CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218275Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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Division of Pediatrics and Maternal Health Review

Date: March 25, 2024 **Date of Consult Request**: January 17, 2024

From: Tamara Johnson, MD, MS, Team Leader, Maternal Health, Division of Pediatrics and Maternal Health (DPMH)

Through Lynne Yao, MD, Director, DPMH

To: Division of Anti-Infectives (DAI)

NDA: 218275

Drug: Zevtera (ceftobiprole medocaril sodium) for injection

Applicant: Basilea Pharmaceutica, LLC

Proposed Indications:

- Adult patients with *Staphylococcus aureus* bloodstream infection (bacteremia) (SAB)
- Adult patients with acute bacterial skin and skin structure infections (ABSSSI)
- Adult and pediatric patients (3 months to less than 18 years old) with community-acquired bacterial pneumonia (CABP)

Subject: Labeling review for compliance with Pregnancy and Lactation Labeling Rule (PLLR)

Materials Reviewed

- Applicant's submission of August 3, 2023
  - Draft labeling
  - Summary of Clinical Safety
  - Reviewer's Guide
- Applicant's response to FDA Information Request (IR) dated January 23, 2023, submitted January 31, 2024

INTRODUCTION

On August 3, 2023, the applicant, Basilea Pharmaceutica, LLC (Basilea), submitted a 505(b)1 NDA 218275 for Zevtera (ceftobiprole medocaril sodium) for injection, a cephalosporin antibacterial for the treatment of adult patients with Staphylococcus aureus bloodstream infection (bacteremia) (SAB), adult patients with acute bacterial skin and skin structure infections (ABSSSI), and adult and pediatric patients (3 months to less than 18 years old) with community-acquired bacterial pneumonia (CABP). DAI requested DPMH to assist to ensure that the labeling complies with the PLLR content and format.

BACKGROUND

Regulatory History

- In May 2007, ceftobiprole medocaril was first submitted to the Agency by Johnson & Johnson Pharmaceutical Research and Development L.L.C. (J&J) under NDA 022132 for the treatment of complicated skin and soft-tissue infections (cSSTIs). The NDA received a Complete Response in December 2009 due to deficiencies in the pivotal Phase 3 trials. Basilea, who initially developed ceftobiprole, regained development rights from J&J, and withdrew the NDA.
- Under IND 064407, Basilea continued development of ceftobiprole medocaril for SAB, ABSSSI, and CABP; received fast track designation in June 2004; and obtained qualified infectious disease product (QIDP) designations for each of the three proposed indications between July 2015 and December 2017. New phase 3 trials for ABSSSI and SAB indications were developed under the Agency's Special Protocol Assessment (SPA) program, with 8 agreements in total related to study design features, endpoint, and study conduct.
- On October 13, 2022, Basilea met with the Agency for a Type B pre-NDA meeting.
- On August 3, 2023, Basilea submitted NDA 218275 for priority review.
- Ceftobiprole medocaril has a 12-year marketing history outside of the US:
    - Ceftobiprole medocaril first approved in Canada, on June 26, 2008, for the treatment of complicated skin and soft-tissue infections (cSSTIs). In 2010, the product was withdrawn from all then-approved markets (Canada, Hong Kong, Switzerland, Ukraine, Russia, and Azerbaijan).
    - Ceftobiprole medocaril was approved on September 30, 2014, for the indications of CABP and hospital-acquired bacterial pneumonia (HABP), excluding VABP, and is currently marketed for these indications in 20 countries outside the US (including the EU and Canada).
    - (b) (4)

Drug Characteristics[1]

Ceftobriprole medocaril sodium is a semisynthetic cephalosporin that is primarily eliminated unchanged by the kidneys.

- Half Life: 3.3 hours
- Molecular Weight: 690.6 Daltons
- Protein bound: 16%
- Proposed Dosing: Varies by indication; for adults, 646 mg every 6-8 hours for either 5-14 days (ABSSSI or CABP) or up to 42 days (SAB); for pediatric patients with CABP, dosing based on body weight for 7-14 days duration
- Serious Adverse Reactions: increased mortality in ventilator-associated bacterial pneumonia patients, serious hypersensitivity and skin reactions, seizures and other CNS reactions, C. difficile associated diarrhea

(b) (4)

REVIEW

Pregnancy

Nonclinical Data

In animal embryofetal development studies, no adverse developmental effects were seen when ceftobiprole medocaril was administered intravenously to pregnant rats and cynomolgus monkeys, during the period of organogenesis, at doses up to approximately 1.4 times and 0.9 times the maximum recommended human dose (MRHD), respectively. In a rat pre-/postnatal developmental study, no adverse developmental effects were seen when ceftobiprole medocaril was administered intravenously to rats, during organogenesis through lactation, at doses up to approximately 1.4 times the MRHD. Maternal toxicity was seen at the highest dose tested, 1.4 times the MHRD.

Clinical Data

No pregnancy cases were reported in the ceftobiprole medocaril global safety database from time of initial marketing up to January 22, 2023, neither in clinical trials (because pregnant individuals were excluded from clinical trials) or postmarketing surveillance.

Applicant's Review of Literature

On January 24, 2024, in response to an IR, the applicant searched PubMed and their Basilea-internal literature list (which includes Embase and congress abstracts) related to search terms "ceftobiprole" and "congenital", "embryo", "fetal", "maternal", "paternal", "pregnancy", and "pregn*". The applicant states no relevant literature related to pregnancy were identified. Only the search terms ceftobiprole and reprod* resulted in three publications that describe analytical chromatographic methods.

DPMH Review of Literature

DPMH searched PubMed, Embase**,** Micromedex, and GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk for use of ceftobiprole medocaril during pregnancy. No publications or reports describing the use of ceftobiprole medocaril in human pregnancy were located.

Summary

Ceftobiprole medocaril was not associated with adverse developmental effects in rats or rabbits when administered parenterally at doses clinically equivalent to the MHRD. No clinical data is available regarding use in pregnancy.

Lactation

Nonclinical Data

In a rat pre-/postnatal developmental study, ceftobiprole medocaril was detected in rat milk at ~20% the concentration level in maternal plasma.

Clinical Data

No lactation cases were reported in the ceftobiprole medocaril global safety database from time of initial marketing up to January 22, 2023. Lactating individuals were excluded from clinical trials.

Applicant's Review of Literature

The applicant searched PubMed and their Basilea-internal literature list (which includes Embase and congress abstracts) related to search terms "ceftobiprole" and "breast feeding", "breast*", "lactation", and "milk". The applicant identified no relevant literature.

DPMH Review of the Literature
This reviewer searched PubMed, Reprotox/Micromedex, GG Briggs & RF Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, Halesmeds.com, and Drugs and Lactation Database (LactMed) regarding ceftobiprole medocaril use during lactation. No published data were identified.

Reviewer Comment: In discussion with the DAI Clinical team, regarding the serious adverse reactions noted for ceftobiprole, none were considered relevant to the breastfed infant. There is no concern for infants <2 years of age for C. difficile associated diarrhea. Clinical illness is rarely reported in this population and gastrointestinal mucosa of neonates/infants may not be able to bind and process the C. Difficile toxin.[2]

Summary
Although ceftobiprole medocaril was detected in rat milk, the concentration in rat milk does not necessarily predict the concentration of drug in human milk. There are no available data on ceftobiprole medocaril presence in human milk, on the effects on the breastfed infant or the effects on milk production. There are no concerns for serious adverse reactions in the breastfed infant, therefore, the risk/benefit statement will be applied to subsection 8.2 *Lactation* of the Zevtera labeling.

Females and Males of Reproductive Potential
Nonclinical Data
The DAI Nonclinical review noted that,

> . . . genotoxicity profile of ceftobiprole medocaril was mixed including a negative Ames assay, a positive mouse lymphoma assay, a negative forward mutation assay, and positive chromosomal assays for both the pro-drug and active metabolite suggesting clastogenic potential. However, in vivo ceftobiprole medocaril was negative in both the micronucleus assay and rat liver unscheduled DNA synthesis reducing concern for potential clastogenic activity.

Fertility studies in male and female rats did not demonstrate an effect on fertility with repeat administration of intravenous ceftobiprole medocaril at doses up to approximately 1.4 times the MRHD.

Clinical Data
The applicant did not report about cases related to ceftobiprole medocaril and human infertility in their global safety database. No publications were identified by the applicant or this reviewer regarding the effects of ceftobiprole on human fertility.

Summary
There is no concern for genotoxicity and no available clinical data regarding effects of ceftobiprole medocaril on human fertility. In addition, because there is no signal of embryofetotoxicity in animal studies, pregnancy testing and contraception recommendations are not warranted in labeling. Therefore, the labeling subsection 8.3 *Females and Males of Reproductive Potential* will be omitted from Zevtera labeling.

CONCLUSION
Despite more than a decade of marketed use outside of the US, there are no available data on ceftobiprole

[2] Committee on Infectious Diseases, Gordon E. Schutze, Rodney E. Willoughby, Michael T. Brady, Carrie L. Byington, H. Dele Davies, Kathryn M. Edwards, Mary P. Glode, Mary Anne Jackson, Harry L. Keyserling, Yvonne A. Maldonado, Dennis L. Murray, Walter A. Orenstein, Theoklis E. Zaoutis; Clostridium difficile Infection in Infants and Children. Pediatrics January 2013; 131 (1): 196–200. 10.1542/peds.2012-2992

medocril use during pregnancy or lactation or related to its effects on human fertility. However, available data from published observational studies and case reports over several decades with cephalosporin use as a class in pregnant women have not established drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There were no safety signals from animal reproduction studies when ceftobiprole medocril was administered parenterally at doses clinically equivalent to the MHRD. Because ceftobiprole medocril is proposed for the treatment of severe, life-threatening conditions, DPMH does not recommend a Post Marketing Requirement (PMR) for a descriptive pregnancy safety study or a lactation milk only study to collect safety data. The information collected will likely be confounded with other medications used in treatment of these patients in the acute hospital setting. Therefore, DPMH recommends routine pharmacovigilance to monitor product use in pregnant or lactating individuals, such that in the event of a new safety signal, further evaluation can be pursued.

DPMH LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of Zevtera labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

(b) (4)

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/s/

TAMARA N JOHNSON
03/25/2024 06:00:23 PM

LYNNE P YAO
03/29/2024 10:09:13 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 28, 2024
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 218275
Product Name, Dosage Form, and Strength:	Zevtera (ceftobiprole medocaril sodium) for Injection, 667 mg/vial
Applicant Name:	Basilea Pharmaceutica International, Ltd., Allschwil (Basilea)
FDA Received Date:	March 27, 2024
TTT ID #:	2023-5788-3
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

Basilea Pharmaceutica International, Ltd., Allschwil submitted revised container label and carton labeling received on March 27, 2024 for Zevtera. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Zevtera (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

Basilea provided in their submission dated March 27, 2024, their response[b] to the container label and carton labeling recommendations dated March 22, 2024.[c]

We note that the revised labeling also includes revisions based on container label and carton labeling recommendations dated October 22, 2023, made by the Office of Pharmaceutical Quality (OPQ). Thus, we defer to OPQ to determine if these revisions are acceptable.

