# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 206473Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

| BIOPHARMACEUTICS REVIEW<br>Office of New Drug Quality Assessment | | | |
|---|---|---|---|
| **Application No.:** | NDA 206473 | **Reviewer:** Elsbeth Chikhale, PhD | |
| **Submission Date:** | November 26, 2013 | | |
| **Division:** | Division of Anti Infective Products | **Team Leader:** Angelica Dorantes, PhD | |
| **Applicant:** | Hospira, Inc. | **Acting Supervisor:** Rik Lostritto, PhD | |
| **Trade Name:** | TBD | **Date Assigned:** | December 11, 2013 |
| **Established Name:** | Linezolid Injection | **Date of Review:** | July 15, 2014 |
| **Indication:** | Treatment of the following infections caused by susceptible strains of the designated microorganisms: Vancomycin-Resistant *Enterococcus faecium* infections; Nosocomial pneumonia; Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; (b) (4) Community acquired pneumonia. | **Type of Submission:** Original New Drug Application – 505(b)(2) | |
| **Dosage form/ strengths** | Injection (intravenous solution for infusion)/ 2 mg/ mL (600 mg/300 mL) | | |
| **Route of Administration** | IV infusion | | |
| **Type of Review:** | Biowaiver Request | | |

**SUBMISSION:**

The Applicant is seeking approval of a New Drug Application (NDA) for Linezolid Injection under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and is referencing Zyvox Solution approved under NDA 21131 on 04/18/2000 (marketed by Pharmacia and Upjohn) as the listed drug.

The Biopharmaceutics review of this NDA will be focused on the evaluation of the information supporting the approvability of the biowaiver request for the proposed Linezolid Injection for Intravenous Infusion, 600 mg/ 300 mL product.

**BIOPHARMACEUTIC INFORMATION:**

The proposed drug product is a 600 mg linezolid in 300 mL 0.9% sodium chloride sterile solution for administration by IV infusion over a period of 30 to 120 minutes. This solution formulation has the same active ingredient (linezolid), concentration (2 mg/mL) and routes of administration (IV infusion) as the listed drug, Zyvox Solution; however, the inactive ingredients are different. The Applicant states that the vehicle of the proposed drug product via the current NDA was modified from 5% dextrose to 0.9% sodium chloride (b) (4) (b) (4) In addition, in the proposed linezolid formulation (by removing sodium citrate and adjusting the contents of citric acid (b) (4)). The comparison of the proposed formulation and the Zyvox formulation is shown in the table below.

| Component | Hospira Quantity per Milliliter (mL) | Innovator Quantity per Milliliter (mL) | Function | Reference to Standards |
|---|---|---|---|---|
| Linezolid[1] | 2 mg | 2 mg | Active Ingredient | Hospira In-house Standard |
| Sodium Citrate, Dihydrate | N/A | 1.64 mg | (b) (4) | N/A |
| Citric Acid, Anhydrous[2] | 1.92 mg | 0.85 mg | | USP, Ph.Eur, BP |
| Dextrose, Monohydrate | N/A | 50.24 mg | | USP, Ph.Eur, BP |
| Sodium Chloride | 9 mg | N/A | | USP, Ph.Eur, BP |
| Sodium Hydroxide[2] | 0.76 mg | A.R. | | NF, Ph.Eur, BP |
| Hydrochloric Acid | q.s. to pH (b) (4) | A.R. | pH adjustment | NF, Ph.Eur, BP |
| Sodium Hydroxide | q.s. to pH | A.R. | pH adjustment | NF, Ph.Eur, BP |
| Water for Injection | q.s. to 1.00 mL | A.R. | Vehicle | USP, Ph.Eur, BP |
| Total Volume | 1.00 mL | 1.00 mL | | |
| q.s. = Quantity sufficient; A.R. = As required. | | | | |

1 This is a non-compendial item and tested according to specifications provided in *Section 3.2.S.4.1 Specifications*. Factored to 100% basis. Refer to *Section 3.2.P.2 Pharmaceutical Development* for the formulation development.

2 (b) (4)

Similarly to the innovator's product, the proposed by Hospira Linezolid Injection, 2 mg/mL, will be packaged in the flexible bags and is intended to be labeled for storage at 25°C (77°F); excursions permitted to 15-30°C (59-86°C) [USP Controlled Room Temperature].

