CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218275Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	218275
Applicant Name	Basilea Pharmaceutica International Ltd, Allschwil
Drug Product Name	ZEVTERA (ceftobiprole medocaril sodium for injection)
Dosage Form.	Powder for reconstitution
Proposed Strength(s)	667 mg/vial ceftobiprole medocaril sodium
Route of Administration	Intravenous
Maximum Daily Dose	2668 mg (equivalent to 2000 mg ceftobiprole)
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of: • Adult patients with *Staphylococcus aureus* bloodstream infection (bacteremia) • Adult patients with acute bacterial skin and skin structure infections, and • Adult and pediatric patients (3 months to less than 18 years old) with community-acquired bacterial pneumonia
Drug Product Description	Ceftobiprole medocaril sodium is the water-soluble prodrug of the active moiety ceftobiprole, an advanced-generation broad-spectrum cephalosporin which has been developed for intravenous administration. Ceftobiprole has potent antimicrobial activity against both Gram-positive and Gram-negative pathogens. The proposed drug product, ceftobiprole medocaril sodium for injection, is to be supplied in a single-dose vial as a lyophilized powder that must be reconstituted and diluted prior to administration. Each single-dose vial contains 667 mg ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole) and is supplied in a carton containing 10 single-dose vials.
Co-packaged product information	N/A
Device information:	N/A

Storage Temperature/ Conditions	2-8ºC		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Daniel Chan	Katherine Windsor
	Drug Product	George Lunn	Dorota Matecka
	Labeling	George Lunn	David Claffey
	Manufacturing	Quamrul Majumder	Christine Falabella
	Biopharmaceutics	Payal Agarwal	Elsbeth Chikhale
	Microbiology	Lauren Walling	Erin Wall
	Other (specify):		
	RBPM	Anh-Thy Ly	
	ATL	Dorota Matecka	
Consults	N/A		

2. Final Overall Recommendation - Approval with QPA(s)

3. Action Letter Information

a. Expiration Dating:

48 months at 2°C to 8°C (36°F to 46°F). Protect from light.

b. Additional Comments for Action:

The following Post Marketing Commitments (PMCs) should be included in the action letter:

4612-5 Conduct studies to establish additional controls in the finished drug product specification and adequate in-process controls in the manufacturing process to demonstrate that the labeled vial content can be withdrawn at the lower end of the fill weight variation range following reconstitution.

The timetable you submitted on March 28, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2024

Final Report Submission: 08/2025

4612-6: Conduct stability studies on three drug product batches manufactured by basing the weight of the drug substance (b) (4) , and propose appropriately revised acceptance criteria for assay and impurities.

The timetable you submitted on March 28, 2024, states that you will conduct this study according to the following schedule:

Interim Report Submission:01/2026

Final Report Submission: 07/2026

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The majority of CMC information provided in the NDA in support of each drug substance and the drug product was found to be adequate by the OPQ review team. All manufacturing facilities were found acceptable, and the overall manufacturing inspection recommendation (OMIR) “Approve” was entered into Panorama on March 25, 2024. In addition, the labeling comments and recommendations (as discussed in the Drug Product and Microbiology reviews), as discussed with other review disciplines including Clinical, Pharmacology/Toxicology and DMEPA, were accepted

by the Applicant. The issue of the drug product name and strength was discussed extensively with the OND and OPPQ, and it was agreed that the drug product established name and strength should be expressed in terms of the salt, to state: ceftobiprole medocaril sodium for injection, 667 mg/vial (for details regarding this decision, refer to the Memorandum filed in DARRTS by Jibril Abdus-Samad, OPQ/OPPQ/COSS and attached to this IQA). There are two outstanding product quality issues identified during the NDA review that will be addressed through PMC studies (agreed on March 28, 2024).

The proposed drug product is an injectable lyophilized powder supplied in a vial, which needs to be reconstituted and further diluted for intravenous administration. As such, the drug product needs to comply with applicable guidances and regulations to ensure that the excess solid in a vial is sufficient to allow for withdrawal and administration of the net container content of the drug product. MAPP 5019.1 describes the finished drug products in-process controls that should be considered for such drug products. In this case, the drug product vial does include an overfill and a withdrawable study was conducted to demonstrate that an appropriate volume of the solution can be withdrawn from a vial following the reconstitution instructions as described in the proposed labeling. However, the Applicant did not demonstrate that the labeled vial content can be withdrawn following reconstitution at the lower end of the proposed fill weight variation range. In addition, some of the additional in-process and finished drug products controls described in MAPP 5019.1, such as (b) (4) were not appropriately established. These issues were discussed extensively between the Drug Product and OPMA teams during the NDA review and with the Applicant; however, they could not be resolved adequately during this review cycle. Upon further internal discussion, it was decided that due to the need of this product and its potential to satisfy unmet medical need, these issues will be further addressed and finalized through a Post Marketing Commitment (PMC) study, described above (*for further details refer to the Drug Product Review, below*).