Additionally, the national drug code (NDC) will need to be updated on the container label and carton labeling once the final NDC is determined.

3 CONCLUSION

Basilea Pharmaceutica International, Ltd., Allschwil implemented all of our recommendations and we have no additional recommendations at this time. Additionally, we defer to OPQ to determine if, based on their recommendations, the submitted revised container label and carton labeling are acceptable.

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[a] Myers, D. Label and Labeling Memo for Zevtera (NDA 218275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAR 22. TTT ID: 2023-5788.

[b] Cover Letter: Response to Information Requests dated March 22, 2024 (Labeling amendment) for Zevtera (ceftobiprole medocaril) NDA 218275. Allschwil (Switzerland): Basilea Pharmaceutica International Ltd, Allscwil; 2024 MAR 27. Available at: \\CDSESUB1\EVSPROD\nda218275\0054\m1\us\12-cover-letter\cover-letter-sn0054-2024-03-27.pdf.

[c] Davi, C. FDA Communication: Information Request (IR) – Identified Issues and Recommendations for Basilea Pharmaceutica International, LTD., Allschwil for Zevtera (ceftobiprole medocaril sodium) NDA 218275. Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2024 MAR 22. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807337c2.

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/s/

DEBORAH E MYERS
03/28/2024 09:18:32 AM

VALERIE S VAUGHAN
03/28/2024 09:27:28 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	March 22, 2024
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 218275
Product Name, Dosage Form, and Strength:	Zevtera (ceftobiprole medocaril sodium) for Injection, 667 mg/vial
Applicant Name:	Basilea Pharmaceutica International, Ltd., Allschwil (Basilea)
FDA Received Date:	March 15, 2024
TTT ID #:	2023-5788-2
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

Basilea Pharmaceutica International, Ltd., Allschwil submitted revised container label and carton labeling, received on March 15, 2024 for Zevtera. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Zevtera (Appendix A) to determine if they are acceptable from a medication error perspective.

2 DISCUSSION

Strength Presentation

Prior to receiving the revised container labels and carton labeling, we noted Basilea currently markets ceftobiprole medocaril sodium in Canada and the United Kingdom with the strength expressed as 500 mg (based on the active moiety, ceftobiprole) and in Australia with the strength expressed as 666.6 mg (based on the salt form, ceftobiprole medocaril sodium). Publicly available literature describes the dosing in adults as 500 mg based on the active moiety, ceftobiprole. However, expressing the strength as 500 mg or 666.6 mg does not align with the FDA's salt policy; thus, Basilea requested a salt policy waiver to express the strength based on ceftobiprole medocaril sodium.

On March 7, 2024, DAI communicated their response[a] to Basilea's email dated January 29, 2024, which included confirming that the strength can be expressed based on the salt amount, ceftobiprole medocaril sodium 667 mg. Additionally, DAI's communication included that further comments and recommendations regarding the container label and carton labeling will be forthcoming. Furthermore, DAI's communication provided a reminder to Basilea to submit their request for proprietary name review, with the updated strength, so that the safety review considering the new 667 mg strength can be completed from a medication error perspective.

Based on internal discussion with our DAI and OPQ colleagues, the Agency's plan to grant a salt policy waiver, and to better understand potential medication error risks involving the 666.6 mg strength marketed outside the U.S., on March 5, 2024, we sent an IR to Basilea requesting that they share any reports of wrong dose medication errors associated with their Zevtera product marketed in Australia. This information was sought to further inform our label and labeling review. Subsequently, on March 12, 2024, Basilea responded via email stating that globally they have received a total of 56 medication errors, of which 24 cases were relative to the dosage. Additionally, Basilea notes in this email that, "*Zevtera 667 mg (ceftobiprole medocaril sodium) Powder for injection was authorized in Australia on November 2nd, 2015 and this marketing authorization was withdrawn due to commercial-related reasons. During that time, the product was never marketed/commercialized in Australia at any time and consequently no reports of wrong dose medication errors associated with Zevtera in Australia are available.*"[b]

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[a] Davi, J. FDA Communication: Information Request – Comments for NDA 218275. Silver Spring (MD): FDA, CDER, OND, DAI (US); 2024 MAR 07. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8072edd4.

[b] Davi, J. Email Communication from Basilea: Re: IR for Zevtera (ceftobiprole medocaril) NDA 218275//Division of Medication Errors. Silver Spring (MD): FDA, CDER, OND, DAI (US); 2024 MAR 12. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80732e97.

Based on Basilea's response received on March 12, 2024, we sent a follow-up IR to Basilea requesting line listing information for the identified 24 medication error cases relevant to dosing.[c] Subsequently, on March 19, 2024, Basilea responded with an email including the requested line listing as an attachment.[d]

We reviewed the line listing data received on March 19, 2024, and limited our analysis to cases that described errors possibly associated with the label and labeling. We note majority of the cases described overdose due to off-label usage of the product (n=11) or overdose with no contributing factor indicated (n=8), underdose with no contributing factor indicated (n=1), missed dose due to drug shortages (n=2), expired drug administered (n=1), and delayed treatment (n=1). Thus, we determined of the included 24 cases, zero described errors relevant to the labels and labeling currently under review.

Revised Container Labels and Carton Labeling

The national drug code (NDC) will need to be updated on the container label and carton labeling once the final NDC is determined. Additionally, the established name and strength statement lack prominence.

We note that on March 12, 2024, DAI communicated recommendations made by the Office of Pharmaceutical Quality (OPQ) for the container label and carton labeling. Thus, we defer to OPQ to determine the acceptability of Basilea's implementation of their recommendations.

3 CONCLUSION

The revised container label and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Basilea Pharmaceutica International, Ltd., Allschwil in Section 4.

4 RECOMMENDATIONS FOR BASILEA PHARMACEUTICA INTERNATIONAL, LTD., ALLSCHWIL

Table 1. Identified Issues and Recommendations for Basilea Pharmaceutica International, Ltd., Allschwil (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The established name is not at least half as large	The current presentation of the established name does	Taking into account all pertinent factors, including typography, layout, contrast,

[c] Davi, J. FDA Communication: IR for Zevtera (ceftobiprole medocaril) NDA 218275//Division of Medication Errors. Silver Spring (MD): FDA, CDER, OND, DAI (US); 2024 MAR 18. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80731a60.

[d] Davi, J. Email Communication from Basilea: Re: IR for Zevtera (ceftobiprole medocaril) NDA 218275//Division of Medication Errors. Silver Spring (MD): FDA, CDER, OND, DAI (US); 2024 MAR 19. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8073388b.

Table 1. Identified Issues and Recommendations for Basilea Pharmaceutica International, Ltd., Allschwil (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	as the letters comprising the proprietary name.	not align with 21 CFR 201.10(g)(2).	and other printing features, revise the appearance of the proprietary name (e.g., decrease font size) and established name to align with 21 CFR 201.10(g)(2).
2.	The strength statement lacks prominence.	The current presentation of the strength statement does not align with 21 CFR 201.15.	Increase the prominence of the strength statement. Additionally, consider use of different font color, boxing, or other means to further distinguish the strength statement from the proprietary name.

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M E M O R A N D U M

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

DATE: March 6, 2024

TO: Peter Kim, M.D.
Director
Division of Anti-Infectives (DIV)
Office of Infectious Diseases (OID)
Office of New Drugs (OND)

FROM: Li-Hong Yeh, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDSI/OSIS

SUBJECT: Record audit of (b) (4) (b) (4) for the analytical portion of study #CSI-1006 submitted in support of NDA 218275.

Note: Two analytical sites 1. (b) (4) (b) (4) and 2. (b) (4) (b) (4) were involved with analysis of samples from study # CSI-1006.

This review is for the record audit conducted for (b) (4) The record audit for (b) (4) (b) (4) was recently completed, and the review was finalized in DARRTS on 3/4/2024.

1. Record Audit Summary

OSIS conducted a record audit of the analytical portion of study #CSI-1006 (NDA 218275, Ceftobiprole medocaril) performed at (b) (4)

(b) (4) went out of business in (b) (4) Study raw data were transferred to Johnson and Johnson (J&J), Titusville, New Jersey. J&J staff facilitated access to those study records.

No objectionable conditions were observed, and Form FDA 483 was not issued. In addition, no items were discussed with J&J staff at the close-out meeting. Based on the record audit, there are no identified concerns regarding the reliability of the analytical data generated from plasma and urine samples. Therefore, I conclude that the data from the analytical studies conducted at (b) (4) are reliable.

2. Reviewed Analytical Studies

Analytical site:

(b) (4)

NDA 218275

Study Number: CSI-1006
Study Title: "An Open-Label Study to Evaluate the Single-Dose Pharmacokinetics and Safety of Ceftobiprole in Pediatric Subjects 3 Months to 17 Years of Age, Inclusive, Undergoing Treatment with Intravenous Antibiotics."
Sample Analysis Dates: 05/01/2008 – 03/19/2009

The three sub-studies listed below were associated with study # CSI-1006.

Study 080426

"The Determination of JNJ-30982081 (Ceftobiprole Medocaril, Prodrug, BAL5788) and JNJ-31059873 (Ceftobiprole, Active Drug, BAL9141) Concentrations in K2EDTA Human Plasma (with Citric Acid) Samples from an Open-Label Study to Evaluate the Single-Dose Pharmacokinetics and Safety of Ceftobiprole in Pediatric Subjects 3 Months to 17 Years of Age, Inclusive, Undergoing Treatment with Intravenous Antibiotics"

Sample Analysis Period: 05/01/2008 – 03/13/2009

Study 080427

"The Determination of JNJ-30982081 (Ceftobiprole Medocaril, Prodrug, BAL5788) and JNJ-31059873 (Ceftobiprole, Active Drug, BAL9141) Concentrations in Human Urine (with Citric Acid) Samples from an Open-Label Study to Evaluate the Single-Dose Pharmacokinetics and Safety of Ceftobiprole in Pediatric

Subjects 3 Months to 17 Years of Age, Inclusive, Undergoing Treatment with Intravenous Antibiotics"

Sample Analysis Period: 06/05/2008 – 03/19/2009

Study 080428

"The Determination of JNJ--39724672 (Ring-opened Metabolite of Ceftobiprole, BAL1029) Concentrations in Human Urine (without Citric Acid) Samples from an Open-Label Study to Evaluate the Single-Dose Pharmacokinetics and Safety of Ceftobiprole in Pediatric Subjects 3 Months to 17 Years of Age, Inclusive, Undergoing Treatment with Intravenous Antibiotics"

Sample Analysis Period: 07/11/2008 – 03/09/2009

3. Record Audit

OSIS scientist Li-Hong Yeh, Ph.D., reviewed the analytical portion of the above study conducted at (b) (4)
(b) (4)

The analytical site, (b) (4) closed on (b) (4) The (b) (4) records were transferred to Johnson and Johnson Pharmaceutical Research & Development when (b) (4) was closed and stored offsite vendor (b) (4). The current record audit was hosted by Johnson and Johnson Records and Information Management, Titusville, NJ.