The proposed drug product has the following specifications for pH and osmolality:

| Test | Acceptance Criteria | Regulatory Analytical Procedure | Justification for Specification[c] |
|---|---|---|---|
| pH | Release: (b) (4) Shelf-life: | USP <791> | Matches pH listed in innovator's package insert. |
| Osmolality | (b) (4) mOsmol/kg | In-house [a,b] | Specification aligns with typical range for isotonic solutions. |

Batch analysis data for the 3 registration batches show that the proposed drug product has a pH of 4.8 (all 3 batches) and an osmolality of 313, 314, and 316 mOsmol/kg.

The Applicant is requesting a waiver for *in-vivo* bioavailability/bioequivalence requirements for the proposed drug product based on 21 CFR § 320.22 (b)(1).

**ASSESSMENT OF THE BIOWAIVER REQUEST:**

According to CFR 320.22(b), for certain drug products the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the requirement for the submission of in vivo BA/BE data of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product meets the following:

- Is a parenteral solution intended solely for administration by injection, and
- Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

However, for the proposed drug product the inactive ingredients are not the same. Since both the proposed drug product and the listed drug product are isotonic and have the (b) (4) the 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.

Although, the concentration of the active ingredient is the same, the proposed drug product is manufactured with a (b) (4)% overage (over fill). The proposed drug product has a proposed target fill volume of (b) (4) mL, which will result in a (b) (4)% higher dose because the whole volume in the bag will be administered. To address this issue, the CMC Reviewer, Dr. Jane Chang sent the following **information request (IR)** to the Applicant on **3/27/14**;

> *The proposed acceptance criterion of (b) (4) mL to (b) (4) mL (target (b) (4) mL), which corresponds to (b) (4)% to (b) (4)% of the label claim for fill volume is not acceptable. Please tighten the acceptance criterion to comply with the USP <1151> recommendation of 2% excess for injectable drug products of 50.0 mL or more.*

**Applicant's Response dated 4/18/14:**

*Hospira has revised the fill volume specification to (b) (4) mL to (b) (4) mL (target (b) (4) mL). The low end of the specification ((b) (4) mL) was selected (b) (4)*

[redacted] *Hospira incorporated the manufacturing line filling capabilities (± [redacted]mL) to set an appropriate range and target for future drug product lots.*

The Applicant's response was not found to be acceptable by the CMC Reviewer, and the following **IR** was sent to the Applicant on **5/27/14**:

*Revise the upper limit of fill volume from [redacted] mL to [redacted] mL for the drug product specification based on the variability observed for the three registration batches. Furthermore, revise the analytical procedure for volume determination from USP <1151> to USP <1> because USP <1151> does not contain analytical procedure for volume determination.*

**Applicant's response dated 6/16/14:**

*Hospira has revised the fill volume specification to reflect an upper limit of [redacted] mL; the proposed specification is [redacted] mL to [redacted] mL (target [redacted] mL). The low end of the specification ([redacted] mL) was selected as it is at the approximate [redacted] recommended by USP <1151>. The manufacturing capabilities of the filling line require ± [redacted]mL range; this results in a [redacted] mL to [redacted] mL specification. Hospira has also corrected the volume determination method to reference USP <1>.*

This response was fond acceptable by the CMC reviewer. The new fill volume specifications will ensure that the proposed product has [redacted]

Based on the overall supportive information and the Applicant's revision of the product's specifications, the Applicant's request for a biowaiver for their proposed Linezolid Injection product 2 mg/mL is acceptable and the biowaiver is granted.

**RECOMMENDATION:**

A waiver from the CFR's requirement to provide data from an *in vivo* bioequivalence study is granted. From the Biopharmaceutics perspective, NDA 206473 for Linezolid Injection, 2 mg/mL is recommended for **APPROVAL**.

| **Signature** | **Signature** |
|---|---|
| Elsbeth Chikhale, Ph.D. | Angelica Dorantes, Ph.D. |
| Biopharmaceutics Reviewer | Biopharmaceutics Team Leader |
| Office of New Drug Quality Assessment | Office of New Drug Quality Assessment |