The other outstanding issue relates to the proposed acceptance criteria for the drug product assay and impurities. The drug substance, ceftobiprole medocaril sodium, is a sodium salt of a prodrug. (b) (4) In response to FDA recommendations, the Applicant agreed to base the assay value (b) (4) in the drug product specifications, and (b) (4) in the drug substance specification. As a result of these changes, the drug product assay acceptance criteria were revised to (b) (4) % (at release) and to

(b) (4)% (on stability). The OPQ team recommended that the currently proposed acceptance criteria for assay and impurities be treated as interim and be revised based on stability data obtained for new drug product batches manufactured by (b) (4). These batches should be monitored using a new specification, in which the assay value is based (b) (4) and the assay and impurity limits should be revised once 12-month stability data are obtained (PMC described above).

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate with QPAs**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments: Note PMC's.

David Claffey

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R REGIONAL INFORMATION

Environmental Assessment

The applicant submitted a claim of categorical exclusion (CE) from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. Also, a required statement of no extraordinary circumstances was provided in accordance with 21 CFR 25.15.

The submitted EIC is (b) (4) ppb. This value, however, is noted as being for the pro-drug ceftobiprole medocaril (CEF-medocaril) in Appendix 7.1.2 of the submission, and as the active moiety CEF, which is the dominant metabolite in human excretion entering the environment following intravenous infusion of CEF-medocaril, in the main section. FDA considered modifying the EIC of CEF to be (b) (4) ppb, but ultimately kept the EIC of (b) (4) ppb.

The applicant conducted environmental fate and ecotoxicity assays as well as a risk assessment for CEF. Results show that CEF is not likely biodegradable and the majority of CEF entering wastewater treatment plants is expected to remain in the aqueous phase and enter the aquatic environment via effluent discharge. In natural

aquatic environments, CEF may rapidly dissipate from the water phase by binding to sediment. It also has low potential for bioaccumulation. Acute and chronic no observed effect concentration (NOEC) values of CEF were obtained for microbes in activated sludge, algae, crustacean, and fish. The lowest NOEC is (b) (4) µg/L for the growth of algae *Anabaena flos-aquae*. The applicant then compared this NOEC to the expected environmental concentration (EEC, EIC/10) of (b) (4) ppb and obtained a safety margin of (b) (4).

FDA assessed the submitted data and agreed with the applicant's conclusion. We found a lower NOEC of CEF, however, in an FASS report (https://www.fass.se/LIF/product?userType=0&nplId=20120809000026&docType=78&scrollPosition=768.6666870117188), in which the NOEC of CEF for algal growth is 0.29 ppb and thus the predicted no effect concentration (PNEC) of CEF is 0.029 ppb. A conservative risk quotient (RQ) of CEF was estimated by FDA to be (b) (4) ((b) (4) ppb/0.029 ppb), which is lower than the threshold value of 1. Considering dilution, the rapid dissipation of CEF from water phase in natural aquatic environments, and other potential depletion mechanisms, the RQ of CEF can be further reduced, suggesting that no significant environmental impact of CEF is anticipated at the expected level of exposure for this NDA. Given, however, that various cephalosporins have already been marketed for years in the US with a cumulative EIC exceeding 1 ppb, a future FDA-led programmatic assessment is recommended for cephalosporin antibiotics. In conclusion, FDA determined that approval of this application would have no significant environmental impact, and therefore the claim of CE is acceptable, and an EA is not needed.

Assessment: *Adequate* The assessment above was provided by Xiaoqin Wu of the EA team in an e-mail dated 9/25/23.

Methods Validation or Verification Package

Assessment: *N/A*

Comparability Protocols

Assessment: *N/A*

Post-Approval Commitments (PMC)

PMC # 1

PMC Description:

Conduct studies to establish additional controls in the finished drug product specification and adequate in-process controls in the manufacturing process to demonstrate that the labeled vial content can be withdrawn at the lower end of the fill weight variation range following reconstitution.

PMC Timelines (*proposed*):

Final Protocol Submission: 6/2024
Final Report Submission: 12/2024

The final report should be submitted to your NDA as a prior approval supplement. The final report submission be identified as "Final Report Submission for PMC XXXX-X" in addition to being identified as a "Prior Approval Supplement".

PMC # 2

PMC Description

Conduct stability studies on three drug product batches manufactured by weighing out the drug substance (b) (4) and propose appropriately revised acceptance criteria for assay and impurities.

PMC Timelines (*proposed*):

Interim Report Submission: 12/2024
Final Report Submission: 08/2025

The interim report submission should include 6-month stability results. The final report should include 12-month stability data and revised acceptance criteria for assay and impurities. The final report submission should be identified as "Final Report Submission for PMC XXXX-X" in addition to being identified as a "Prior Approval Supplement". The stability studies beyond 12-month time point should be continued through the expiration dating period and reported in the subsequent annual reports.