3.1 Previous Record Audit

This is the first OSIS record audit of (b) (4)

The previous OSIS inspection of the (b) (4)
were conducted from (b) (4). At the conclusion of the inspection, a one item Form 483 was issued because the firm (b) (4). In addition, an item was discussed because (b) (4)

3.2 Current Record Audit

The current record audit included opening and close-out meetings with staff from J&J, Titusville, NJ that hosted the record audit of the reviewed sub-studies conducted at (b) (4)
Request for study documents were made via

communication letters. J&J send the requested documents in email communication.

The current record audit included the following items:

-Study records.
-Method validation.
-Sample analysis.

4.Record Audit Finding

At the conclusion of the current record audit, I did not observe any objectionable conditions and did not issue Form FDA 483 to the analytical site. In addition, no items were discussed with J&J at the close-out meeting.

Draft: PY 03/04/2024, 03/06/2024
Edit: RCA 3/4/2024, 3/6/2024

OSIS File #: BE [redacted]

eNSpect Assignment ID: [redacted]
eNSpect OP ID: [redacted]

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LI-HONG P YEH
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RUBEN C AYALA
03/06/2024 09:51:54 AM

M E M O R A N D U M

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

DATE: March 1, 2024

TO: Peter Kim, MD
Director
Division of Anti-Infectives
Office of Infectious Diseases
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Division Director
DNDSI/OSIS

SUBJECT: Record audit of (b) (4) for the analytical portion of study # CSI-1006 submitted in support of NDA 218275.

Note: Two analytical sites 1. (b) (4) and 2. (b) (4) were involved with analysis of samples from study # CSI-1006.

This review is for the record audit conducted for (b) (4) A record audit for (b) (4) was recently completed and OSIS review for (b) (4) record audit will be communicated to the review division in the near future.

1. Record Audit Summary

OSIS conducted a record audit of the analytical portion of study # CSI-1006 (NDA 218275, Ceftobiprole medocaril) performed at (b) (4).

No objectionable conditions were observed, and Form FDA 483 was not issued at the close-out of the record audit. No items were discussed with site's management at the close-out meeting. Based on the record audit, there are no identified concerns regarding reliability of the analytical data generated from plasma and urine samples of Subjects (b) (6),

[redacted] and the samples were analyzed at [redacted].

NDA 218275

Study Number: CSI-1006
Study Title: "An open-label study to evaluate the single-dose pharmacokinetics and safety of ceftobiprole in pediatric subjects ≥3 months to <18 years of age undergoing treatment with systemic antibiotics."
Sample Analysis Dates: July 15, 2009 to July 6, 2010.

Analytical site: [redacted]

3. Record Audit

OSIS scientist Gajendiran Mahadevan, Ph.D. reviewed the analytical portion of the above study conducted at [redacted] on [redacted] In [redacted], [redacted] site was closed, and all site operations, equipment, and study records were relocated to a new place at [redacted]. The current record audit was hosted by [redacted]

3.1 Previous Record Audit

The previous OSIS record audit of [redacted] was conducted from [redacted], and covered sample analyses performed from [redacted]. At the conclusion of the record audit, a two-item Form FDA 483 was issued because 1. [redacted], and 2. [redacted]

3.2 Current Record Audit

The current record audit included opening and close-out meetings with [redacted] that hosted the record audit of the reviewed study conducted at [redacted] Requests for study documents were made via communication letters. [redacted] directly uploaded the requested documents in FDA's cloud File Sharing (CFS) service facilitated by Box.com. During the record audit, screen sharing was used to review study data when clarifications were needed.

The current record audit included the following items:

(b) (4)

3.3 Record Audit Finding

At the conclusion of the current record audit, I did not observe any objectionable conditions and did not issue Form FDA 483 to the analytical site. In addition, no items were discussed with site's management at the close-out meeting. (b) (4)

(b) (4)

Draft: GM 2/27/2024; 3/01/2024
Edit: RCA 2/27/2024, 3/1/2024

OSIS File #: (b) (4)

eNSpect Assignment ID: (b) (4)
eNSpect Op ID: (b) (4)

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/s/

GAJENDIRAN MAHADEVAN
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03/04/2024 08:30:58 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 4, 2024

To: Shabnam Naseer, Medical Officer, Cross-Discipline Team Leader (CDTL)
Division of Anti-Infectives (DAI)

J. Christopher Davi, Regulatory Project Manager, DAI

Abimbola Adebowale, Associate Director for Labeling, DAI

From: Qumerunnisa Syed, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZEVTERA (ceftobiprole medocaril) for injection, for intravenous use

NDA: 218275

Background:
In response to DAI's consult request dated August 07, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and Carton/Container for the original NDA submission for ZEVTERA (ceftobiprole medocaril) for injection, for intravenous use.

PI:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on February 23, 2024, and our comments are provided below.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on February 26, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Qumerunnisa Syed at 301-796-8897 or Qumerunnisa.syed@fda.hhs.gov.

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M E M O R A N D U M

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

DATE: March 1, 2024

TO: John Farley, MD
Director
Office of Infectious Diseases (OID)
Office of New Drugs (OND)

FROM: Sarmistha Sanyal, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Review of Clinical Inspection of University Multiprofile Hospital for Active Treatment Sveti, Georgi', Plovdiv, Bulgaria

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of study BPR-PIP-002 (NDA 218275) conducted at University Multiprofile Hospital for Active Treatment Sveti, Georgi', Plovdiv, Bulgaria. Study BPR-PIP-002 was conducted in additional sites as well.

Objectionable conditions were found during the inspection as Form FDA 483 was issued at the inspection close-out and there was an item discussed at the close-out meeting.

Based on the inspection observations, exhibits, and the firm's response to Form FDA 483, for study BPR-PIP-002, OSIS recommends the review division should consider whether certain subjects (included in Inspection Findings – Section 3.3.) should be considered for efficacy and safety consideration.

2. Inspected Studies:

NDA 218275

Study Number: BPR-PIP-002
Study Title: A multicenter, randomized, investigator-blind, active-controlled study to evaluate the safety,

tolerability, pharmacokinetics, and efficacy of ceftobiprole versus intravenous standard-of-care cephalosporin treatment with or without vancomycin in pediatric patients aged from 3 months to less than 18 years with hospital acquired pneumonia or community-acquired pneumonia requiring hospitalization.

Dates of study conduct: 11/27/2017 – 03/16/2020

Clinical site: University Multiprofile Hospital for Active Treatment "Sveti, Georgi"
Vassil Aprilov Str 15a
Plovdiv, Thrace, Bulgaria

3. Inspectional Findings

University Multiprofile Hospital for Active Treatment Sveti, Georgi', Plovdiv, Bulgaria

ORA investigator Dina Tallman inspected University Multiprofile Hospital for Active Treatment Sveti, Georgi', Vassil Aprilov Str 15a Plovdiv, Thrace, Bulgaria from January 15-19, 2024.

3.1 Previous Inspection(s)

This was the first OSIS inspection of University Multiprofile Hospital for Active Treatment Sveti, Georgi' under the BA/BE program.

3.2 Current Inspection

The current inspection included auditing the following items:
-Subject source documents
-Informed consent
-Protocol deviations
-Institutional review board approvals
-Test article accountability and storage
-Randomization
-Adverse events

3.3 Inspection finding(s)

At the conclusion of the inspection, investigator Tallman observed objectionable conditions. Form FDA 483 was issued to the clinical site and an item discussed at the close-out meeting. The Form FDA 483 observation(s) (**Attachment 1**), the firm's response dated 01/31/2024 (**Attachment 2**), and my evaluations are presented below.

3.3.1 FDA 483 Observations

Observation 1A1:
Specifically, study BPR-PIP-002 was not conducted in accordance with the investigational plan:
According to the protocol BPR-PIP-002, for patients <12 years of age, the study drug is to be administered at a concentration of 4 mg/mL. However, 8 out of 27 subjects randomized to receive the study drug received an incorrect concentration of infusion solution.

Subject Number	Age of Subject in years	Infusion Concentration per protocol	Infusion Concentration Administered	Number of Infusions	Date Range
(b) (6)	5	4 mg/mL	2 mg/mL	12	(b) (6)
	9	4 mg/mL	2.0476 mg/mL	9	
	4	4 mg/mL	2 mg/mL	9	
	9	4 mg/mL	2 mg/mL	9	
	5	4 mg/mL	2 mg/mL	9	
	3	4 mg/mL	2 mg/mL	9	
	2	4 mg/mL	2 mg/mL	12	
	5	4 mg/mL	2 mg/mL	18	

OSIS Evaluation:
The protocol (Section 6.1.1 and 6.2.1)states that for subjects less than 12 years of age, the study drug should be administered at a concentration of 4 mg/ml. Based on reviewing source documents for the listed subjects that were available except for subject (b) (6), the correct mg/kg doses were calculated. However, the protocol was not followed by the CI regarding infusion volume and the sponsor was not consulted before changing the infusion volume. I recommend the review division consider infusion volume deviation of these subjects in the final efficacy and safety evaluation.

Firm's Response
The CI stated that these subjects, who received wrong concentration of the infusion, were suffering from dehydration due to fever and pneumonia. To meet the fluid demand, the CI decided to increase the infusion volume and administered the IP at a concentration of 2 mg/ml instead of 4 mg/ml, while maintaining the infusion time as per the protocol. The CI also stated that these deviations took place in the beginning of 2018 but later in the year, site monitor discussed these deviations

with the CI, provided retraining and stronger protocol adherence was implemented. Please refer to **Attachment 2** for details.

OSIS Evaluation of the response:
Providing retraining to the CI and implementing adherence to protocol is an acceptable course of action.

Observation 1A2:
Subject (b) (6) was enrolled in study BPR-PIP-002 without meeting one of the eligibility criteria required by the protocol. Inclusion criterion #3 requires a diagnosis of CAP requiring hospitalization and administration of IV antibiotic therapy, characterized by leukocytosis or leucopenia. Subject (b) (6) did not meet eligibility criteria #3 prior to randomization to treatment.