---

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

---

/s/

---

ELSBETH G CHIKHALE
07/15/2014

ANGELICA DORANTES
07/15/2014

# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| **NDA: 206-473** | Submission Date(s): 11/26/2013 |
| **Drug** | Linezolid (RLD: ZYVOX) |
| **Trade Name** | Linezolid in 0.9% Sodium Chloride Injection |
| **OCP Reviewers** | Ryan P. Owen, Ph.D. |
| **OCP Team Leader** | Kimberly L. Bergman, Pharm.D. |
| **OCP Division** | DCP4 |
| **OND division** | DAIP |
| **Sponsor** | Hospira, Inc. |
| **Relevant IND(s)** | None |
| **Submission Type; Code** | 505(b)(2) |
| **Formulation; Strength(s)** | 300 mL (600 mg linezolid) single-use, ready-to-use flexible plastic VisIV™ containers in a foil laminate overwrap |
| **Indication** | Nosocomial pneumonia; Community-acquired pneumonia, including concurrent bacteremia; Complicated skin and skin structure infections; Vancomycin-resistant *Enterococcus faecium* infections, including concurrent bacteremia |
| **Dosage and Administration** | Adults and Adolescents: 600 mg intravenously every 12 hours<br><br>Pediatrics (Birth through 11 years of age): 10 mg/kg intravenously every 8 hours |

**Background**

Hospira submitted a 505(b)(2) New Drug Application (NDA) dated 11/26//2013 for Linezolid for Injection, 600 mg/vial, which is currently FDA-approved for the treatment of nosocomial pneumonia; community-acquired pneumonia, including concurrent bacteremia; complicated skin and skin structure infections; and vancomycin-resistant *Enterococcus faecium* infections, including concurrent bacteremia. Linezolid is also approved for the treatment of uncomplicated skin and skin structure infection, but the Sponsor is not seeking that particular indication because the recommended dosing is with oral linezolid and their product is IV only. The active ingredient, strength, route of administration, and dosage form are the same between the proposed

product and the RLD (ZYVOX, Linezolid for Injection, NDA 21-131; approved in 2000, manufactured by Pfizer).

The composition of Hospira Inc.'s Linezolid in 0.9% Sodium Chloride Injection (b) (4) ZYVOX (b) (4) the drug product vehicle and (b) (4) (see below):

- Hospira has replaced 5% Dextrose with 0.9% Sodium Chloride as the drug product vehicle. This change was made (b) (4) Saline was selected as it was a commonly used vehicle.
- Hospira has removed the sodium citrate and increased the quantities of citric acid (b) (4) . This change was necessary due to (b) (4)

The Sponsor intends to rely upon the Agency's findings for safety and efficacy and information provided in the approved labeling for the RLD, ZYVOX® (linezolid) for Injection.

No new clinical pharmacology information was submitted in this application, and the applicant has submitted a request for waiver of the regulatory requirement for bioavailability as outlined in 21 CFR 320.21. Please refer to the Office of New Drug Quality Assessment (ONDQA) Biopharmaceutics review for further evaluation of the request for waiver of bioavailability requirements. The scope of this review will be limited to recommended edits on the proposed labeling (see Appendix 1).

**Recommendation**

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed the application, and no new clinical pharmacology information was submitted. Thus, this application is acceptable from a clinical pharmacology perspective.

**Appendix 1: Recommended Labeling Changes**

*Reviewer comment: For the most part, the submitted label is very similar to the ZYVOX label. Throughout the label, the Sponsor has replaced the tradename ZYVOX with the common name linezolid. Additionally, since the current NDA is for intravenous linezolid,* (b) (4) *, some data derived using oral linezolid* (b) (4) *the label (e.g. drug interactions, special populations, etc.). The Reviewer agrees with all of those decisions. However,* (b) (4) *. Section 12.3 with Reviewer changes shown in Track Changes is included below.*

**12.3 Pharmacokinetics**

The mean pharmacokinetic parameters of linezolid in adults after single and multiple oral and intravenous doses are summarized in Table 8.