Assessment: *Adequate*

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES

See the PMCs described above.

Primary Drug Product Assessor Name and Date: George Lunn, Ph.D., 3/20/24

Secondary Assessor Name and Date (and Secondary Summary, as needed): David Claffey, Ph.D., 3/20/24

George Lunn

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David Claffey

Digitally signed by David Claffey
Date: 3/20/2024 05:05:18PM
GUID: 508da71e00029e20b201195abff380c2
Comments: Signing on behalf of Dorota Matecka

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	218275
Assessment Cycle Number	1
Drug Product Name	**ZEVTERA (ceftobiprole medocaril sodium for injection)**

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	**SDN-053**
Patient Information	N/A	
Instruction for Use (IFU)	N/A	
Container Labels	Adequate	**SDN-054**
Carton Labeling	Adequate	**SDN-054**

Brief Description of Outstanding Issues: None

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
Docubridge Cumulative View as of 3/27/24		

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

For injection: 667 mg of ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole) as a lyophilized powder for reconstitution in a single-dose vial (3).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	**ZEVTERA (ceftobiprole medocaril sodium for injection)**
Route(s) of administration	Adequate	Intravenous
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	For injection: 667 mg of ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole). 500 mg ceftobiprole is the corresponding amount of the active metabolite and was added to the label at the request of OND. Note that apart from the equivalency statements noted in this review they are present in Section 2 (footnotes to Tables 1,2,3,and 4) and in Sections 6,12,and 14.

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)
[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).
[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	Adequate	667 mg of ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8]	Adequate	Single-dose vial

Assessment: *Adequate*

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(The proposed text is lengthy and is not copied here.)

[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] 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); USP <659>
[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	Adequate	All aspects of Section 2 have undergone extensive review by the entire review team.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	In-use hold times are supported by CMC information in the application.
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	Adequate	Statement in Section 2.5: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution for infusion should be clear to slightly opalescent and yellowish in color. Discard if discoloration or visible particles are observed. [Found in Section 2.5]
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare	N/A	

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments
[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
practitioner(s) who administer the drug		
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: *Adequate*

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

3 DOSAGE FORMS AND STRENGTHS

ZEVTERA (ceftobiprole medocaril sodium for injection) is available in a single-dose vial as a white, yellowish to slightly brownish, cake to broken cake or powder containing 667 mg of ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole) for reconstitution.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Statement: ZEVTERA (ceftobiprole medocaril sodium for injection) is available in a single-dose vial as a white, yellowish to slightly brownish, cake to broken cake or powder containing 667 mg of ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole) for reconstitution. The equivalency statement was added at the request of OND.
Strength(s) in metric system	Adequate	667 mg of ceftobiprole medocaril sodium

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	After extensive discussion it was agreed that the name and strength should be expressed in terms of the API, Ceftobiprole Medocaril Sodium for Injection 666.7 mg/vial (see the Memo to File from Jibril Abdus-Samad CDER/OPQ/OPPQ/COSS for a discussion of the issues (filed in DARRTS 3/21/24))
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	a white, yellowish to slightly brownish, cake to broken cake or powder A description of the solution is not found here but is found in Section 2.5. This is acceptable.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	Adequate	Single-dose vial is used throughout

Assessment: *Adequate*

1.2.3 Section 11 (DESCRIPTION)[14]

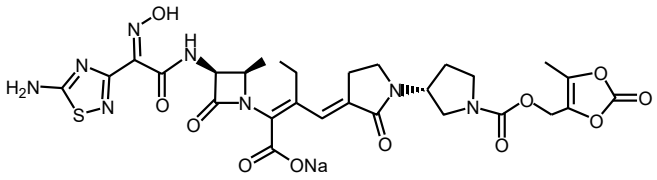
11 DESCRIPTION

ZEVTERA (ceftobiprole medocaril sodium for injection) contains sodium salt of ceftobiprole medocaril, a semisynthetic, cephalosporin antibacterial, for intravenous use. Chemically,

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

ceftobiprole medocaril is (6*R*,7*R*)-7-[[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-hydroxyiminoacetyl]amino]-3-[(*E*)-[1-[(3*R*)-1-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]pyrrolidin-3-yl]-2-oxopyrrolidin-3-ylidene]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Its molecular weight is 690.6 g/mol. The empirical formula is $C_{26}H_{25}N_8NaO_{11}S_2$.

Figure 1 Chemical Structure of ceftobiprole medocaril sodium



ZEVTERA vials contain 667 mg of ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole). The powder for injection is a white, yellowish to slightly brownish sterile powder. Each vial includes inactive ingredient citric acid monohydrate (26.3 mg/vial) as a buffer component and sodium hydroxide (q.s.) as a pH adjustment agent. Each vial of ZEVTERA contains approximately 32 mg of sodium.