OSIS Evaluation:
As observation 1A(2) states, subject (b) (6) was randomized and enrolled in the study without meeting one of the inclusion criteria (#3) described in the protocol. This deviation is included in the protocol deviation listing 1.11. Subject (b) (6) did not meet the criteria of having leucocytosis or leucopenia (as evident from the screening lab report of subject (b) (6) as well as Listing 5.1.1) relevant to patient age (Please refer to page 11 of **Attachment 3**). Based on this finding, I conclude that subject (b) (6) should be excluded from efficacy consideration.

Firm's Response
In the response to Form FDA-483 (**Attachment 2**), the CI stated that she used the totality of clinical information available during screening to include this subject.

OBSERVATION 1B:
Min/Max temperature logs used to document the storage conditions for study drug could not be attributed to the temperature monitor assigned to that refrigeration unit as the first page of the temperature log was blank.

OSIS Evaluation:
This observation is only relevant to Ceftobiprole. According to the pharmacy manual, Ceftobiprole IP, reconstituted as well as the infusion solution should be stored in refrigerator (2-8°C).

The first page of the refrigerator temperature log does not provide any information except the study, the site number and the name of the investigator. Therefore, the temperature records could not be attributed to the sponsor provided thermometer since the serial number was missing in the temperature log. Additionally, the calibration certificate for the thermometer

and the refrigerator temperature log did not cover the entire range of dosing period for all subjects dosed at this site.

Since the thermometer cannot be attributed to the source temperature logbook, the stability of Ceftobiprole cannot be relied upon during the study conduct. Therefore, I conclude that this observation may affect the data reliability, specifically the stability of Ceftobiprole IP. The review division may consider whether subjects who received Ceftobiprole, should be considered for the efficacy analysis.

Firm's Response:
During a discussion at the close-out meeting, the CI acknowledged this observation and provided assurance that the IP was maintained under refrigerated condition.

3.3.2. Discussion Item 1:
At the close-out meeting, Investigator Tallman discussed with the CI about non-availability of calibration records for weighing scale used in the study within investigational site files.

OSIS Evaluation:
Email communication with ORA Investigator Tallman reveals that there were two scales used in the study – one scale was to weigh infants and another one for adults. The study site had calibration certificates for the scales used for infants for following dates: 14th. September 2018, 5th. September 2019 and 30th. August 2021 (**Attachment 4**). The study protocol does not specify the age range for infants but among enrolled subjects, four are less than or one year of age. Among these subjects, only subject (b) (6) was dosed before validated calibration period (first dose on (b) (6)). Therefore, dosing for subject (b) (6) may be affected if the scale is not properly calibrated and the review division may consider whether subject (b) (6) should be included in the efficacy analysis.

Additional communication with ORA investigator revealed that the scales for adults were maintained and calibrated annually by the university hospital through an outside vendor and no calibration certificate was issued. The site provided payment invoices for calibrating scales for adults, for 2018 and 2019. The invoices are written in non-English language. Additionally, the dates on payment invoices may not reflect the exact calibration dates for adult scales and the specific calibration date was not available to review. Therefore, calibration for these adult scales cannot be verified for the relevant period of dosing for subjects who more than one year of age.

Since the validity of calibration for adult scales could not be established, dosing for all subjects who are more than one year of age, may be affected. The review division may consider subjects, who are more than one year of age, should be included in the efficacy analysis.

Firm's Response:
The CI acknowledged the discussion item during the close-out meeting.

3.3.3. Other Issue
In the protocol deviations log obtained from the site (**Attachment 5**), there is a reference called 'blinded data' for certain subjects. These deviations are not included in either of the protocol deviations listings 1.5 or 1.11. The review division should contact the sponsor and find out what 'blinded data' in the protocol deviation refers to and its impact on the study, if any.

Attachment(s)
Attachment 1: (b) (4)
Attachment 2:
Attachment 3:
Attachment 4:
Attachment 5:

Draft: SS 02/15/2024, 2/20/24, 2/23/24, 2/27/24, 2/28/24, 2/29/24, 3/1/24
Edit: SA 2/15/24. 02/21/24, 2/26/24, 2/27/24, 2/28/24, 2/29/24, 3/1/24; JC 02/26/2024, 2/28/2024, 2/29/2024, 3/1/24

OSIS File #: BE 10044

eNSpect Assignment ID: 234682
eNSpect OpID: 271508

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/s/

SARMISTHA SANYAL
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STANLEY AU
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Team Lead

SEONGEUN CHO
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M E M O R A N D U M

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

DATE: February 27, 2024

TO: Debra Birnkrant, M.D.
Director
Division of Antivirals (DAV)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDSI, OSIS

SUBJECT: Review of Analytical Remote Regulatory Assessment (RRA) of (b) (4)

RRA Summary

Per the request of OND/DAV, OSIS conducted an RRA of analytical portion of **Studies BPR-PIP-001** and **BPR-PIP-002** (NDA 218275, Ceftobiprole medocaril) conducted at (b) (4) (b) (4)

At the closeout of the RRA, objectional conditions were observed for (b) (4) for Study BPR-PIP-002 (b) (4). No objectional conditions were observed for Study BPR-PIP-001 (b) (4) .

Based on the RRA findings and the site's response, I conclude that the observations are unlikely to have an impact on (b) (4) of Study BPR-PIP-002. However, (b) (4)

Reviewed Studies

NDA 218275

Study #1: BPR-PIP-001

Study Title: "An open-label study to evaluate the single-dose pharmacokinetics and safety of ceftobiprole in neonate and infant patients aged up to 3 months undergoing treatment with systemic antibiotics"

Dates of Study Conduct: December 2016 - March 2020

Study #2: BPR-PIP-002

Study Title: "A multicentre, randomized, investigator-blind, active-controlled study to evaluate the safety, tolerability, pharmacokinetics and efficacy of ceftobiprole versus intravenous standard-of-care cephalosporin treatment with or without vancomycin in pediatric patients aged from 3 months to less than 18 years with hospital acquired pneumonia or community-acquired pneumonia requiring hospitalization"

Dates of Study Conduct: August 2018 - February 2020

Analytical Site: (b) (4)

OSIS scientist Yiyue Zhang conducted an RRA of (b) (4) (b) (4) from (b) (4).

- Previous inspection/RRA

The site has no previous FDA inspection and RRA history.

- Current RRA

The current RRA included a thorough examination of (b) (4) (b) (4)

- RRA findings

At the conclusion of the RRA, I observed objectionable conditions. The RRA observation, the site's response dated (b) (4) (**Attachment 1**), and my evaluations are presented below.

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Attachments:

Attachment 1. [redacted] (b) (4)

Attachment 2.

Attachment 3.

Attachment 4.

Attachment 5.

Draft: YZ 02/16/2024, 02/21/2024, 02/22/2024, 02/26/2024, 02/27/2024
Edit: GB 02/20/2024, 02/21/2024, 02/23/2024, 02/27/2024; AD 02/25/2024 02/27/2024

OSIS File#: BE [redacted] (b) (4)

eNSpect Assignment ID: [redacted] (b) (4)
eNSpect Op ID: [redacted] (b) (4)

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YIYUE ZHANG
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02/27/2024 05:07:42 PM

ARINDAM DASGUPTA
02/27/2024 05:09:14 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 13, 2024
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 218275
Product Name, Dosage Form, and Strength:	Zevtera (ceftobiprole medocaril) for Injection, 666.6 mg/vial
Applicant/Sponsor Name:	Basilea Pharmaceutica International, Ltd., Allschwil (Basilea)
TTT ID #:	2023-5788-1
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted their revised container label and carton labeling received on February 13, 2024, for Zevtera. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Zevtera (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

As currently presented, we note that Basilea revised the strength statement on both their proposed container label and carton labeling to the recommended "total quantity of drug per vial" format which DMEPA finds acceptable from a medication error perspective. However, we further note that Basilea has included the proposed strength as "666.6 mg/vial" on both their proposed container label and carton labeling. As DAI and the Office of Pharmaceutical Quality (OPQ) are still negotiating this product strength and appropriate equivalency statement, we defer to them to determine if the strength and equivalency statement on the container label

[a] Myers, D. Label and Labeling Review for Zevtera (NDA 218275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JAN 08. TTT ID No.: 2023-5788.

and carton labeling are acceptable and if not, to recommend the appropriate strength, as well as equivalency statement, to Basilea and subsequently confirm their inclusion on the container label and carton labeling.

3 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

However, noting that negotiations are currently ongoing, we defer to DAI and OPQ to determine if the strength and equivalency statements included on the proposed container label and carton labeling are acceptable and if not, to recommend the appropriate strength, as well as equivalency statement, to Basilea and subsequently confirm their inclusion on the container label and carton labeling.

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/s/

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VALERIE S VAUGHAN
02/13/2024 01:58:42 PM

Clinical Inspection Summary (CIS)

Date	2/7/2024
From	John Lee, M.D., Primary Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Gregory Mak, M.D., Medical Officer Joseph Chang, M.D., Medical Officer Shabnam Naseer, D.O., Team Leader Mukil Natarajan, M.D., Deputy Director for Safety Peter Kim, M.D., M.S., Director Chris Davi, M.S., Regulatory Project Manager Division of Anti-Infectives (DAI)
Application	NDA 218275
Applicant	Basilea Pharmaceutica International, LTD (Basilea)
Drug	Ceftobiprole Medocaril (pending trade name Zevtera®)
NME	Yes
Proposed Indications	Treatment of community-acquired bacterial pneumonia, *Staphylococcus aureus* bacteremia, or acute bacterial skin and skin structure infections
Consult Date	9/27/2023
CIS Goal Date	2/10/2024
Review Clock	Priority
Action Goal Date	4/3/2024
PDUFA Due Date	4/3/2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Seven good clinical practice (GCP) inspections were performed in auditing three pivotal studies for this NDA, 6 clinical investigators (Drs. Chuang, Bray, Overcash, Ninov, Dzharov, and Poromanski) and the sponsor (Basilea). The three studies were each conducted for the respective proposed indication for ceftobiprole medocaril: (1) Study 30982081-CAP-3001, in community-acquired bacterial pneumonia (CABP); (2) Study BPR-CS-008, in acute bacterial skin and skin structure infections (ABSSSI); and (3) Study BPR-CS-009, in *Staphylococcus aureus* bacteremia (SAB). Two clinical investigators were inspected for each study.

Based on the inspection results, the three studies appear to have been conducted in adequate compliance with GCP principles and regulations; the data from the inspected clinical investigators appear acceptable in support of the proposed indications. For all three studies, the major efficacy and safety data were verifiable. Evidence of underreporting important to data quality was not discovered, whether for adverse events or for major protocol deviations.