**Table 8. Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid in Adults**

| Dose of Linezolid | $C_{max}$ mcg/mL | $C_{min}$ mcg/mL | $T_{max}$ hrs | AUC* mcg•h/mL | $t_{1/2}$ hrs | CL mL/min |
|---|---|---|---|---|---|---|
| **400 mg tablet** | | | | | | |
| single dose[†] | 8.10 | --- | 1.52 | 55.10 | 5.20 | 146 |
| | (1.83) | | (1.01) | (25.00) | (1.50) | (67) |
| every 12 hours | 11.00 | 3.08 | 1.12 | 73.40 | 4.69 | 110 |
| | (4.37) | (2.25) | (0.47) | (33.50) | (1.70) | (49) |
| **600 mg tablet** | | | | | | |
| single dose | 12.70 | --- | 1.28 | 91.40 | 4.26 | 127 |
| | (3.96) | | (0.66) | (39.30) | (1.65) | (48) |
| every 12 hours | 21.20 | 6.15 | 1.03 | 138.00 | 5.40 | 80 |
| | (5.78) | (2.94) | (0.62) | (42.10) | (2.06) | (29) |
| **600 mg IV injection[‡]** | | | | | | |
| single dose | 12.90 | --- | 0.50 | 80.20 | 4.40 | 138 |
| | (1.60) | | (0.10) | (33.30) | (2.40) | (39) |
| every 12 hours | 15.10 | 3.68 | 0.51 | 89.70 | 4.80 | 123 |
| | (2.52) | (2.36) | (0.03) | (31.00) | (1.70) | (40) |
| **600 mg oral suspension** | | | | | | |
| single dose | 11.00 | --- | 0.97 | 80.80 | 4.60 | 141 |
| | (2.76) | | (0.88) | (35.10) | (1.71) | (45) |

* AUC for single dose = $AUC_{0-\infty}$; for multiple dose = $AUC_{0-\tau}$

[†] Data dose-normalized from 375 mg

[‡] Data dose-normalized from 625 mg, intravenous dose was given as 0.5-hour infusion.

$C_{max}$ = Maximum plasma concentration; $C_{min}$ = Minimum plasma concentration; $T_{max}$ = Time to $C_{max}$; AUC = Area under concentration-time curve; $t_{1/2}$ = Elimination half-life; CL = Systemic clearance

Absorption

Linezolid is extensively absorbed after oral dosing. Maximum plasma concentrations are reached approximately 1 to 2 hours after dosing, and the absolute bioavailability is approximately 100%. Therefore, linezolid may be given orally or intravenously without dose adjustment.

Linezolid may be administered without regard to the timing of meals. The time to reach the maximum concentration is delayed from 1.5 hours to 2.2 hours and $C_{max}$ is decreased by about 17% when high fat food is given with linezolid. However, the total exposure measured as $AUC_{0-\infty}$ is similar under both conditions.

Distribution

Animal and human pharmacokinetic studies have demonstrated that linezolid readily distributes to well-perfused tissues. The plasma protein binding of linezolid is approximately 31% and is concentration-independent. The volume of distribution of linezolid at steady-state averaged 40 to 50 liters in healthy adult volunteers.

Linezolid concentrations have been determined in various fluids from a limited number of subjects in Phase 1 volunteer studies following multiple dosing of linezolid. The ratio of linezolid in saliva relative to plasma was 1.2 to 1 and the ratio of linezolid in sweat relative to plasma was 0.55 to 1.

Metabolism

Linezolid is primarily metabolized by oxidation of the morpholine ring, which results in two inactive ring-opened carboxylic acid metabolites: the aminoethoxyacetic acid metabolite (A), and the hydroxyethyl glycine metabolite (B). Formation of metabolite A is presumed to be formed via an enzymatic pathway whereas metabolite B is mediated by a non-enzymatic chemical oxidation mechanism *in vitro*. *In vitro* studies have demonstrated that linezolid is minimally metabolized and may be mediated by human cytochrome P450. However, the metabolic pathway of linezolid is not fully understood.

Excretion

Nonrenal clearance accounts for approximately 65% of the total clearance of linezolid. Under steady-state conditions, approximately 30% of the dose appears in the urine as linezolid, 40% as metabolite B, and 10% as metabolite A. The mean renal clearance of linezolid is 40 mL/min which suggests net tubular reabsorption. Virtually no linezolid appears in the feces, while approximately 6% of the dose appears in the feces as metabolite B, and 3% as metabolite A.

A small degree of nonlinearity in clearance was observed with increasing doses of linezolid, which appears to be due to lower renal and nonrenal clearance of linezolid at higher concentrations.

