

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206473Orig1s000

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 206473
Supporting document/s: 001
Applicant's letter date: 11/26/2013
CDER stamp date: 11/26/2013
Product: Linezolid in 0.9% Sodium Chloride
Indication: (b) (4)
Applicant: Hospira, Inc.
Review Division: Division of Anti-Infective Products
Reviewer: Wendelyn Schmidt, Ph.D.
Secondary Reviewer: Amy Ellis, Ph.D.
Division Director: Sumathi Nambiar, M.D.
Project Manager: Susmita Samanta

Template Version: December 7, 2009

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1 Executive Summary

1.1 Recommendations:

1.1.1 Approvability

There are no Pharmacology/Toxicology issues with the approval of this NDA for linezolid in 0.9% sodium chloride.

1.1.2 Additional Non Clinical Recommendations: none.

1.1.3 Labeling: There are no changes to the label from a pharmacology/toxicology perspective.

1.2 Brief Discussion of Nonclinical Findings

For this 505(b)2 application, the sponsor (Hospira) submitted a series of toxicology and genotoxicity studies on a series of new (b) (4) impurities in the drug product 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. The degradants can be considered qualified.

2 Drug Information

2.1 Drug: Linezolid in 0.9% sodium chloride

2.2 Relevant IND/s, NDA/s, and DMF/s: Reference NDA is Pharmacia/UpJohn NDA 21131 for Zyvox, approved in 2000.

2.3 Clinical Formulation

2.3.1 Drug Formulation:

Table 1. Composition of Linezolid Hospira and Zyvox®

Composition	Linezolid Injection 600 mg/300 mL	Zyvox® 2 mg/ml Solution for Infusion
Active Ingredient	Linezolid	Linezolid
Inactive ingredient(s)	Sodium Citrate – N/A* Citric Acid – 1.92 mg/mL Dextrose – N/A Sodium Chloride – 9 mg/mL Water for Injection – q.s. to 1 mL Sodium Hydroxide – 0.76 mg/mL Additionally added as needed for pH adjustment Hydrochloric Acid – As needed for pH adjustment	Sodium Citrate – 1.64 mg/ml Citric Acid – 0.85 mg/ml Dextrose – 50.24 mg/ml Sodium Chloride – N/A Water for Injection – q.s. to 1 ml Sodium Hydroxide – As needed for pH adjustment to pH 4.8 Hydrochloric Acid – As needed for pH adjustment to pH 4.8

(b) (4)

2.3.2 Comments on Novel Excipients:

There are no novel excipients in this new formulation for linezolid injection. Sodium chloride (b) (4) being used for the vehicle of the new linezolid in place of dextrose (b) (4). They are used in similar or greater amounts in other approved products.

2.3.3 Comments on Impurities/Degradants of Concern: Please see the “Discussion of nonclinical findings” above.

2.4 Proposed Clinical Population and Dosing Regimen:

The maximum recommended daily dose for the approved Zyvox is 1.2 g/day (600 mg every 12 hours) for up to 28 days by the intravenous route. The indication is treatment of an assortment of Gram-positive infections.

2.5 Regulatory Background: This is a 505(b)(2) application for linezolid, which was originally approved in 2000. The formulation has been changed by substituting sodium chloride for dextrose.

3 Studies Submitted

3.1 Studies Reviewed

General Toxicology

1. Linezolid Impurities ((b) (4)): a 4-week bolus intravenous toxicity study in rats. Study # 1550-028.
2. Linezolid impurity ((b) (4)): a 4-week bolus intravenous toxicity study in rats. Study # 1550-041.

Genotoxicology:

1. Derek and Leadscope Genotoxicity Evaluation of (b) (4) (Impurity (b) (4) of Linezolid). Report DEREK (b) (4).
2. Linezolid Impurity (b) (4) Salmonella-E. Coli/mammalian microsome reverse mutation assay. Study # (b) (4) 11-35.
3. Linezolid Impurity (b) (4) In vitro chromosome aberration test in cultured human peripheral blood lymphocytes. Study # (b) (4) 11-346.
4. Linezolid Impurity (b) (4) Salmonella-E.coli/mammalian microsome reverse mutation assay. Study # (b) (4) 11-347.
5. Linezolid Impurity (b) (4) In vitro chromosome aberration test in cultured human peripheral blood lymphocytes. Study # (b) (4) 11-348.