II. BACKGROUND

This original NDA from Basilea Pharmaceutica International, LTD supports the marketing approval of ceftobiprole medocaril (pending, Zevtera®) in the United States (US), a broad-spectrum antibiotic developed for the treatment of CABP in adults and children, SAB in adults, and ABSSSI in adults.

- CABP, SAB, and ABSSSI are potentially life-threatening infections. CABP is the leading cause of infection-related mortality in the US, typically after hospitalization. ABSSSI is common and may progress to life-threatening sepsis that often require immediate surgery and/or intravenous (IV) antibiotic therapy. *Staphylococcus aureus* is a leading cause of bacteremia responsible for a wide variety of clinical complications with significant mortality.
- Ceftobiprole medocaril is an inactive prodrug metabolized in vivo to the active drug ceftobiprole, an advanced-generation broad-spectrum cephalosporin with potent activity against both Gram-negative and Gram-positive bacterial pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA).

The three major pivotal studies that support this NDA were audited at 7 GCP inspections, for 6 clinical investigators (two per study) and the sponsor. The following protocol summaries highlight the major study features examined for GCP compliance at the 7 NDA pre-approval inspections.

Study 30982081-CAP-3001: *Randomized, Double-Blind, Multicenter Study of Ceftobiprole Medocaril versus Ceftriaxone with/without Linezolid in the Treatment of Subjects Hospitalized with Community-Acquired Pneumonia*

The sponsorship of this study was transferred from Johnson & Johnson Pharmaceutical Research and Development, LLC (J&J) to Basilea in 2011. Under J&J, this double-blind randomized controlled trial (DB-RCT) was conducted over 13 months (2006-07) in 638 hospitalized subjects with CABP at 102 clinical investigator (CI) sites in 17 countries: US (16 sites), Ukraine (11), Czech Republic (10), Russia (10), Argentina (8), Brazil (8), China (8), Taiwan (6), Germany (5), Lithuania (5), South Korea (4), Poland (4), Mexico (3), Panama (2), Costa Rica (2), and Hungary (1).

Note about inspection planning: Basilea conducted an internal audit of this legacy study upon assuming the study sponsorship in 2011. Based on the internal audit findings, Basilea disqualified one CI site in Costa Rica and the data from that site were excluded from the NDA. The 11 CI sites in Ukraine could not be considered for FDA inspection due to current travel restrictions.

The primary study objective was to demonstrate the *non-inferiority* of ceftobiprole medocaril relative to ceftriaxone (with and without linezolid) in curing adults hospitalized for CABP. The study consisted of: screening, baseline evaluation, double-blinded treatment, early follow-up (7-14 days after last dose of study drug), and long-term follow up (4-5 weeks after last dose of study drug), for a total study duration of 7 weeks for any given subject.

- Subjects were randomized in equal ratio (1:1) to ceftobiprole or comparator, stratified by: (1) *Pneumonia Outcomes Research Trial* (PORT) *Severity Index* score < or ≥ 91; and (2) need for anti-staphylococcal therapy (placebo or linezolid), per CI judgment.
- All subjects were typically treated for 5 – 10 days (range 3-14 days) with double-blinded IV infusion (except pharmacist, unblinded for study medication preparation).
- Per CI judgment, the study medication was switched to oral cefuroxime (500 mg every 12 hours) after 3 days of sufficient clinical improvement, per CI judgment.

Subject Selection

Adults (excluding women of pregnancy potential) with CABP requiring hospitalization and IV antibiotics were initially selected at screening, as evidenced by (all of):

- Clinical symptoms and signs, including dyspnea
- Laboratory testing, including microbiology and hypoxemic oxygen saturation
- Radiography, including chest X-ray (CXR)

Major Exclusion Criteria (for screen-selected subjects):

- Any condition that complicates study execution (e.g., severe cardiac, pulmonary, hepatic, renal, or other physical impairment) or study results interpretation (e.g., recent receipt of ceftobiprole or other antibiotics), per CI judgment
- Inability to receive penicillin, cephalosporin, or other antibiotics structurally related to the study medications (including ceftriaxone and linezolid)

Treatment Regimens

- Ceftobiprole 500 mg every 8 hours (Q8H) IV over 2 hours (+ placebo IV)
- Ceftriaxone 2.0 g every 24 hours (Q24H) IV over 30 minutes (+ placebo IV)
- Placebo IV infusion (concurrent with and complementary to active study medication): Q8H over 2 hours, for ceftriaxone; or Q24H over 30 minutes, for ceftobiprole medocaril
- Linezolid or placebo was added for ceftriaxone-resistant *Streptococcus pneumoniae* after confirmation by culture and antibiotic sensitivity.

Major Efficacy Endpoints

- Primary efficacy endpoint: clinical cure (CC) at test-of-cure (TOC) visit based on physical examination, laboratory tests, microbiology culture, and radiography
- Major secondary efficacy endpoints (TOC visit): (1) microbiologic eradication; (2) CC in subjects requiring mechanical ventilation within 48 hours of enrollment; (3) microbiologic cure (MC) in subjects requiring mechanical ventilation within 48 hours of enrollment; and (4) death from pneumonia within 30 days after randomization
- Major safety endpoints: adverse events (AEs), physical examination, laboratory testing, and electrocardiogram (ECG)

TOC assessment, at end of therapy (EOT): *Cure, Failure, or Unevaluable*
Long-term follow up, at 4-5 weeks after EOT: EOT *Cure* re-evaluated for *Relapse*

Study BPR-CS-008: *A randomized, double-blind, multicenter study to establish the safety and efficacy of ceftobiprole medocaril compared with vancomycin plus aztreonam in the treatment of acute bacterial skin and skin structure infections*

This DB-RCT was conducted over 14 months (2018-19) in 679 subjects at 32 CI sites in 4 countries: US (16 sites), Ukraine (10), Bulgaria (4), and Hungary (2). The primary study objective was to demonstrate the *non-inferiority* of ceftobiprole medocaril relative to vancomycin + aztreonam in treating ABSSSI. The study consisted of: screening, baseline evaluation, double-blinded treatment, EOT and TOC visits, and long-term follow up (4-5 weeks after EOT), for a total study duration of 6 weeks for any given subject.

- Randomization 1/1 to ceftobiprole/comparator, stratified by study site and ABSSSI type
- All subjects (hospitalized) treated IV for one week (3 – 14 days), double-blinded

Subject Selection

Adults with ABSSSI requiring IV antibiotic therapy were initially selected at screening. The major infections were: cellulitis, erysipelas, major cutaneous abscess, and wound infections.

Major Exclusion Criteria (for screen-selected subjects):

- Uncomplicated SSSI, infections related to prosthetic devices, infections requiring more than two surgical interventions in the operating room
- Systemic antibiotic therapy within 14 days prior to randomization, or topical antibiotic on primary skin lesion within 96 hours before the first infusion of the study medication

Treatment Regimens

- Ceftobiprole 500 mg Q8H IV over 2 hours
- Comparator: vancomycin 1000 mg (or 15 mg/kg) every 12 hours (Q12H) IV over 2 hours + aztreonam 1000 mg Q12H IV over 30 minutes
- Placebo IV infusions (concurrent with and complementary to active study medication)

Major Efficacy Endpoints

The following primary and secondary endpoints for US sites were switched for European sites (primary for secondary, secondary for primary).

Primary endpoint (US): early clinical response (ECR) within 48 – 72 hours of therapy start

- ≥ 20% reduction in size (area) of the primary lesion, survival for ≥ 72 hours after first dose of study drug, and no concomitant antibiotic use (systemic or topical)
- No unplanned surgery for the primary lesion after start of therapy, other than: (1) bedside debridement or wound care; (2) drainage of abscess forming within 48 hours of study treatment initiation; or (3) extension of original surgical incision

Major secondary endpoint (US): TOC evaluation (15 – 22 days after randomization and ≥ 5 days after EOT) as *Cured, Improved, Stable,* or *Worsened*

- Clinical success: complete (*Cured*) or nearly complete (*Improved*) resolution of the primary infection (no further antibiotic need)
- Clinically unsuccessful: *Stable* (no significant clinical change) or *worsened* (*Worsened*) based on signs and symptoms documented as AEs (e.g., bacteremia, osteomyelitis, amputation)

Study BPR-CS-009: *A randomized, double-blind, multi-center study to establish the efficacy and safety of ceftobiprole medocaril compared to daptomycin in the treatment of Staphylococcus aureus bacteremia, including infective endocarditis*

This DB-RCT was conducted over 4 years (2018-22) in 390 subjects at 60 CI sites in 17 countries: Argentina (3 sites), Bulgaria (4), Colombia (1), Georgia (7), Germany (1), Greece (1), Israel (5), Italy (4), Mexico (2), Panama (1), Russian Federation (8), Serbia (2), South Africa (2), Spain (5), Turkey (2), Ukraine (7), and US (5). The primary study objective was to demonstrate the *non-inferiority* of ceftobiprole medocaril relative to daptomycin for overall success in treating SAB, including SAB with infective endocarditis (IE).

Note about inspection planning: Nearly half of all subjects were enrolled at the 7 sites in Ukraine, with greater treatment success than in any other country and typically with little to no AEs. Given the current travel restriction for Ukraine, a limited indirect audit for 4 sites in Ukraine (Sites 322 – 325, emphasis on site monitoring of Site 325) were conducted at the sponsor inspection of Basilea.