However, the difference in clearance was small and was not reflected in the apparent elimination half-life.

Specific Populations

*Geriatric Patients*

The pharmacokinetics of linezolid are not significantly altered in elderly patients (65 years or older). Therefore, dose adjustment for geriatric patients is not necessary.

*Pediatric Patients*

The pharmacokinetics of linezolid following a single intravenous dose were investigated in pediatric patients ranging in age from birth through 17 years (including premature and full-term neonates), in healthy adolescent subjects ranging in age from 12 through 17 years, and in pediatric patients ranging in age from 1 week through 12 years. The pharmacokinetic parameters of linezolid are summarized in Table 9 for the pediatric populations studied and healthy adult subjects after administration of single intravenous doses.

The $C_{max}$ and the volume of distribution ($V_{ss}$) of linezolid are similar regardless of age in pediatric patients. However, plasma clearance of linezolid varies as a function of age. With the exclusion of pre-term neonates less than one week of age, weight-based clearance is most rapid in the youngest age groups ranging from <1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and a shorter half-life as compared with adults. As the age of pediatric patients increases, the weight-based clearance of linezolid gradually decreases, and by adolescence mean clearance values approach those observed for the adult population. There is increased inter-subject variability in linezolid clearance and systemic drug exposure (AUC) across all pediatric age groups as compared with adults.

Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed every 8 hours relative to adolescents or adults dosed every 12 hours. Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg every 8 hours. Pediatric patients 12 years and older should receive 600 mg every 12 hours [*see Dosage and Administration (2)*].

**Table 9. Pharmacokinetic Parameters of Linezolid in Pediatrics and Adults Following a Single Intravenous Infusion of 10 mg/kg or 600 mg Linezolid (Mean: (%CV); [Min, Max Values])**

| Age Group | $C_{max}$ mcg/mL | $V_{ss}$ L/kg | AUC* mcg•h/mL | $t_{1/2}$ Hrs | CL mL/min/kg |
|---|---|---|---|---|---|
| Neonatal Patients | | | | | |
| Pre-term** | 12.7 (30%) | 0.81 (24%) | 108 (47%) | 5.6 (46%) | 2.0 (52%) |
| <1 week (N = 9)† | [9.6, 22.2] | [0.43, 1.05] | [41, 191] | [2.4, 9.8] | [0.9, 4.0] |
| Full-term*** | 11.5 (24%) | 0.78 (20%) | 55 (47%) | 3.0 (55%) | 3.8 (55%) |
| <1 week (N = 10) | [8.0, 18.3] | [0.45, 0.96] | [19, 103] | [1.3, 6.1] | [1.5, 8.8] |
| Full-term*** | 12.9 (28%) | 0.66 (29%) | 34 (21%) | 1.5 (17%) | 5.1 (22%) |
| ≥1 week to ≤28 days (N = 10)† | [7.7, 21.6] | [0.35, 1.06] | [23, 50] | [1.2, 1.9] | [3.3, 7.2] |
| Infant Patients | | | | | |
| >28 days to <3 Months (N = 12)† | 11.0 (27%) [7.2, 18.0] | 0.79 (26%) [0.42, 1.08] | 33 (26%) [17, 48] | 1.8 (28%) [1.2, 2.8] | 5.4 (32%) [3.5, 9.9] |
| Pediatric Patients | | | | | |
| 3 months through 11 years† (N = 59) | 15.1 (30%) [6.8, 36.7] | 0.69 (28%) [0.31, 1.50] | 58 (54%) [19, 153] | 2.9 (53%) [0.9, 8.0] | 3.8 (53%) [1.0, 8.5] |
| Adolescent Subjects and Patients | | | | | |
| 12 through 17 years‡ (N = 36) | 16.7 (24%) [9.9, 28.9] | 0.61 (15%) [0.44, 0.79] | 95 (44%) [32, 178] | 4.1 (46%) [1.3, 8.1] | 2.1 (53%) [0.9, 5.2] |
| Adult Subjects§ | 12.5 (21%) | 0.65 (16%) | 91 (33%) | 4.9 (35%) | 1.7 (34%) |
| (N = 29) | [8.2, 19.3] | [0.45, 0.84] | [53, 155] | [1.8, 8.3] | [0.9, 3.3] |