The pH of the reconstituted solution is 4.5–5.5.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	ZEVTERA (ceftobiprole medocaril sodium for injection)
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	powder for injection
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency	Adequate	After extensive discussion it was agreed that the name and strength should be expressed in terms of the

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].		API, Ceftobiprole Medocaril Sodium for Injection 666.7 mg/vial (see the Memo to File from Jibril Abdus-Samad CDER/OPQ/OPPQ/COSS for a discussion of the issues (filed in DARRTS 3/21/24)). The equivalency statement was added at the request of OND.
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	Each vial includes inactive ingredient citric acid monohydrate (26.3 mg/vial) as a buffer component and sodium hydroxide (q.s.) as a pH adjustment agent.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	Adequate	citric acid monohydrate (26.3 mg/vial) as a buffer component and sodium hydroxide (q.s.) as a pH adjustment agent.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	Adequate	sterile powder
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	semisynthetic, cephalosporin antibacterial

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	Each item is present
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	The pH of the reconstituted solution is 4.5–5.5.
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: *Adequate*

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

16.1 How Supplied

ZEVTERA (ceftobiprole medocaril sodium for injection), a white, yellowish to slightly brownish sterile powder for reconstitution, supplied in a single-dose clear glass vial (NDC XXX XXX-01) sealed with a rubber stopper (not made with natural rubber latex) and an aluminum seal with a flip-off cap. Each vial contains 667 mg ceftobiprole medocaril sodium

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).
[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)
[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

(equivalent to 500 mg of ceftobiprole) and is supplied in a carton containing 10 single-dose vials (NDC XXX XXX-10).

16.2 Storage and Handling

Store ZEVTERA vials refrigerated at 2 °C to 8 °C (36 °F to 46 °F) protected from light. Store in carton until time of use.

ZEVTERA must be reconstituted and then further diluted prior to administration by intravenous infusion. Store reconstituted and diluted solution of ZEVTERA as described elsewhere in the labeling *[see Dosage and Administration (2.7)].*

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	For injection
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	667 mg ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole). This wording was agreed after extensive discussions with OPPQ/COSS. The equivalency statement was added at the request of OND.
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	carton containing 10 single-dose vials
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	white, yellowish to slightly brownish sterile powder for reconstitution A description of the solution is found in Section 2.5 but not in this section. This is acceptable.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	Adequate	single-dose clear glass vial
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	Adequate	Store … protected from light. Store in carton until time of use
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	Store ZEVTERA vials refrigerated at 2 °C to 8 °C (36 °F to 46 °F) protected from light. Store in carton until time of use
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21]	Adequate	rubber stopper (not made with natural rubber latex)

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Include information about child-resistant packaging[22] (if chosen by manufacturer).	N/A	

Assessment: *Adequate*

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	Manufactured by: Nipro Pharma Corporation – Odate plant 5–7, Niida Aza Maedano Odate-Shi, Akita, 018-5751 Japan Manufactured for: Basilea Pharmaceutica International Ltd, Allschwil, Hegenheimermattweg 167b CH-4123 Allschwil Switzerland

Assessment: *Adequate*

Applicant may supply US contact information but this is not required.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	ZEVTERA
Special preparation instructions (if applicable).	N/A	The product is administered IV in a health-care setting. Patient Counseling Information is provided.
Storage and handling information (if applicable).	Adequate	

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)
[24] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	N/A	
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

3.0 CONTAINER AND CARTON LABELING[25]

3.1 Container Labels[26]

[25] Carton and Container Labeling Resources

[26] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

(b) (4)

3.2 Carton Labeling

(b) (4)

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size	Adequate	Yes	ZEVTERA® 667 mg/vial (ceftobiprole medocaril sodium for injection)

[27] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
and prominence) [§ 201.10(g)(2)].			equivalent to 500 mg ceftobiprole. The equivalency statement was added at the request of OND.
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	For injection
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	intravenous infusion
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Adequate	Yes	667 mg ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole). This wording was agreed after extensive discussions with OPPQ/COSS. The equivalency statement was added at the request of OND.
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	667 mg/vial
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).	Adequate	Yes	Originally the carton front panel used "single use vials". At the request of FDA this was changed to "single-dose vial". Also Carton side panel stated: (b) (4) This was removed at the request of FDA.
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Adequate	No	Not present on container label but this is acceptable for reasons of space.
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	Adequate	No	Not present on container label but this is acceptable for reasons of space.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Choose an item.	

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	N/A	Choose an item.	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Choose an item.	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	Adequate	Yes	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Choose an item.	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance	N/A	Choose an item.	