- The study was conducted in two parts: (1) initial treatment limited to subject Cohort 1 for up to 28 days, based on safety concern (seizure); and (2) extended treatment for all subjects for up to 42 days, extended after interim safety assessment of Cohort 1
- The study consisted of: screening, baseline evaluation, double-blinded treatment, EOT visit within 72 hours after last treatment dose, and post-randomization evaluations on Days 35, 42, and 70 for a total study duration of 10 weeks for any given subject.
- Randomization in equal ratio (1:1) to ceftobiprole or comparator, stratified by: study site, dialysis status, and prior antibiotic use

Subject Selection

Adults with complicated SAB were selected at initial subject screening, with the requirement for at least one positive baseline blood culture for *S. aureus*, signs/symptoms of bacteremia (fever, elevated white blood cell count, tachycardia, and/or hypotension), and any of the following:

- Chronic intermittent hemodialysis or peritoneal dialysis
- Persistent SAB, definitive native-valve RIE, or ABSSSI
- Metastatic infections (e.g., septic arthritis, visceral abscess, septic emboli)

Major Exclusion Criterion (for screen-selected subjects): anti-staphylococcal systemic antibiotic for over 48 hours within 7 days of randomization (unless for persistent SAB)

Treatment Regimens

- Ceftobiprole 500 mg IV over 2 hours: every 6 hours (Q6H) for 8 days, then Q8H
- Daptomycin 6 mg/kg (up to 10 mg/kg) IV over 30 minutes Q24H, with or without optional aztreonam for qualifying subjects (standard regimen)
- Placebo IV infusion (concurrent with and complementary to active study medication)

Major Efficacy Endpoints

Primary endpoint: Overall Success (OS) as assessed by the Data Review Committee (DRC) at Duke University (Durham, NC) at the Post-Treatment Evaluation (PTE) visit, as meeting all of the following clinical and microbiologic criteria:

- Alive at post-randomization Day 70
- No new metastatic foci or complications of the SAB infection
- Resolution or improvement of SAB-related clinical signs and symptoms
- Two negative blood cultures for S. aureus, without any subsequent positive cultures

Major secondary endpoints:

- All-cause mortality assessed at Day 70 (PTE visit)
- Microbiologic eradication as assessed by DRC at Day 70 (PTE visit)

III. INSPECTION RESULTS

1. Yin-Ching Chuang, M.D.

901 Chungh-Wa Road
Yung Kang Township 710
Tainan, Republic of China (Taiwan)

Inspection Dates: 11/20-24, 2023

Protocol 30982081-CAP-3001, Site 886005: The CI (Dr. Chuang) had retired and was not available; a sub-investigator (Dr. Hung-Jen Tang) assisted with the inspection. All subjects were hospital in-patients: 30 were screened, all were enrolled, and all completed the study.

The inspection found that the case records for 11 subjects were destroyed accidently during records storage and were unavailable for review (discussed further below). All available records were reviewed in detail, including case records for the remaining 19 of the total 30 subjects enrolled at this CI site. No significant GCP deficiencies were identified. GCP compliance appeared acceptable for financial disclosure, adverse event (AE) monitoring, protocol deviations reporting, and drug accountability. The major study data (safety and efficacy) were verifiable for the 19 subjects with available records (of total 30 subjects, 63%).

- Much of the paper source records for this legacy study (sponsorship transferred from J&J to Basilea) had been destroyed, apparently accidently in 2022 during the long-term storage (for over 10 years) managed by the contract research organization (CRO) (b) (4) and its subcontractor, the storage company (b) (4).
- According to the hospital recordkeeping policy (and record management practices at the CI site, J&J, Basilea, (b) (4) and (b) (4)), records older than 10 years and not otherwise identified for long-term retention were to be destroyed. Boxes of paper records at this CI site to be retained for long-term storage were identified using unreliable labeling stickers, many of which apparently failed (fell off) during storage of over 10 years. The major study files destroyed consisted of records for CI site monitoring (by J&J), subject informed consent, and subject case records for the following 11 subjects: (b) (6)
- The records were destroyed 11 years after Basilea had conducted an internal audit of the study in 2011. The electronic versions (scanned by Basilea) were available for some of the destroyed records, including records for subject randomization, *PORT Severity Index* (PSI) scores for stratifying pneumonia severity, pharmacokinetic sample collection, study medication preparation (pharmacy records), staff training, and monthly monitoring correspondence.

2. Wesley R. Bray, M.D.

522 North Avenue
Marietta, GA 30060-1155

Inspection Dates: 10/10-16, 2023

Protocol 30982081-CAP-3001, Site 001003: 34 subjects were screened, 28 were enrolled, and 17 completed the study (11 withdrew consent). Case records were reviewed in detail for all subjects, including source and summary documents for: site monitoring, Institutional Review Board (IRB) and sponsor communications, financial disclosure, study medication accountability, subject selection, AEs, laboratory results, concomitant medications, protocol deviations, and major efficacy data.

No significant GCP deficiencies were observed. The sponsor's monitoring appeared adequate. The study records showed appropriately signed informed consent forms for all subjects, complete financial disclosure documentation, complete AE reporting, and acceptable drug accountability. Protocol deviations reporting was limited to major deviations; significant unreported major deviations were not discovered. The primary, major secondary, and safety endpoint data were verifiable.

3. Borislav T. Ninov, M.D.

Multiprofile Hospital for Active Treatment
8a Georgi Kochev Street
Pleven 5800, Bulgaria

Inspection Dates: 12/11-15, 2023

Protocol BPR-CS-008, Site 044: The CI (Dr. Ninov) had retired and was available by phone only; a sub-investigator (Dr. Yanko V. Parvanov) primarily assisted with the inspection. Most subjects were hospital in-patients or referred from outside clinics: 35 subjects were screened, all were enrolled, and all completed the study.

All case records were reviewed (source and summary documents), including detailed review for 21 subjects, including records for: site monitoring, IRB and sponsor communications, financial disclosure, study medication accountability, study task delegation, staff training, subject selection, study medication dosing, AEs, laboratory results, concomitant medications, protocol deviations, and major efficacy data.

No significant GCP deficiencies were observed. The sponsor's monitoring appeared adequate. The study records showed appropriately signed informed consent forms for all subjects, complete financial disclosure documentation, and acceptable drug accountability. No unreported AEs or protocol deviations were discovered. The primary, major secondary, and safety endpoint data were verifiable.

4. Jeffrey S. Overcash, M.D.

Velocity Clinical Research
5565 Grossmont Center Drive
La Mesa, CA 91942-3000

Inspection Dates: 11/14-17, 2023

Protocol BPR-CS-008, Site 067: 79 subjects were screened, 74 were enrolled, and 59 completed the study. Two deaths appeared unrelated to the study medications: both subjects were randomized to control (vancomycin/aztreonam) and died of sepsis as a complication of IV drug abuse, either before receiving any study therapy (Subject (b) (6)) or after completing therapy (Subject (b) (6)). 13 subjects were lost to follow up.

Subject case records were reviewed (source and summary documents) for 26 subjects, including detailed review for 15 subjects, for: site monitoring, IRB and sponsor communications, financial disclosure, study medication accountability, subject selection, AEs, concomitant medications, protocol deviations, and major efficacy data.

Noteworthy finding was limited to an isolated data mismatch for Subject (b) (6) randomized to control (vancomycin/aztreonam). The CI reported "yes" for ECR (US primary efficacy endpoint), for the adequacy of the reduction in lesion size at 48-72 hours (apparently accurate, consistent among all source records and the eCRF), discrepant with the ECR of "no" as reported in the NDA (apparently inaccurate). This single isolated data discrepancy appears unlikely to be significant to determining the overall study outcome.

Significant GCP deficiencies were otherwise not observed. The sponsor's monitoring appeared adequate. The study records showed appropriately signed informed consent forms for all subjects, complete financial disclosure documentation, and acceptable drug accountability. No unreported AEs or protocol deviations were discovered. Other than the ECR for Subject (b) (6), all audited primary, major secondary, and safety endpoint data were verifiable.

5. Georgi Z. Dzharov, M.D.

Evrohospital University Hospital
79 Komatevsko Shose Str.
Plovdiv, Plovdiv, 4004 Bulgaria

Inspection Dates: 12/11-15, 2023

Protocol BPR-CS-009, Site 203: 20 subjects were screened, all were enrolled, and 19 completed the study. Subject case records (source and summary documents) were reviewed in detail for 15 subjects, including records for: site monitoring, ethics committee (EC) and sponsor communications, financial disclosure, study medication accountability, study task delegation, subject selection, AEs, laboratory results, concomitant medications, protocol deviations, and major efficacy data. Noteworthy GCP deficiency findings were limited to missing blood culture results for the follow up period (EOT through PTE, 4 subjects); all were reported in the NDA as protocol deviations.

Significant GCP deficiencies were otherwise not observed. The sponsor's monitoring appeared adequate. The study records showed appropriately signed informed consent forms for all subjects, complete financial disclosure documentation, and acceptable drug accountability. No unreported AEs or protocol deviations were discovered.

The central DRC records for primary efficacy assessment were not available at this CI site (or at any other CI site in the study); electronic records were sent from DRC directly to the sponsor without concurrent distribution to the respective CI sites (per protocol). The DRC data presented in the NDA appeared to be consistent with the local CI site data. The major audited data at this CI site were verifiable.

6. Ivan G. Poromanski, M.D., Ph.D.

Bulevard Gen Totleben 21
Sofia, Sofia, 1606 Bulgaria

Inspection Dates: 12/4-7, 2023

Protocol BPR-CS-009, Site 205: 20 subjects were screened, all were enrolled, and 16 completed the study. Subject case records (source and summary documents) were reviewed in detail for 15 subjects, including records for: site monitoring, EC and sponsor communications, financial disclosure, study medication accountability, study task delegation, subject selection, AEs, laboratory results, concomitant medications, protocol deviations, and major efficacy data.

No significant GCP deficiencies were observed. The sponsor's monitoring appeared adequate. The study records showed appropriately signed informed consent forms for all subjects,

complete financial disclosure documentation, and acceptable drug accountability. No unreported AEs or protocol deviations were discovered.

The central DRC records for primary efficacy assessment were not available at this CI site (or at any other CI site in the study); electronic records were sent from DRC directly to the sponsor without concurrent distribution to the respective CI sites (per protocol). The DRC data presented in the NDA appeared to be consistent with the local CI site data. The major audited data at this CI site were verifiable.

7. Basilea Pharmaceutica International, LTD

Hegenheimermattweg 167b
Allschwil, 4123 Switzerland

Inspection Dates: 12/11 – 21, 2023

Studies 30982081-CAP-3001, BPR-CS-008, and BPR-CS-009

This sponsor inspection was conducted with special guidance from the review division primarily as a directed inspection to investigate specific NDA review concerns about GCP: (1) for Study 30982081-CAP-3001, the legacy study originally sponsored by J&J; and (2) for CIs in Ukraine in Study BPR-CS-009 with large site-specific efficacy and few AEs; these sites were identified for inspection but could not be inspected due to the current travel restrictions to Ukraine. The inspection consisted of: (1) directed investigation of these review concerns; and (2) general audit, to evaluate the overall compliance with GCP standards and regulations applicable to the sponsor, with emphasis on CI site monitoring.

The study files reviewed included the trial master file (TMF) and the records for: CI agreement, financial disclosure, IRB oversight, staff training, subject enrollment, CI monitoring, drug accountability, and subject case records limited to subject selection, AEs, concomitant medications, and protocol deviations. Some original (source) records were available to confirm study dates, study locations, and subject enrollment at CI sites.

GCP deficiencies were observed for the sponsor oversight of CI sites, specifically for: protocol deviation reporting, record retention, and inconsistencies in *Serious, Unexpected, or Suspected Adverse Reaction* (SUSAR) reporting. Evidence of biased study conduct or other GCP deficiencies important to data integrity was not observed.