* AUC = Single dose $AUC_{0-\infty}$

** In this data set, "pre-term" is defined as <34 weeks gestational age (Note: Only 1 patient enrolled was pre-term with a postnatal age between 1 week and 28 days)

*** In this data set, "full-term" is defined as ≥34 weeks gestational age

† Dose of 10 mg/kg

‡ Dose of 600 mg or 10 mg/kg up to a maximum of 600 mg

§ Dose normalized to 600 mg

$C_{max}$ = Maximum plasma concentration; $V_{ss}$ = Volume of distribution; AUC = Area under concentration-time curve;

$t_{1/2}$ = Apparent elimination half-life; CL = Systemic clearance normalized for body weight

*Gender*

Females have a slightly lower volume of distribution of linezolid than males. Plasma concentrations are higher in females than in males, which is partly due to body weight differences. After a 600-mg dose, mean oral clearance is approximately 38% lower in females than in males. However, there are no significant gender differences in mean apparent elimination-rate constant or half-life. Thus, drug exposure in females is not expected to substantially increase beyond levels known to be well tolerated. Therefore, dose adjustment by gender does not appear to be necessary.

*Renal Impairment*

The pharmacokinetics of the parent drug, linezolid, are not altered in patients with any degree of renal impairment; however, the two primary metabolites of linezolid accumulate in patients with renal impairment, with the amount of accumulation increasing with the severity of renal dysfunction (see Table 10). The pharmacokinetics of linezolid and its two metabolites have also been studied in patients with end-stage renal disease (ESRD) receiving hemodialysis. In the ESRD study, 14 patients were dosed with linezolid 600 mg every 12 hours for 14.5 days (see Table 11). Because similar plasma concentrations of linezolid are achieved regardless of renal function, no dose adjustment is recommended for patients with renal impairment. However, given the absence of information on the clinical significance of accumulation of the primary metabolites, use of linezolid in patients with renal impairment should be weighed against the potential risks of accumulation of these metabolites. Both linezolid and the two metabolites are eliminated by hemodialysis. No information is available on the effect of peritoneal dialysis on the pharmacokinetics of linezolid. Approximately 30% of a dose was eliminated in a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered; therefore, linezolid should be given after hemodialysis.

**Table 10. Mean (Standard Deviation) AUCs and Elimination Half-lives of Linezolid and Metabolites A and B in Patients with Varying Degrees of Renal Impairment After a Single 600 mg Oral Dose of Linezolid**

| **Parameter** | **Healthy Subjects $CL_{CR}$ >80 mL/min** | **Moderate Renal Impairment 30< $CL_{CR}$ <80 mL/min** | **Severe Renal Impairment 10< $CL_{CR}$ <30 mL/min** |
|---|---|---|---|
| **LINEZOLID** | | | |
| $AUC_{0-\infty}$, mcg h/mL | 110 (22) | 128 (53) | 127 (66) |
| $t_{1/2}$, hours | 6.4 (2.2) | 6.1 (1.7) | 7.1 (3.7) |

| | | | |
|---|---|---|---|
| **METABOLITE A** | | | |
| $AUC_{0-48}$, mcg h/mL | 7.6 (1.9) | 11.7 (4.3) | 56.5 (30.6) |
| $t_{1/2}$, hours | 6.3 (2.1) | 6.6 (2.3) | 9.0 (4.6) |
| **METABOLITE B[1]** | | | |
| $AUC_{0-48}$, mcg h/mL | 30.5 (6.2) | 51.1 (38.5) | 203 (92) |
| $t_{1/2}$, hours | 6.6 (2.7) | 9.9 (7.4) | 11.0 (3.9) |

[1] Metabolite B is the major metabolite of linezolid.

**Table 11. Mean (Standard Deviation) AUCs and Elimination Half-lives of Linezolid and Metabolites A and B in Subjects with End-Stage Renal Disease (ESRD) After the Administration of 600 mg Linezolid Every 12 Hours for 14.5 Days**

| **Parameter** | **ESRD Subjects[1]** |
|---|---|
| **LINEZOLID** | |
| $AUC_{0-12}$, mcg h/mL (after last dose) | 181 (52.3) |
| $t_{1/2}$, h (after last dose) | 8.3 (2.4) |
| **METABOLITE A** | |
| $AUC_{0-12}$, mcg h/mL (after last dose) | 153 (40.6) |
| $t_{1/2}$, h (after last dose) | 15.9 (8.5) |
| **METABOLITE B[2]** | |
| $AUC_{0-12}$, mcg h/mL (after last dose) | 356 (99.7) |
| $t_{1/2}$, h (after last dose) | 34.8 (23.1) |

[1] between hemodialysis sessions

[2] Metabolite B is the major metabolite of linezolid.