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[31]			
And others if space is available.	Adequate	No	On Carton: (b) (4) Reconstitute each single-dose vial with 10 ml of diluent as specified in the prescribing information to obtain a concentration of 66.7 mg/ml ceftobiprole medocaril sodium. Shake vigorously until dissolution is complete. The reconstituted solution in a vial can be stored for up to 1 hour at room temperature. Further dilute into an appropriate container prior to administration per prescribing information.

Assessment of Carton Labels and Container Labeling: *Adequate*
Description of prepared solutions is found in Sections 2.5 and 3. Template suggests that the description should be in Sections

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

None

Primary Labeling Assessor Name and Date: George Lunn, Ph.D., 3/27/2024

[31] USP General Notices 3.20 Indicating Conformance

Secondary Assessor Name and Date (and Secondary Summary, as needed): David Claffey, Ph.D., 3/27/2024

George Lunn

Digitally signed by George Lunn
Date: 3/27/2024 02:27:29PM
GUID: 508da72000029f40833369b0a181e8b3

David Claffey

Digitally signed by David Claffey
Date: 3/28/2024 10:49:46AM
GUID: 508da71e00029e20b201195abff380c2

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	CEFTOBIPROLE MEDOCARIL 646 mg FOR INJECTION
NDA Number	218275
Assessment Cycle Number	1
Drug Product Name/ Strength	ZEVTERA (ceftobiprole medocaril) for injection, 646 mg.
Route of Administration	IV infusion
Applicant Name	Basilea Pharmaceutica International, Ltd, Allschwil
Therapeutic Classification/ OND Division	DAI
RLD/RS Number	N/A
Proposed Indication	For the treatment of adult patients with Staphylococcus aureus bloodstream infections (bacteremia) (SAB)

Assessment Recommendation: **Adequate**

Executive Summary: Basilea Pharmaceutica has developed Ceftobiprole medocaril for injection, 646 mg. The clinical program for Ceftobiprole medocaril for injection, 646 mg includes twenty Phase 1 and five Phase 3 studies. Three different formulations (referred as "(b) (4)", "(b) (4)" and "Commercial") were used in these studies. The detailed information about these formulations is described in section B12.

The Biopharmaceutics review is focused on the evaluation of data to support the bridging between the proposed Commercial formulation and the (b) (4) and (b) (4) formulations.

The (b) (4) (b) (4) and proposed Commercial formulations are comparable as they have similar physical appearance, color, reconstitution time, osmolality, and pH. The differences in excipients between the formulations are not expected to have any clinically significant effect on the distribution, metabolism, or elimination of the drug and/or prodrug. A bridge between the three different formulations used in Phase 1/Phase 3 is adequately established, and it is scientifically justified for the Applicant to rely on safety, efficacy, and/or PK information from the Commercial, (b) (4) and (b) (4) formulations.

RECOMMENDATION: From the Biopharmaceutics perspective, NDA 218275 for Ceftobiprole medocaril for Injection, 646 mg is recommended for **APPROVAL.**

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Solubility	Low	Drug substance is developed as a prodrug to increase the solubility. pH is controlled	Very Low	Ceftobiprole medocaril is very soluble in aqueous media
Polymorphism	Low	The API is (b) (4) during manufacturing, and the product is administered as a solution.	Very Low	Ceftobiprole medocaril is an amorphous material

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
NDA 218275 ORIG-1, SDN#001	**August 3, 2023**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

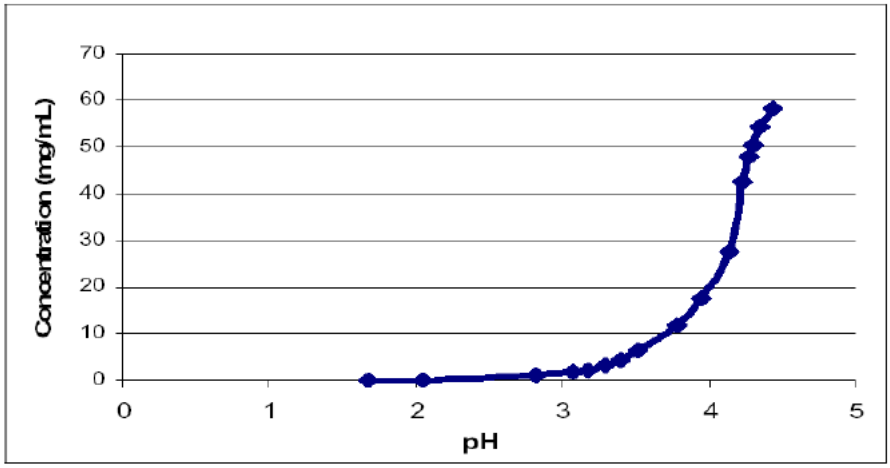
Concise Description of Outstanding Issues: N/A

B.1 BCS DESIGNATION

Assessment: BCS is not Applicable (the proposed drug product is not an orally administered drug product)

Solubility: Ceftobiprole medocaril is freely soluble in water, i.e., more than 250 mg can be dissolved in 1.0 mL of water. This allows formulating 500 mg of ceftobiprole (active metabolite) per dosage unit, corresponding to 666.6 mg of the prodrug salt (ceftobiprole medocaril sodium), in a small volume for intravenous infusion.

