drug, Zyvox® (linezolid) Injection. As stated in the clinical review, upon review of the cases reporting labeled adverse events as reported in the recent Periodic Adverse Drug Experience Report (PSUR) submitted for Zyvox®, there is no new safety information that would significantly alter the risk-benefit profile of linezolid. In addition, the recent Annual Report submitted for Zyvox® did not reveal any significant new clinical information that might affect the safety, effectiveness, or labeling of this product. The excerpts from the USPI

for the RLD, Zyvox® (linezolid) Injection describing adverse events reported during the postmarketing experience such as myelosuppression, peripheral neuropathy, optic neuropathy, lactic acidosis, serotonin syndrome in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin inhibitors (SSRIs) and linezolid, convulsions, anaphylaxis, angioedema, and bullous skin disorders such as those described as Stevens-Johnson syndrome, and other adverse events (e.g., superficial tooth discoloration and tongue discoloration) have also been included in the proposed draft labeling for the Hospira's product (for details refer to the clinical review by Dr. Davidson dated August 14, 2014 in DARRTS).

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 initial 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*".

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 includes 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".

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 all reviewers were incorporated in the proposed labeling for Hospira's product.

Several revisions were made to the proposed product labeling to reflect the recently approved changes to the Zyvox[®] labeling. In addition, as described in the clinical review, a pediatric use language has been added in the Highlights of Prescribing Information for this particular formulation and product container to prevent potential overdose or other medication errors in pediatric patients: "Pediatric Patients -The recommended dose is 10 mg per kg intravenously every 8 hours. Linezolid Injection, a single use in VisIV[™] Container should be used only in pediatric patients who require the entire 600 mg dose and not any fraction thereof.(2.1)" Similar statement was also added in the Dosage and Administration section.

In addition, the Division of Medication Errors Prevention Analysis (DMEPA) evaluated the proposed container and carton labels and package insert and provided several recommendations to improve prominence of product and use information. DMEPA recommended that the proposed carton and container labels be revised to clarify the content of the bag to state: 600 mg/300 mL and in a smaller font below (2 mg/mL). Other recommendations included, for example: 1) revising the letter case of the established name "LINEZOLID" from all capitals to title case, "Linezolid"; and 2) revising the statement ^{(b) (4)} to "For Intravenous Infusion" and relocating it below the strength statement to ensure appropriate prominence (for other recommendations refer to the DMEPA review dated July 3, 2014 in DARRTS). In addition, several comments and recommendations were also provided by the Office of Prescription Drug Promotion (OPDP).

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, [REDACTED] (b) (4) [REDACTED]. 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. However, due to the unexpired patents for Zyvox® Injection, a Tentative Approval is recommended at the present time.

The Sponsor has provided Paragraph III certification for patent number 5688792 according to 21 CFR 314.50(i)(1)(i)(A)(3). With the pediatric exclusivity extension, the expiry date is 5/18/2015. The product would not be eligible for final approval until then.

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/s/

DOROTA M MATECKA
09/25/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206473
Priority or Standard	Standard
Submit Date(s)	November 26, 2013
Received Date(s)	November 26, 2013
PDUFA Goal Date	September 26, 2014
Division / Office	DAIP/OAP
Reviewer Name(s)	Alma C. Davidson, M.D.
Review Completion Date	August 13, 2014
Established Name	Linezolid Injection
(Proposed) Trade Name	Linezolid Injection
Therapeutic Class	Oxazolidinone
Applicant	Hospira, Inc.
Formulation(s)	600 mg/300 mL
Dosing Regimen	600 mg q12h I.V.
Indication(s)	Nosocomial pneumonia; Community-acquired pneumonia; Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; and Vancomycin-resistant <i>Enterococcus faecium</i> infections
Intended Population(s)	Adults and Pediatric patients

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical standpoint, this application is recommended for approval. The chemistry, manufacturing, and controls (CMC) review is pending. The Linezolid Injection label in Physician's Labeling Rule (PLR) format has been reviewed by all respective disciplines.

1.2 Risk Benefit Assessment

Risk-benefit assessment for this product has been demonstrated and supported by prior evidence and experience with the RLD (ZYVOX[®]I.V.). No new safety information has been identified that would significantly alter the risk/benefit assessment of linezolid in the treatment of the labeled indications.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no new safety issues associated with this proposed formulation that require any postmarketing risk evaluation and mitigation strategies at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no new safety issues associated with this proposed formulation that require any postmarketing requirements or commitments at this time.