*Hepatic Impairment*

The pharmacokinetics of linezolid are not altered in patients (n = 7) with mild-to-moderate hepatic impairment (Child-Pugh class A or B). On the basis of the available information, no dose adjustment is recommended for patients with mild-to-moderate hepatic impairment. The pharmacokinetics of linezolid in patients with severe hepatic impairment have not been evaluated.

Drug Interactions

***Drugs Metabolized by Cytochrome P450***

Linezolid is not an inducer of cytochrome P450 (CYP450) in rats. In addition, linezolid does not inhibit the activities of clinically significant human CYP isoforms (e.g., 1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, linezolid is not expected to affect the pharmacokinetics of other drugs metabolized by these major enzymes. Concurrent administration of linezolid does not substantially alter the pharmacokinetic characteristics of (S)-warfarin, which is extensively metabolized by CYP2C9. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with linezolid without changes in dosage regimen.

(b) (4)

*Aztreonam*: The pharmacokinetics of linezolid or aztreonam are not altered when administered together.

*Gentamicin*: The pharmacokinetics of linezolid or gentamicin are not altered when administered together.

***Antioxidants***

The potential for drug-drug interactions with linezolid and the antioxidants Vitamin C and Vitamin E was studied in healthy volunteers. Subjects were administered a 600 mg oral dose of linezolid on Day 1, and another 600 mg dose of linezolid on Day 8. On Days 2-9, subjects were given either Vitamin C (1000 mg/day) or Vitamin E (800 IU/ day). The $AUC_{0-\infty}$ of linezolid increased 2.3% when co-administered with Vitamin C and 10.9% when co-administered with Vitamin E. No linezolid dose adjustment is recommended during co-administration with Vitamin C or Vitamin E.

***Strong CYP 3A4 Inducers***

Rifampin: The effect of rifampin on the pharmacokinetics of linezolid was evaluated in a study of 16 healthy adult males. Volunteers were administered oral linezolid 600 mg twice daily for 5 doses with and without rifampin 600 mg once daily for 8 days. Co-administration of rifampin with linezolid resulted in a 21% decrease in linezolid $C_{max}$ [90% CI, 15% - 27%] and a 32% decrease in linezolid $AUC_{0-12}$ [90% CI, 27% - 37%]. The clinical significance of this interaction is unknown. The mechanism of this interaction is not fully understood and may be related to the induction of hepatic enzymes. Other strong inducers of hepatic enzymes (e.g. carbamazepine, phenytoin, phenobarbital) could cause a similar or smaller decrease in linezolid exposure.

***Monoamine Oxidase Inhibition***

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

***Adrenergic Agents***

Some individuals receiving Linezolid may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response.

Tyramine: A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of more than 100 mg. Therefore, patients receiving linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content. [*see Patient Counseling Information (17)*].

Pseudoephedrine HCl or phenylpropanolamine HCl: A reversible enhancement of the pressor response of either pseudoephedrine HCl (PSE) or phenylpropanolamine HCl (PPA) is observed when linezolid is administered to healthy normotensive subjects [*see Warnings and Precautions (5.6) and Drug Interactions (7)*]. A similar study has not been conducted in hypertensive patients. The interaction studies conducted in normotensive subjects evaluated the blood pressure and heart rate effects of placebo, PPA or PSE alone, linezolid alone, and the combination of steady-state linezolid (600 mg every 12 hours for 3 days) with two doses of PPA (25 mg) or PSE (60 mg) given 4 hours apart. Heart rate was not affected by any of the treatments. Blood pressure was increased with both combination treatments. Maximum blood pressure levels were seen 2 to 3 hours after the second dose of PPA or PSE, and returned to baseline 2 to 3 hours after peak. The results of the PPA study follow, showing the mean (and range) maximum systolic blood pressure in mm Hg: placebo = 121 (103 to 158); linezolid alone = 120 (107 to 135); PPA alone = 125 (106 to 139); PPA with linezolid = 147 (129 to 176). The results from the PSE study were similar to those in the PPA study. The mean maximum increase in systolic blood pressure over baseline was 32 mm Hg (range: 20-52 mm Hg) and 38 mm Hg (range: 18-79 mm Hg) during co-administration of linezolid with pseudoephedrine or phenylpropanolamine, respectively.