Fig 1. pH solubility profile of ceftobiprole medocaril in the pH range up to a pH of 4.4



Permeability: Not Applicable. It is an Injection formulation for IV route.

Dissolution: Not Applicable. It is a powder formulation for reconstitution as a solution for IV route of administration.

B.11 EXTENDED RELEASE DOSAGE FORMS –*Extended Release Claim*

Assessment:
N/A

B.12 BRIDGING OF FORMULATIONS

Assessment: ADEQUATE

Formulation Bridging: In NDA 218275, the Applicant seeks approval for Ceftobiprole medocaril for injection, 646 mg developed as a powder for injection formulation for the treatment of adult patients with Staphylococcus aureus bloodstream infections (bacteremia) (SAB).

Ceftobiprole medocaril sodium (BAL5788-001), is an amorphous white to yellowish or slightly brownish powder, it is very soluble in aqueous media (>250 mg/mL) in the pH range >4. Ceftobiprole medocaril sodium (BAL5788-001) is a prodrug that decomposes very rapidly in non-acidic media (pH >6) and produces the active drug moiety ceftobiprole (BAL9141-000).

The solubility data in media up to pH 4.4 are shown in Figure 1. Furthermore, the stability of the dissolved drug solution is temperature dependent and

sensitive to exposure to direct sunlight. (b) (4) because of limited stability of ceftobiprole medocaril in aqueous solution. To achieve a stable dry solid drug product, (b) (4) lyophilization process was utilized by the Applicant. The lyophilized product should be reconstituted with 10 mL of sterile water for injection (USP, Ph. Eur.) or dextrose 5% for injection (USP, Ph. Eur.) to a concentration of 66.7 mg/mL of ceftobiprole medocaril sodium (BAL5788-001) which is equivalent to 50.0 mg/mL ceftobiprole (BAL9141-000) and 64.6 mg/mL of ceftobiprole medocaril. This should be further diluted with dextrose 5% for injection, sodium chloride 0.9% solution for injection, (b) (4) to the required concentration of ceftobiprole (2 mg/mL or 4 mg/mL) for administration by intravenous infusion, as described in the product information label[1].

The following three powder for injection formulations were used during the drug product development[2]:

1. (b) (4) Formulation with (b) (4) (Table 1) and reconstituted with a customized diluent.
2. (b) (4) Formulation with (b) (4) (Table 2) and reconstituted with a customized diluent.
3. **Commercial:** Formulation with (b) (4) (Table 3) and reconstituted with commercially available vehicles for injection.

The Biopharmaceutics review is focused on the evaluation of data to support the bridging between these three formulations.

Table 1. Composition of the (b) (4) drug product formulation (250 mg[a] of ceftobiprole)

Component	Unit quantity (per Vial)[b]	% Composition of lyophilized cake (% w/w)
Ceftobiprole medocaril sodium	333.3 mg	(b) (4)
Citric acid monohydrate, USP/Ph.Eur.	(b) (4) mg	
Sodium hydroxide (b) (4)[c]	q.s.to pH 4.5	
(b) (4)		(b) (4)
Total Weight	(b) (4) mg	100

[a] Equivalent to 333.3 mg of ceftobiprole medocaril sodium
[b] Declared quantity. Actual filled vial contains (b) (4) overfill to allow for withdrawal of nominal volume.
(b) (4)
NA = not applicable

[1] \\CDSESUB1\EVSPROD\nda218275\0002\m1\us\114-labeling\1141-draft-label\draft-uspi-zevtera.pdf
[2] \\CDSESUB1\EVSPROD\nda218275\0001\m3\32-body-data\32p-drug-prod\ceftobiprole500mg-forinjection\32p2-pharm-dev\pharmaceutical-development-22-drug-product-nda.pdf

Table 2. Composition of the (b) (4) drug product formulation (500 mg[a] of ceftobiprole)

Component	Unit Quantity (per vial)[b]	% Composition of Lyophilized Cake (% w/w)
Ceftobiprole medocaril sodium	666.6 mg	(b) (4)
Citric acid monohydrate, USP/Ph.Eur.	(b) (4) mg	
Sodium hydroxide	(b) (4) q.s. to pH 4.5	
(b) (4)		
Total weight[e]	(b) (4) mg	100

[a] Equivalent to 666.6 mg of ceftobiprole medocaril sodium
[b] Declared quantity. Actual filled vial contains (b) (4) % overfill to allow for withdrawal of nominal volume.
(b) (4)
NA = not applicable

Table 3. Composition of the Commercial drug product formulation (500 mg[a] of ceftobiprole)