Study 30982081-CAP-3001 (CABP)

Basilea conducted an internal audit of this legacy study upon assuming the study sponsorship from J&J in 2011. Fourteen CI sites with the largest subject enrollment were evaluated for GCP compliance. The data from one CI site in Costa Rica were excluded from the NDA based on the audit findings. The findings of the three FDA inspections for this study (Basilea, 2 CIs) appeared to be consistent with the sponsor's audit findings.

- CI site monitoring records (J&J) were missing for many of the monitoring visits for about one-half of all CI sites in the study (141 subjects, 22% of 638 total). Monitoring records were missing for ≥ one-half of the visits for 9 sites (63 subjects, 10%), and missing for > one-fourth of the visits for 8 sites (18 subjects, 3%). The extent of the missing monitoring visit records appeared to be unrelated to enrollment or to any other site-specific GCP attribute.

- Of the 14 largest sites sampled in Basilea's internal audit, 6 sites were missing monitoring records for 3-75% of the visits, typically 10% or fewer (5 of 6 sites). Site 886005 inspected by the FDA (Dr. Chuang, Taiwan) appeared to be an isolated outlier, with monitoring records missing for 75% of the monitoring visits.

The missing monitoring visit records appeared to be unrelated to the records destruction by (b) (4) for Site 886005 (See page 7, *Inspection Results*); the monitoring records maintained at the sponsor site were never destroyed. Basilea's audit findings for Site 886005 in 2011 was not affected by (b) (4)'s destruction of the records for this CI site in 2022.

Study BPR-CS-009 (SAB)

Nearly one-half of the subjects in this study were enrolled at CI sites in Ukraine. Collectively, the overall efficacy for the sites in Ukraine was greater than for any other country, and with fewer AEs. The single most influential CI site for this study was identified as Site 325 in Ukraine.

- Central DRC records for primary efficacy assessment were not made available at CI sites; electronic records were sent from DRC directly to the sponsor without concurrent distribution to the respective CI sites. The DRC data presented in the NDA were audited against the case report forms submitted by the DRC to the sponsor for 16 subjects (identified by review division): (b) (6) . All audited data were verifiable.
- Per review division guidance, echocardiogram results reported in the NDA were audited against the echocardiogram reports to verify the presence of an oscillating intracardiac mass for 12 of these 16 subjects: (b) (6) All audited results were verifiable.
- An unusually large number of protocol deviations were reported from the Ukraine sites in this study, typically for central laboratory (safety) testing. Most were for missed sample collection or sample rejection due to incorrect sample storage or transport.
- The subjects in Ukraine (relative to other countries) often had infections more treatable procedurally (e.g., abscess drainage) typically with fewer clinical management complications (e.g., dialysis). Site 324 was a proctology center where the enrolled subjects shared similar infections, demographics, and general clinical status.

For all three audited studies, evidence of unblinding or biased data collection was not discovered. Study monitoring appeared adequate for the two studies sponsored by Basilea. The audited NDA data were consistent with the sponsor's records for the primary efficacy, major secondary efficacy, and safety data.

{See appended electronic signature page}

John Lee, M.D.
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APPEARS THIS WAY ON ORIGINAL

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/s/

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 8, 2024
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 218275
Product Name, Dosage Form, and Strength:	Zevtera (ceftobiprole) for Injection, 500 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Basilea Pharmaceutica International, Ltd., Allschwil (Basilea)
FDA Received Date:	August 3, 2023 and August 15, 2023
TTT ID #:	2023-5788
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 REASON FOR REVIEW

As part of the approval process for Zevtera (ceftobiprole) for Injection, the Division of Anti-Infectives (DAI) requested that we review the proposed Zevtera prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND/REGULATORY HISTORY

NDA 218275 is a 505(b)(1) application submitted on August 3, 2023.

The proposed proprietary name, Zevtera, under NDA 218275 was found conditionally acceptable on October 26, 2023.[a]

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Label and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Basilea Pharmaceutica International, Ltd., Allschwil.

[a] Myers, D. Proprietary Name Review for Zevtera (NDA 218275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 OCT 26. PNR ID No. 2023-1044725273.

4 RECOMMEDATIONS FOR DIVISION OF ANTI-INFECTIVES (DAI)

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
Full Prescribing Information – Section 2 *Dosage and Administration*			
1.	As currently presented, we note the use of error-prone symbols throughout the *Dosage and Administration* section.	Error prone symbols may lead to misinterpretation and medication error.	We recommend replacing the occurrences of the symbols (i.e., "<" and "≥") with their intended meanings (i.e., "less than" and "greater than or equal to," respectively). See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.[b]
2.	As currently presented, subsection 2.3 is titled "*Preparation of* (b) (4)	The current title of subsection 2.3 does not convey its inclusion of both reconstitution and dilution steps.	For clarity, we recommend revising the title of subsection 2.3 from "*Preparation of* (b) (4) to "*Preparation of Solutions."*
3.	As currently presented, in subsection 2.3 *Preparation of* (b) (4) , the third paragraph under the subheading "Reconstitution of ZEVTERA in the vial" includes the text "The volume of the resulting reconstituted solution is approximately 10.6 mL…	With a final volume of 10.6 mL, it is unclear if the reconstituted vial contains a (b) (4) concentration. Dosing errors could result if the listed resultant concentration is incorrect. For example, underdose could occur if the vial contains (b) (4) /10.6 mL and the healthcare provider	We recommend subsection 2.3 be revised to provide clarity for the final resultant concentration to minimize dosing errors.

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	The reconstituted solution contains (b) (4) 66.7 mg/mL of ceftobiprole medocaril sodium (b) (4)"	removes only 10 mL (approximately (b) (4) mg).	
4.	As currently presented, in subsection 2.3 *Preparation of* (b) (4), under the subheading "Dilution of ZEVTERA (b) (4)		

Unclear preparation instructions may lead to wrong dose medication errors. For example, the current dilution instructions could result in healthcare professionals (HCPs) attempting to administer weight-based doses that are less than 500 mg using prepared 500 mg/250 mL and 500 mg/125 mL infusion bags. Wrong dose errors (e.g., overdose) could occur if the entire bags are used to administer doses less than the 500 mg. For pediatric and adolescent patients, doses less than 500 mg should be prepared in empty containers (e.g., infusion bags, syringes).

To provide clarity we recommend that a table might be a better manner to communicate this information (see example below):

Table X. Preparation of ZEVTERA Solution for Infusion

	Volume of diluent to be added to the vial	Volume of reconstituted solution to be withdrawn from the vial	Volume of Infusion solution*	Concentration and final volume of the reconstituted product
Adult (18 years of age and older)	10 mL	10 mL	250 mL	2 mg/mL in a 250 mL infusion bag (500 mg/250 mL)
Adolescent Patients 12 Years of Age to Less than 18 Years of Age	10 mL	Refer to Table 2 to determine volume of reconstituted solution needed according to weight-based dosing	The final volume to be administered should be calculated based on the patient body weight and must not exceed a maximum of 250 mL (500 mg dose) and a concentration of 2 mg/mL	
Adult patients with severe renal impairment	10 mL	5 mL	125 mL	2 mg/mL in a 125 mL infusion bag

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	<table><tr><td></td><td></td><td></td><td>(250 mg/125 mL)</td></tr><tr><td>Pediatric Patients Less than 12 Years of Age</td><td>10 mL</td><td>Refer to Table 2 to determine the volume of reconstituted solution needed according to weight-based dosing**</td><td>The final volume to be administered should be calculated based on the patient body weight and must not exceed a maximum of 125 mL (500 mg dose) and a concentration of 4 mg/mL</td></tr></table> * Gently invert 5-10 times to form a homogenous solution. Avoid vigorous agitation to prevent foaming. ** For administration via a 50 mL syringe if the calculated dose does not exceed 200 mg: Withdraw 4 mL of the reconstituted solution from the vial and withdraw 46 mL of the appropriate infusion solution into the syringe.		
5.	As currently presented, in subsection 2.5 *Storage of Reconstituted and Infusion Solutions*, (b) (4) [redacted] do not include stability time for the reconstituted solution.	It is unclear whether Tables 5 and 6 are intended to convey storage information from the point of reconstitution through administration of the final infusion solution or from the point of dilution through administration of the final infusion solution. Ambiguous stability data could lead to administration of deteriorated drug.	We recommend Tables 5 and 6 be revised to provide clarity of the intended storage.
6.	(b) (4) [redacted]		

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
7.	As currently presented, subsection 2.5 *Storage of Reconstituted and Infusion Solutions* the sentence prior to Table 5 (b) (4) [redacted]	As currently stated there could be confusion regarding which "ZEVTERA solution" is being referenced (e.g., reconstituted solution in the vial and/or infusion (diluted) solutions).	To help decrease the risk of confusion, we recommend revising the current sentence (b) (4) [redacted]
Full Prescribing Information – Section 3 *Dosage Forms and Strengths*			
1.	As currently presented, the dosage form (i.e., for injection) is not provided in Section 3.	The dosage form is required per 21 CFR 201.57(c)(4).	Add the dosage form (i.e., for injection) in Section 3 in accordance with 21 CFR 201.57(c)(4). Additionally, ensure the *Dosage Forms and Strengths* section of the "Highlights of Prescribing Information" is updated accordingly.
2.	As currently presented, the package type term, "single-dose vial" is not included in Section 3.	Consistent use of the correct package type term will promote proper use of the drug product. The lack of this information may lead to wrong technique medication errors during preparation or administration of the product.	Add the appropriate package type term, (i.e., "Single-Dose vial"). See *Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)*.[c]
Full Prescribing Information – Section 16 *How Supplied/Storage and Handling*			

[c] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2018. Available from https://www.fda.gov/media/117883/download.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	As currently presented, the strength is not provided in Section 16.	The strength is required per 21 CFR 201.57(c)(17).	Add the strength in [Section 16 in accordance with 21 CFR 201.57(c)(17).
2.	As currently presented, in subsection 16.2 *Storage and Handling*, the final sentence incorrectly references (b) (4)	Incorrect reference (b) (4)	If the Applicant's intent is to reference the reader to the (b) (4) For example, (b) (4)

5 RECOMMENDATIONS FOR BASILEA PHARMACEUTICA INTERNATIONAL, LTD., ALLSCHWIL

Table 3. Identified Issues and Recommendations for Basilea Pharmaceutica International, Ltd., Allschwil (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, the format for the expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the