3.2 Studies Not Reviewed

1. Full validation of an HPLC-UV assay for (b) (4) and (b) (4) in vehicle. Study # 1550-029.
2. Partial validation of an HPLC-UV assay for (b) (4) and (b) (4) in DMSO. Study # 1550-035.

3. Full validation of an HPLC-UV assay for (b) (4) in (b) (4). Study # 1550-045.

3.3 Previous Reviews Referenced: None, as this is a 505(b)2, only the previous findings of safety and efficacy as appear in the label or other published literature may be referenced.

6.2 Repeat-Dose Toxicity

1.

Study title: Linezolid Impurities ((b) (4)): a 4-week bolus intravenous toxicity study in rats.

Study no.: 1550-028
 Study report location: EDR
 Conducting laboratory and location: (b) (4)
 Date of study initiation: 3/1/2012
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: (b) (4), lot # TH02550-064, 97.3% pure;
 (b) (4) lot # TH04450-015, 96.3% pure

Key Study Findings

The dose was based on a (b) (4) % specification for each impurity. Assuming a maximum dose of 1.2 g/day, then a (b) (4) % dose would be (b) (4) mg/day, and assuming a 60 kg human, the dose would be (b) (4) mg/kg/day. Using a BSA comparison with rats, the human equivalent dose would be (b) (4) mg/kg/day for the low dose (equivalent to the proposed human dose), with 3 and 10 fold margins for the higher doses. There were no toxicologically significant findings at any dose tested. The testing was adequate to support a (b) (4) % specification for the drug product.

Methods

Doses: (b) (4) mg/kg/dose ((b) (4) mg/kg/day for each impurity, given together)
 Frequency of dosing: Twice daily by bolus injection (approximately 12 h apart), daily for 28 consecutive days.
 Route of administration: intravenous
 Dose volume: 3 mL/kg/dose (6 mL/kg/day)
 Formulation/Vehicle: (b) (4)
 Species/Strain: Crl:CD(SD) rats
 Number/Sex/Group: 10/sex/dose
 Age: 7-8 weeks
 Weight: M: 211-243 g; F: 160-194 g

Satellite groups: none
Unique study design: No
Deviation from study protocol: None that would affect the outcome or interpretation of the study.

Observations and Results

Mortality and Clinical Signs (twice daily): All of the rats survived to scheduled necropsy. The observations made (sporadic high carriage, tail scabs or edema, sparse hair on forelimbs etc.) were seen at all doses with relatively similar incidence and were considered unrelated to test article.

Body Weights (weekly): There were no remarkable differences in body weight between treated and control males and females.

Feed Consumption (weekly): There were no noteworthy differences in food consumption between treated and control rats.

Ophthalmoscopy (pretest, week 4): There were no remarkable findings with dosing.

Hematology, Clinical Chemistry, and Urinalysis (prior to terminal necropsy): There were no remarkable changes in hematology, coagulation, clinical chemistry, or urinalysis in either sex as compared to controls.

Gross Pathology: There were no noteworthy findings with test article treatment.

Organ Weights: The organ weights did not differ significantly between treated and control in either sex.

Histopathology

Adequate Battery: Yes

Peer Review: Not stated.

Histological Findings (only control and (b) (4) animals examined): Findings were primarily at the injection site and did not differ in severity or extent to a noteworthy degree with treatment in either sex.

Stability and Homogeneity (measured weekly): The homogeneity and concentration of the test article was within 5% of the nominal values at all timepoints measured.

Study title: Linezolid impurity ((b) (4)): a 4-week bolus intravenous toxicity study in rats.

Study no.:	1550-041
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	5/31/13
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	(b) (4) (impurity (b) (4)); Lot # TH11663-046; 99.3% pure

Key Study Findings: The doses chosen for testing the purified impurity/ (b) (4) were 1, 3 and 10X the recommended human dose specification of on a body surface area basis, based on a proposed specification of (b) (4)%. The NOEL was the highest dose tested, (b) (4) mg/kg/day, and the specification is considered qualified.