Component	Unit Quantity (per vial)
Ceftobiprole medocaril sodium	666.6 mg
Citric acid monohydrate	26.3 mg

a Equivalent to 666.6 mg of ceftobiprole medocaril sodium

During early drug product development, the (b) (4) formulation's stability was improved through pH adjustment and use of buffer (b) (4) process. For the (b) (4) formulation, initially (b) (4) . Therefore, a separate sterile reconstitution solution (**Customized diluent, shown in Table 4**) was introduced to ensure (b) (4) in the infusion solution. The composition of the customized diluent is given below:

Table 4. Composition of Customized Diluent

Component	Quantity (mg/mL)	Per vial (mg) [Declared][a]
(b) (4)	(b) (4)	
Citric Acid Monohydrate, USP/Ph.Eur.		
Sodium Hydroxide USP/Ph.Eur.		
(b) (4)		

[a] Each vial contains (b) (4) overfill to allow for withdrawal of nominal volume.

The Applicant (Basilea) conducted further formulation development trials at (b) (4) to improve the drug product's appearance. The addition of (b) (4) (resulting in the (b) (4) formulation) improved the stability and appearance of the

lyophilized cake. Based on supportive stability data, the (b) (4) formulation was further used in the development program. The composition of the reconstituted (b) (4) **formulation** that was further diluted into an infusion solution for use in clinical trials (Phase 1 and Phase 3) is presented in **Table 5**

Table 5. Composition of reconstituted solution of the (b) (4) formulation

Component	Quantity (mg/mL)
Ceftobiprole medocaril sodium	66.7
(b) (4)	(b) (4)
Citric acid monohydrate	
Sodium hydroxide q.s. to:	
(b) (4)	
(b) (4)	
(b) (4)	

The Applicant improved the stability of the (b) (4) formulation by replacing the customized diluent with commercially available vehicles for injection and removal of (b) (4) resulting in the proposed **Commercial formulation.** The compositions of the (b) (4) and Commercial ((b) (4) as excipient) formulations after reconstitution are compared and shown in **Table 6**.

Table 6. Comparison of composition of (b) (4) and Commercial formulation for the reconstituted solution (before further dilution)

	(b) (4) formulation	Commercial formulation	
Reconstitution solvent	**Customized diluent[a]**	**5% dextrose injection USP, Ph.Eur.**	**Water for injection USP-NF, Ph.Eur**
Reconstitution volume	10 mL	10 mL	10 mL
Component		**Quantity (mg/mL)**	
Ceftobiprole medocaril sodium[b]	66.7[c]	66.7[c]	66.7[c]
(b) (4)	(b) (4)		
Citric acid monohydrate			
Sodium hydroxide			
(b) (4)			
(b) (4)			
[a] (b) (4)			

[b] Ceftobiprole amounts will vary based on the potency
[c] Equivalent to 50 mg of ceftobiprole
[d] (b) (4)

The **Commercial formulation** was used in one of the Phase 1 studies and in three pivotal Phase 3 studies as shown in **Table 7**.

A detailed comparison of the three different formulations used in the development program of Ceftobiprole medocaril for Injection, 646 mg is shown in **Table 7**

Table 7. Detailed Comparison of (b) (4) and Commercial formulations

	(b) (4)		Commercial
Composition attributes before further dilution			
Ceftobiprole medocaril sodium	66.7 mg/mL	66.7 mg/mL	66.7 mg/mL
(b) (4)	(b) (4)		x
Citric acid monohydrate			2.63 mg/mL
(b) (4)			(b) (4)
Sodium Hydroxide			(b) (4)
Reconstitution Solvent	Customized Diluent	Customized Diluent	Commercially available diluents
Solution used for further dilution for Infusion	D5W	D5W	D5W or 0.9% Saline solution (b) (4) as per label directions
Other attributes of the reconstituted solution after further dilution for Infusion			
pH	(b) (4)		
Osmolality	310-325 mOsm/kg	310-325 mOsm/kg	300 ± 20 mOsm/kg
Color	clear to slightly opalescent, yellowish to brownish solution	clear to slightly opalescent, yellowish to brownish solution	clear to slightly opalescent, yellowish to brownish solution
Particles	free from visible foreign material	free from visible foreign material	free from visible foreign material
Reconstitution time	-	-	(b) (4)
Use of respective formulation in the Clinical development program			
	(b) (4)		**Commercial**

Clinical Stage[3],[4]	Phase 1	Phase 1	Phase 3	Phase 1	Phase 3
STUDY ID:	NP16104 BAP00006 BAP00010 BAP00018 BAP00034 BAP00036 BAP00058 BAP00210 CSI-1002 CSI-1006 CSI-1007 CSI-1008 PED-1001 NOS-1001	BAP00393 CSI-1001 CSI-1003 CSI-1004 CSI-1005	CAP-3001 (Pivotal) BAP248/307 (Supportive)	BPR-PIP-001	BPR-PIP-002 (Pivotal) BPR-CS-008 (Pivotal) BPR-CS-009 (Pivotal)

The Applicant stated that the PK parameters for the 3 formulations, obtained during the various clinical trials, are comparable. In addition, any differences, and similarities between the 3 formulations are explained and justified as follows:

pH: The reported pH ranges ((b) (4)) of the proposed Commercial product after reconstitution and dilution in 0.9% Sodium Chloride Injection USP, or dilution in 5% Dextrose injection, USP, are comparable to the (b) (4) and (b) (4) formulations ((b) (4)) after reconstitution and dilution in 5% Dextrose solution.