Table 3. Identified Issues and Recommendations for Basilea Pharmaceutica International, Ltd., Allschwil (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).*
2.	As currently presented, the product strength is not expressed in terms of the total quantity of drug per vial.	The product strength should be expressed as the total quantity of drug per vial, as described in United States Pharmacopoeia (USP) General Chapter <7>. Failure to express the strength statement in the total amount of drug per vial may lead to confusion regarding the total content of the drug in the container.	Revise the strength statement to express the total quantity of drug per vial, for example, 500 mg/vial or 500 mg per vial in accordance with USP General Chapter <7>.
3.	As currently presented, the statement “For intravenous use only” does not SPECIFY how to	This lack of information may lead to wrong technique drug administration errors.	We recommend revising the statement “For intravenous use only” to “For intravenous infusion” to minimize the risk

Table 3. Identified Issues and Recommendations for Basilea Pharmaceutica International, Ltd., Allschwil (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	administer the product intravenously (e.g., intravenous infusion or bolus). Additionally, we note that the route of administration statement contains the word "only".	Additionally, we reserve the use of the word "only" when there is a safety concern or data that supports the product must be given by a specific route.	of the product being administered as an intravenous bolus.
4.	As currently presented the package type term, "single-use" is included on the principal display panel (PDP) of the container label and carton labeling.	The package type term, "single use" is not considered an appropriate package type term. For more information, see guidance, *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)*.[d]	Revise the package type term from "single use vials" to "single-dose vial" on the PDP of the container label and carton labeling.
5.	As currently presented, there is a placeholder for (b) (4)	The label of an official drug product shall include the "lot number" per USP General Chapter <7>.	To be consistent with USP General Chapter <7> replace (b) (4) with "Lot."
Container Label			
1.	As currently presented, the current storage statement is missing the degree symbol (°) and	The storage statement should be clearly stated to avoid storage errors, as well	To provide clarity, add the degree and Centigrade symbols (°C) following the number "2" and the degree and Fahrenheit

[d] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2018. Available from https://www.fda.gov/media/117883/download.

Table 3. Identified Issues and Recommendations for Basilea Pharmaceutica International, Ltd., Allschwil (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	units of temperature measurement (e.g., Centigrade symbol (C) and Fahrenheit symbol (F)) following the first numbers of the temperature ranges.	as deteriorated drug medication errors.	symbols (°F) following the number "36" of the temperature ranges.
2.	As currently presented, what appears to be duplicate machine readable (2D data matrix) codes appearing on both the principal display panel (PDP) and side/rear panel.	The presence of duplicate machine readable (2D data matrix) codes is unnecessary.	If these machine readable (2D data matrix) codes appearing on both the principal display panel (PDP) and side/rear panel are duplicative, we recommend removing the machine readable (2D data matrix) that currently appears on the PDP so that it does not compete with, distract from the presentation of other required or recommended information on the container label.
3.	As currently presented, the equivalency statement appears on the PDP.	The equivalency statement can be removed and/or relocated to the side panel to ensure minimal required info/other important info (e.g., proprietary name, established name, product strength, route of administration) is present and legible on the PDP.	To increase the legibility of the PDP, we recommend removing *or* relocating the equivalency statement to the side panel.
4.	As currently presented, the discard statement "Discard unused portion" is separated from the package type term statement. Additionally, the package type term	Inclusion of the discard statement immediately following the correct package type term helps to convey how the vial is intended to be handled.	We recommend revising the statement "single use vials" to read as "Single-Dose Vial. Discard Unused Portion." See *Guidance for Industry: Selection of the Appropriate Package Type Terms and*

Table 3. Identified Issues and Recommendations for Basilea Pharmaceutica International, Ltd., Allschwil (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	"single use vials" is incorrect.		*Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)*.[e]
5.	As currently presented, the linear barcode is missing on the container label.	The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2).	Add the product's linear barcode to each individual container label in accordance with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text. The barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation). Additionally, we recommend orienting the linear barcode on the container label in a vertical position to improve the scannability of the barcode. To ensure sufficient space is available, we recommend removing non-critical information (e.g., MKZEV500) from the container label.
Carton Labeling			
1.	As currently presented, the storage statement (i.e., "Store: Refrigerate	The presentation of the storage statement should be clearly stated to avoid	To provide clarity, add the Centigrade symbol (C) following the number "2" and

[e] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2018. Available from https://www.fda.gov/media/117883/download.

Table 3. Identified Issues and Recommendations for Basilea Pharmaceutica International, Ltd., Allschwil (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	at 2°-8°C (36°-46°F)") is missing the units of temperature measurement (e.g., Centigrade symbol (C) and Fahrenheit symbol (F)) following the first numbers of the temperature ranges. Additionally, as currently presented the statement "(b) (4) " is separated from the storage statement by the statement of dosage (i.e., "Dosage and Administration: See prescribing information"). Furthermore, the statement "(b) (4) is different from the statement "Store in carton until time of use" that appears in subsection 16.2 *Storage and Handling* in the proposed prescribing information (PI).	storage errors, as well as deteriorated drug medication errors. To help mitigate storage errors, as well as deteriorated drug medication errors, the storage statement should be consistent across all elements of the labeling (e.g., container label, carton labeling, PI).	the Fahrenheit symbols (F) following the number "36" of the temperature ranges. Additionally, we recommend revising the statement (b) (4) to "Store in carton until time of use" and relocating the statement to immediately follow the storage information, for example: "Store refrigerated at 2°C to 8°C (36°F to 46°F). Protect from light. Store vials in carton until time of use."
2.	Reconstitution instructions are not provided on the carton labeling.	Including the preparation instructions on the label will increase visibility of this information and may help mitigate the risk of medication errors.	We recommend including instructions for reconstituting the product and the resultant concentration (XX mg/mL) on the carton labeling if space permits. See *Guidance for*

Table 3. Identified Issues and Recommendations for Basilea Pharmaceutica International, Ltd., Allschwil (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).[f]
3.	As currently presented, the information on post-reconstitution storage is missing.	Including information on post-reconstitution storage will inform healthcare providers during product preparation and minimize the risk of administering deteriorated products.	If space permits, we recommend including information on post-reconstitution storage. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*[g]
4.	The product identifier is missing.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).[h] If you determine that the product identifier requirements apply to your product's labeling, we request

[f] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

[g] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

[h] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

Table 3. Identified Issues and Recommendations for Basilea Pharmaceutica International, Ltd., Allschwil (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	you add a place holder to the carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Zevtera that Basilea Pharmaceutica International, Ltd., Allschwil submitted on August 3, 2023.

Table 4. Relevant Product Information for Zevtera	
Initial Approval Date	N/A
Active Ingredient	ceftobiprole
Indication	Indicated for the treatment of: • Adult patients with *Staphylococcus aureus* bloodstream infection (bacteremia) (SAB) • Adult patients with acute bacterial skin and skin structure infections (ABSSSI) • Adult and pediatric patients (aged from 3 months to less than 18 years) with community-acquired bacterial pneumonia (CABP)
Route of Administration	intravenous infusion
Dosage Form	for Injection
Strength	500 mg/vial (equivalent to 666.6 mg ceftobiprole medocaril)

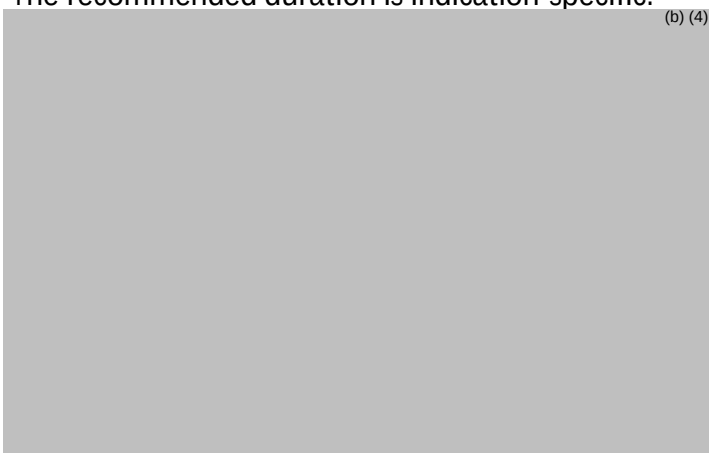
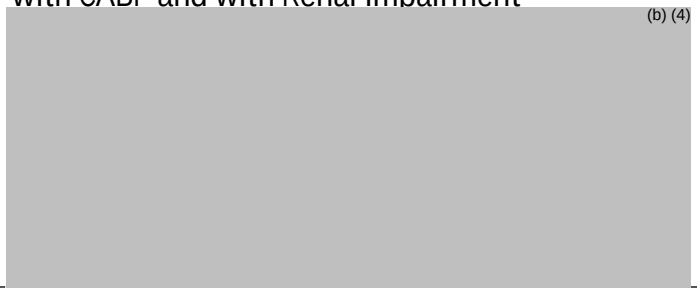
Table 4. Relevant Product Information for Zevtera	
Dose and Frequency	The recommended dosage is based on patient age and weight. The recommended duration is indication-specific. (b) (4)  Dose adjustment is required for patients with renal impairment. In patients with moderate renal impairment (CLCR 30 to < 50 mL/min), patients with severe renal impairment (CLCR < 30 mL/min), and patients with end-stage renal disease (ESRD) including patients requiring dialysis, the dosage of ZEVTERA should be adjusted. Zevtera Recommended Dosage Regimens for Adult Patients with Renal Impairment (b) (4)  Zevtera Recommended Dosage Regimens for Pediatric Patients with CABP and with Renal Impairment (b) (4) 
How Supplied	In a single-dose clear glass vial sealed with a rubber stopper (not made of latex rubber) and an aluminum seal with a flip-off cap. Each vial is supplied in carton containing 10 single-dose vials.

Table 4. Relevant Product Information for Zevtera	
Storage	Vials should be stored refrigerated at 2°C – 8°C (36°F to 46°F) and light protected. Store in carton until time of use.
Container Closure	(b) (4) glass vial, stoppered with a (b) (4) rubber stopper, and sealed with an aluminum crimp seal cap with a (b) (4) flip-off seal.

APPENDIX F. LABEL AND LABELING

F.1 List of Label and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error experiences with similar products, we reviewed the following Zevtera labels and labeling submitted by Basilea Pharmaceutica International, Ltd., Allschwil.

- Container label(s) received on August 3, 2023
- Carton labeling received on August 3, 2023
- Prescribing Information (PI) (Images not shown)
    - Clean proposed (Draft) PI received on August 15, 2023, available at the following link: \\CDSESUB1\EVSPROD\nda218275\0002\m1\us\114-labeling\1141-draft-label\draft-uspi-zevtera.docx.
    - Annotated (Draft) PI received on August 3, 2023, available at the following link: \\CDSESUB1\EVSPROD\nda218275\0001\m1\us\114-labeling\1141-draft-label\draft-uspi-zevtera-annotated.pdf.

F.2 Label and Labeling Images

Container label

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

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