Methods

Doses:	(b) (4) mg/kg/dose of (b) (4); (b) (4) mg/kg/day
Frequency of dosing:	Twice daily for 28 consecutive days
Route of administration:	Intravenous (bolus via tail vein)
Dose volume:	3 mL/kg
Formulation/Vehicle:	(b) (4)
Species/Strain:	CD [CrI: Cd(SD)] rats

Number/Sex/Group: 10/sex/dose
Age: Approximately 8 weeks
Weight: M: 209-247 g; F: 160-190 g
Satellite groups: none
Unique study design: none
Deviation from study protocol: None that were significant.

Observations and Results

Mortality and Clinical Signs (twice daily, with detailed clinical exam weekly): All rats survived to scheduled sacrifice at week 4. Clinical signs, which mostly consisted of abrasions/scabs on the tail and struggling/vocalization during dosing, did not differ in incidence with dose or duration of study.

Body Weights (weekly): Body weight increased in the (b) (4) males by 7% above controls (statistically significant, but not likely to be toxicologically relevant). There were no remarkable changes with dose in the females.

Feed Consumption (weekly): There was a slight increase in food consumption in the (b) (4) rats, but it was not statistically significant.

Ophthalmoscopy (pretest, prior to necropsy): There were no abnormalities detected in any of the study animals.

Hematology, Clinical Chemistry, and Urinalysis (prior to necropsy): There were no noteworthy differences between hematology, coagulation, clinical chemistry, or urinalysis parameters between treated and control rats of either gender.

Gross Pathology: There were no findings in any of the rats on the study.

Organ Weights: There were no remarkable differences in absolute or relative (to brain or body) weights between treated and control rats.

Histopathology

Adequate Battery: Yes, standard

Peer Review: Not noted.

Histological Findings: The majority of the microscopic findings were at the injection site, were minimal to mild in severity, and did not differ remarkably in incidence between treated and control rats.

Stability and Homogeneity (tested weekly): The concentration at different levels of the vial remained within 6% of the nominal concentration at each week.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Linezolid impurity (b) (4): Salmonella/E. coli/mammalian microsome reverse mutation assay.

Study no.: (b) (4) 11-345

Study report location: EDR

Conducting laboratory and location: (b) (4)

Date of study initiation: 5/17/12

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: (b) (4), Lot # TH02550-64, 97.3% pure

Key Study Findings: The study was valid and (b) (4) was not mutagenic in the strains tested with or without metabolic activation.

Methods

Strains: Salmonella strains TA1537, TA98, TA100,
and TA 1535, E. coli strain WP2
uvrA

Concentrations in definitive study: 0, 100, 250, 500, 1000, 2500, and 5000
ug/plate

Basis of concentration selection: Lack of precipitates, toxicity to bacterial
lawn

Negative control: DMSO

Positive control: ICR-191 acridine, 2-aminoanthracene, 2-
nitrofluorene, sodium azide, 4-
nitroquinoline-N-oxide

Formulation/Vehicle: DMSO

Incubation & sampling time: 48 hours

Study Validity: The study was valid in that the negative controls were comparable to historical values and the positive controls significantly increased the revertants to a comparable level with historical controls.

Results: There were no dose dependent elevations (>2 fold of negative control) of revertants in any strain tested.

Study title: Linezolid impurity (b) (4): Salmonella/E. coli/mammalian
microsome reverse mutation assay.

Study no.: (b) (4) 11-347

Study report location: EDR

Conducting laboratory and location: (b) (4)

Date of study initiation: 5/18/12

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: (b) (4), Lot # TH04450-015, 96.3% pure

Key Study Findings: The study was valid and (b) (4) was not mutagenic in the strains tested with or without metabolic activation.