2 Introduction and Regulatory Background

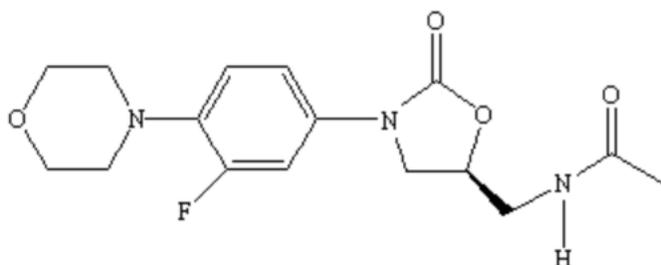
The Applicant, Hospira Inc., has submitted this 505(b)(2) new drug application (NDA) for Linezolid in 0.9% Sodium Chloride Injection, which relies upon the Agency's previous findings of safety and efficacy for referenced Pharmacia & UpJohn Company product, for ZYVOX[®]I.V. (linezolid) injection (NDA 21131). No clinical trials were conducted by the Applicant to support this 505(b)(2) NDA.

The Applicant is proposing Linezolid Injection in a 0.9% Sodium Chloride vehicle (b) (4)

2.1 Product Information

Linezolid for injection is a sterile, pyrogen-free, synthetic, broad-spectrum, oxazolidinone antibacterial for intravenous administration. Its chemical name is (S)-N-[[3-[3-Fluoro-4-(4morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide.

Molecular structure:



Molecular formula: C₁₆H₂₀FN₃O₄

Molecular weight: 337.35

RLD (USA) Approved Dosage Strength: ZYVOX[®] I.V. (linezolid) Injection 600 mg in 300 mL.

Applicant's Proposed Dosage Strength: Linezolid Injection 600 mg in 300 mL.

The proposed active ingredient, concentration, dosage form and strength for the proposed drug product are the same as the Reference Listed Drug. The proposed (b) (4) those in the Reference Listed Drug, (b) (4) the vehicle and (b) (4).

The Applicant's product has the same proposed indications, with the exception of the uncomplicated skin and skin structure infection because the recommended dosing is with oral linezolid and the applicant's product is IV formulation only: Nosocomial pneumonia; Community-acquired pneumonia, Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; and Vancomycin-resistant *Enterococcus faecium* infections. The Applicant's product has also the same dosing regimens and the same intended populations as the RLD.

2.2 Tables of Currently Available Treatments for Proposed Indications

No new proposed indications are included in this application. Related drugs, however, include vancomycin, linezolid, tigecycline, daptomycin, telavancin, ceftaroline, and dalbavancin.

2.3 Availability of Proposed Active Ingredient in the United States

The original NDA # 021131 for Zyvox[®] was approved on April 18, 2000. Zyvox[®] is also available in oral tablet (600 mg) and oral suspension (100 mg/5 mL) used for the following indications: Nosocomial pneumonia; Community-acquired pneumonia
Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; Uncomplicated skin and skin structure infections and Vancomycin-resistant *Enterococcus faecium* infections. Other generic linezolid injection product includes an injectable, 200 mg/100 mL formulation.

2.4 Important Safety Issues with Consideration to Related Drugs

There are recent major safety labeling changes to the RLD, ZYVOX[®] I.V. Injection label as of May, 2013 which include: In the “5. Warnings and Precautions section: Serotonin syndrome (5.3); and Hypoglycemia (5.9).”

It is notable that there are major safety issues with other similar antibacterial drugs with MRSA activity including vancomycin (e.g., “Red-Man Syndrome” and nephrotoxicity); daptomycin (e.g., myopathy and rhabdomyolysis); tigecycline (e.g., increase in all-cause mortality in Phase 3 and 4 clinical trials); telavancin (e.g., nephrotoxicity); ceftaroline (e.g., direct Coombs’ test seroconversion); and dalbavancin (e.g., rapid intravenous infusion can cause reactions that resemble “Red-Man Syndrome”).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Agency had no presubmission interaction with the Applicant related to this Submission. There is no IND associated with the application.

2.6 Other Relevant Background Information

According to the Applicant, the formulation of Linezolid for Injection is based on the reference list drug (RLD), ZYVOX[®] I.V. ZYVOX[®] I.V. is available as a 600mg/vial injection presentation in the USA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Although no clinical studies, from a clinical perspective there were no deficiencies and the application was determined to be filable. Responses to information requests were timely and complete.