***Serotonergic Agents***

Dextromethorphan: The potential drug-drug interaction with dextromethorphan was studied in healthy volunteers. Subjects were administered dextromethorphan (two 20-mg doses given 4 hours apart) with or without linezolid.

No serotonin syndrome effects (confusion, delirium, restlessness, tremors, blushing, diaphoresis, hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan.

---

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

---

/s/

---

RYAN P OWEN
06/20/2014

KIMBERLY L BERGMAN
06/20/2014

# CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

# Office of Clinical Pharmacology

## New Drug Application Filing and Review Form

| | | | |
|---|---|---|---|
| **NDA/BLA Number** | **NDA 206473** | **Brand Name** | **Linezolid** |
| **OCP Division (I, II, III, IV, V)** | **DCP4** | **Generic Name** | **Linezolid Injection** |
| **Medical Division** | **DAIP** | **Drug Class** | **Oxazolidinone** |
| **OCP Reviewer** | **Ryan Owen, PhD** | **Indication(s)** | **Nosocomial pneumonia, CAP, cSSSI, VRE** |
| **OCP Team Leader** | **Kimberly Bergman, PharmD** | **Dosage Form** | **Intravenous solution** |
| **Pharmacometrics Reviewer** | **NA** | **Dosing Regimen** | **600 mg q12h** |
| **Date of Submission** | **November 26, 2013** | **Route of Administration** | **Intravenous** |
| **Estimated Due Date of OCP Review** | | **Sponsor** | **Hospira** |
| **Medical Division Due Date** | | **Priority Classification** | **505(b)(2)** |
| **PDUFA Due Date** | | **AC Meeting (if applicable)** | **None** |

## Clinical Pharmacology and Biopharmaceutics Information

| | **"X" if included at filing** | **Number of studies submitted** | **Number of studies reviewed** | **Critical Comments If any** |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | | | | |
| **Tabular Listing of All Human Studies** | **NA** | | | **505(b)(2) NDA with no human studies conducted. Biowaiver was requested.** |
| **HPK Summary** | **NA** | | | |
| **Labeling** | **X** | | | |
| **Reference Bioanalytical and Analytical Methods** | **NA** | | | |
| **I. Clinical Pharmacology** | **NA** | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| **HEALTHY VOLUNTEERS -** | **NA** | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **PATIENTS -** | **NA** | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |

# CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

| | | | | |
|---|---|---|---|---|
| **PD -** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD -** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | **NA** | | | |
| **Absolute bioavailability** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies** | | | | |
| **Bio-waiver request based on BCS** | | | | |
| **BCS class** | | | | |
| **Dissolution study to evaluate alcohol induced dose-dumping** | | | | |
| **III. Other CPB Studies** | **NA** | | | |
| **Genotype/phenotype studies** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| ***TOTAL NUMBER OF STUDIES*** | ***0*** | ***0*** | ***0*** | |

# CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | | X | | Biowaiver requested. |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | | | X | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | | X | | Biowaiver requested |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | | | X | |
| 5 | Has a rationale for dose selection been submitted? | | X | | Same dose as innovator. |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | | | X | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | | | X | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | | | X | |
| **Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)** | | | | | |
| | **Data** | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | | | X | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | X | |
| | **Studies and Analyses** | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | | | X | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | | | X | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | | | X | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | | X | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | X | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | | | X | |
| | **General** | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of | | | X | |

| | | | | | |
|---|---|---|---|---|---|
| | appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | | X | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

**If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.**

The application is fileable.

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

There have been no issues identified for the 74 day letter.

Ryan P. Owen, Ph.D. 1/8/14
Reviewing Clinical Pharmacologist Date

Kimberly L. Bergman, Pharm.D.
Team Leader/Supervisor Date

---

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

---

/s/

---

RYAN P OWEN
01/08/2014

KIMBERLY L BERGMAN
01/21/2014