Methods

Strains: Salmonella strains TA1537, TA98, TA100, and TA 1535, E. coli strain WP2 uvrA

Concentrations in definitive study: 0, 100, 250, 500, 1000, 2500, and 5000 ug/plate, preincubation method

Basis of concentration selection: Lack of precipitates, toxicity to bacterial lawn (seen at 5000 ug/mL in TA98 and TA100)

Negative control: DMSO

Positive control: ICR-191 acridine, 2-aminoanthracene, 2-nitrofluorene, sodium azide, 4-nitroquinoline-N-oxide

Formulation/Vehicle: DMSO

Incubation & sampling time: 48 hours

Study Validity: The study was valid in that the negative controls were comparable to historical values and the positive controls significantly increased the revertants to a comparable level with historical controls.

Results: There were no dose dependent elevations (>2 fold of negative control) of revertants in any strain tested.

7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

Study title: Linezolid impurity (b) (4): *in vitro* chromosome aberration test in cultured human peripheral blood lymphocytes.

Study no.: (b) (4) 11-346

Study report location: EDR

Conducting laboratory and location: (b) (4)

Date of study initiation: 3/14/12

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: (b) (4), lot # TH02550-064, purity 97.3%

Key Study Findings: The study was valid and negative for clastogenicity.

Methods

Cell line: Human peripheral blood lymphocytes
 Concentrations in definitive study: 0, 20.3, 40.6, 81.3, 163, and 325 ug/mL
 Basis of concentration selection: Lack of precipitation, hemolysis; decrease in mitotic index
 Negative control: DMSO
 Positive control: Cyclophosphamide and mitomycin C
 Formulation/Vehicle: DMSO and RPMI-1640 media
 Incubation & sampling time: 3, 22 hours

Study Validity: The study was valid based on historical controls, cell survival, lack of precipitates, and performance of positive controls.

Results: There were no remarkable increases in the number of chromosomal aberrations with either 3 or 22 hour incubation in the presence/absence of metabolic activation with increasing concentrations of (b) (4).

Study title: Linezolid impurity (b) (4): in vitro chromosome aberration test in cultured human peripheral blood lymphocytes.

Study no.: (b) (4) 11-348
 Study report location: EDR
 Conducting laboratory and location: (b) (4)
 Date of study initiation: 3/14/12
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: (b) (4), lot # TH04550-064, purity 96.3%

Key Study Findings: The study was valid and negative for clastogenicity.

Methods

Cell line: Human peripheral blood lymphocytes
 Concentrations in definitive study: 0, 20.3, 40.6, 81.3, 163, and 325 ug/mL
 Basis of concentration selection: Lack of precipitation, hemolysis; decrease in mitotic index
 Negative control: DMSO
 Positive control: Cyclophosphamide and mitomycin C
 Formulation/Vehicle: DMSO and RPMI-1640 media
 Incubation & sampling time: 3, 22 hours

Study Validity: The study was valid based on historical controls, cell survival, lack of precipitates, and performance of positive controls.

Results: There was no dose dependent increase in the number of chromosomal aberrations with 3 or 22 hour exposure to (b) (4) in the presence or absence of microsomal activation.

The sponsor also used the DEREK Leadscope to determine the genotoxic potential for (b) (4) and did not note any portions of the molecule with likely genotoxic potential.

11 Integrated Summary and Safety Evaluation

The 3 (b) (4) in the linezolid drug product were neither toxicologically significant nor genotoxic at clinically relevant levels. (b) (4) at (b) (4)%, (b) (4) at (b) (4)% and (b) (4) at (b) (4)%, are considered qualified from a pharmacology/toxicology viewpoint.

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/s/

WENDELYN J SCHMIDT
04/15/2014

AMY L ELLIS
04/15/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA/BLA Number: 206473 Applicant: Hospira

Stamp Date: 11/26/13

Drug Name: Linezolid, i.v. NDA/BLA Type: 505(b)2

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		Several toxicity and genotoxicity studies of 3 impurities were submitted
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		3 new impurities (or impurities that will exceed the specifications) were tested for 2/4 weeks or for genotoxicity. Formulation differs in that (b) (4) is replaced by sodium chloride
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

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

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?	X		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	n/a		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

Reviewing Pharmacologist

Date

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

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/s/

WENDELYN J SCHMIDT
01/15/2014