3.2 Compliance with Good Clinical Practices

Not applicable.

3.3 Financial Disclosures

No new clinical trials were conducted for this submission.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Linezolid Injection is available as a sterile aqueous solution, which is intended for intravenous administration. The drug product is comprised of a clear, colorless to slightly yellow solution, free from visible particulate, presented in a VisIV flexible container in a foil laminate overwrap. The flexible container is (b) (4) mL flex bags with a 300 mL fill and will be closed with administration and additive port assemblies. The composition of the drug product consists of the active ingredient, Linezolid, and the inactive ingredients: citric acid, sodium hydroxide and sodium chloride, and water for Injection prepared with the aid of hydrochloric acid and/or sodium hydroxide for pH adjustment. The pH range is (b) (4). This is a (b) (4) sterilized product containing no antimicrobial preservatives. Linezolid Injection is stored at 20 to 25°C (68 to 77°F). The sodium content is 3.98 mg/mL (52 mEq/300 mL container).

The final chemistry, manufacturing, and controls (CMC) review recommendation for this NDA is pending. Note: The reader is referred to the CMC review by the chemistry reviewer, Dr. Jane Chang, for detailed descriptions of the drug product and manufacturing process.

4.2 Clinical Microbiology

No new clinical microbiology information was included in the application other than described in the approved RLD product labeling. Note: The reader is referred to the microbiology review by the microbiologist, Dr. Kerry Snow for details.

4.3 Preclinical Pharmacology/Toxicology

No non-clinical studies were conducted for this application. No additional Pharmacology/toxicology data were included in the application other than described in the approved RLD product labeling. Note: The reader is referred to the Pharmacology/toxicology review by Dr. W. Schmidt.

4.4 Clinical Pharmacology

No new clinical pharmacology information was included in the application other than described in the approved RLD product labeling. (Note: The reader is referred to the clinical pharmacology review by Dr. Ryan Owen.

According to the Biopharmaceutics reviewer, based on the overall supportive information, as well as the Applicant's revision of the product's specifications for the fill volume specification [REDACTED] (b) (4), the Applicant's request for a biowaiver for the proposed Linezolid Injection product was found to be acceptable and the biowaiver is granted. (Note: The reader is referred to the Biopharmaceutics review by Dr. Elsbeth Chikhale).

4.4.1 Mechanism of Action

Linezolid inhibits bacterial protein synthesis through a mechanism of action different from that of other antibacterial agents. It 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.

4.4.2 Pharmacodynamics

No new pharmacodynamic data submitted with this application.

4.4.3 Pharmacokinetics

No new pharmacodynamic data submitted with this application.

5 Sources of Clinical Data

No clinical studies were conducted in support for this application. The clinical studies conducted in support of efficacy of linezolid injection for the approved indications are described in the approved RLD product labeling.

6 Review of Efficacy

Not applicable.

7 Review of Safety

The recent Periodic Adverse Drug Experience Report (PSUR) submitted for Zyvox[®] were reviewed. Upon review of the cases reporting labeled adverse events, there is no new safety information that would significantly alter the risk-benefit profile of linezolid.

The recent Annual Report submitted for Zyvox[®] was also reviewed which showed no significant new clinical information has been received that might affect the safety, effectiveness, or labeling of this product. A labeling update pertains to amend section 6.1 Clinical Studies Experience of the Zyvox[®] package insert for both adult and pediatric populations. Adverse reaction rates previously calculated based on treatment-related events (investigator's assessment) were converted to rates derived from all reported adverse events (all-causality). As a consequence of changes to section 6.1, the Highlights (Adverse Reactions) section was also updated accordingly.

No new safety information was identified in the annual PSURs that would alter the risk/benefit assessment of linezolid.

MO Comment: Any future safety issues identified with the RLD will be applied to this product accordingly.

8 Postmarket Experience

The following excerpt is from the USPI for the RLD, ZYVOX[®] (linezolid) Injection and describes adverse events reported during the postmarket experience:

“Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported during postmarketing use of (b) (4) Peripheral neuropathy, and optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with (b) (4) Lactic acidosis has been reported with the use of (b) (4) Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter

courses of therapy. Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and (b) (4). Convulsions have been reported with the use of (b) (4). Anaphylaxis, angioedema, and bullous skin disorders such as those described as Stevens-Johnson syndrome have been reported.

Superficial tooth discoloration and tongue discoloration have been reported with the use of linezolid. The tooth discoloration was removable with professional dental cleaning (manual descaling) in cases with known outcome. Hypoglycemia, including symptomatic episodes, has been reported.”

This information is also included in the draft label for the proposed product.

9 Appendices

9.1 References

- Current approved ZYVOX[®](linezolid) prescribing information dated September 2013
- Annual Periodic Adverse Drug Experience Report (PSUR) submitted for ZYVOX[®]
- Recent Annual Report submitted for ZYVOX[®]

9.2 Labeling Recommendations

The reviewer has the following labeling changes to be added to the Linezolid in 0.9% Sodium Chloride Injection for consistency with the recent safety labeling changes to the RLD, ZYVOX[®] I.V. (linezolid) Injection label as of January, 2014. The Agency's proposed labeling language for pediatric use under Dosage and Administration section is specific for this product formulation and container only and not in the RLD label.

(Additions are underlined and deletions are marked with strikethroughs.)

- In the Highlights of Prescribing Information:

- Delete the (b) (4)
- Under the Dosage and Administration- table, a Pediatric use language has been added for this particular formulation and product container to prevent potential overdose or other medication errors in pediatric patients:

"Pediatric Patients -The recommended dose is 10 mg per kg intravenously every 8 hours. Linezolid Injection, a single use in VisIV[™] Container should be used only in pediatric patients who require the entire 600 mg dose and not any fraction thereof. (2.1)"

- In the Dosage and Administration section: A similar language for pediatric use is placed under "2.1 General Dosage and Administration" subsection.

“(b) (4)

The maximum dose for pediatric patients should not exceed the recommended adult dose. The recommended dose is 10 mg per kg intravenously every 8 hours. Linezolid Injection, a single use in VisIV™ Container should be used only in pediatric patients who require the entire 600 mg dose and not any fraction thereof.”

- Under the Adverse Reactions heading: Revise the text as follows:

“Most common adverse reactions ((b) (4) greater than 5% of adult and (b) (4) pediatric patients treated with (b) (4)) include: diarrhea, vomiting, headache, nausea, and (b) (4) anemia. (6) To report SUSPECTED ADVERSE REACTIONS, contact Hospira (b) (4) Inc at 1-800- 441-4100 (b) (4) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”

- Clinical Trials Experience subsection 6.1 of the RLD package insert:

“ 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults:

The safety of Linezolid formulations was evaluated in 2046 adult patients enrolled in seven Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days. Table 2 shows the incidence of drug-related adverse reactions reported in at least 1% of adult patients in these trials by dose of Linezolid.

Table 3 shows the incidence of (b) (4) adverse reactions reported in more than 1% of pediatric patients (and more than 1 patient) in either treatment group in the comparator-controlled Phase 3 trials.”

- In the “PATIENT COUNSELING INFORMATION” section, the first bullet regarding advise to patient: (b) (4)

(Note: The reader is referred to the final draft PLR label for Linezolid Injection.)

9.3 Advisory Committee Meeting

None applicable.

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

/s/

ALMA C DAVIDSON
08/14/2014

BENJAMIN D LORENZ
08/14/2014
Acting Clinical Team Leader

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206473

Applicant: Hospira, Inc.

Stamp Date: November 26, 2013

Drug Name: Linezolid in 0.9% Sodium Chloride Injection **NDA/BLA Type:** 505(b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?			X	
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?			X	
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?			X	
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			The applicant submitted their draft labeling for Linezolid Injection in PLR format which needs revision under DESCRIPTION section regarding the inclusion of the inactive ingredients (b) (4)
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?			X	
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				This application is a 505(b)(2). The Reference Listed Drug is Pharmacia and Upjohn Company, ZYVOX I.V. Injection.
DOSE					

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	There are no clinical studies conducted by

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					the applicant.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes __X_

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The applicant should submit a revised version of the proposed Linezolid in 0.9% Sodium Chloride Injection label in PLR format.

Alma C. Davidson, M.D.	January 24, 2014
Reviewing Clinical Reviewer	Filing Date
Benjamin D. Lorenz, M.D.	January 24, 2014
Clinical Team Leader	Filing Date

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

/s/

ALMA C DAVIDSON
01/08/2014

BENJAMIN D LORENZ
01/09/2014
Acting Team Leader