Osmolality: The proposed Commercial drug product after reconstitution and further dilution with commercially available diluents (0.9% Saline, (b) (4) and 5% Dextrose solution) has the same osmolality values (300 to 325 mOsm/kg) when compared to the (b) (4) and (b) (4) formulations after reconstitution and further dilution with 5% Dextrose solution (also 300 to 325 mOsm/kg). These osmolality values are close to the physiological range of 275 to 295 mOsm/kg of plasma and should not result in any adverse effect.

Excipients: The increased amount of (b) (4) (b) (4) mg/mL) in the reconstituted Commercial formulation compared to (b) (4) mg/mL in the (b) (4) formulation, (see Table 6) do not exceed the levels in current CDER-approved drug products[5] with the same route of administration based on total Maximum Daily Intake (MDI). Therefore, the safety of the levels of (b) (4) in the proposed Commercial

[3] \\CDSESUB1\EVSPROD\nda218275\0001\m3\32-body-data\32p-drug-prod\ceftobiprole500mg-forinjection\32p2-pharm-dev\pharmaceutical-development-22-drug-product-nda.pdf

[4] \\CDSESUB1\EVSPROD\nda218275\0001\m3\32-body-data\32p-drug-prod\ceftobiprole500mg-forinjection\32p5-contr-drug-prod\32p54-batch-analys\batch-analyses-nda.pdf

[5] https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm?event=BasicSearch.page

formulation is justified because the [redacted] concentration = [redacted] mg/mL = [redacted]% w/v does not exceed the Inactive Ingredient Database (IID) levels for [redacted] [redacted]%) for the intravenous route of administration based on the total Maximum Daily Intake. The difference in the amount of [redacted] is not expected to affect the safety, efficacy or PK of the drug product.

For the Commercial formulation, the total citrate concentration in the reconstituted solution before further dilution for infusion (2.63 mg citrate /mL) is [redacted] the total citrate concentration ([redacted] mg citrate /mL) in the reconstituted solution before further dilution for the [redacted] formulation, as shown in Table 7. [redacted] no safety and efficacy concerns are expected for the Commercial drug product due to this change in citric acid concentration.

[redacted] from the Commercial formulation ([redacted] mg/mL) compared to the [redacted] mg/mL in the reconstituted solution) and [redacted] formulations ([redacted] mg/mL). Pivotal phase-3 studies conducted using the Commercial formulation ([redacted]) indicates that there are no safety, efficacy and PK concerns related to [redacted] the formulation.

Color: As shown in Table 7, there is no difference in the physical appearance of the three formulations. The color of the proposed Commercial formulation is found to be similar (clear to slightly opalescent, yellowish to brownish) to the [redacted] and [redacted] formulations after reconstitution.

Conclusion: In Applicant's clinical development program for Ceftobiprole medocaril for injection, 646 mg, three formulations were used: '[redacted]', '[redacted]', **and 'Commercial'**. The Applicant conducted three pivotal Phase 3 studies (BPR-PIP-002, BPR-CS-008, BPR-CS-009) using the proposed Commercial formulation. In addition, one supportive Phase 3 study (BAP248/307) and one pivotal Phase 3 study (CAP-3001) used the [redacted] formulation and the [redacted] formulation was used only for Phase 1 studies. Since the proposed Commercial formulation was used in all 3 pivotal clinical studies, bridging studies may not be needed. However, since some of the information in the proposed drug product's label is derived from studies using the [redacted] or [redacted] formulations, bridging among the three formulations was assessed. The [redacted] and proposed Commercial formulations are expected to have the same PK, safety and efficacy profiles because:

1. The [redacted] and proposed Commercial formulations all required reconstitution and dilution before administration,
2. All three formulations after reconstitution and dilution have the same prodrug concentration.
3. All three formulations have similar osmolality and pH
4. The differences in excipients in the three formulations are not expected to have any clinically significant effect on the distribution, metabolism or elimination of the drug and/or prodrug.

Based on the review of the provided information/data, a bridge between the three different formulations has been adequately established. No clinically relevant PK differences were noted among the three formulations by the Applicant. Therefore, it is scientifically justified for the Applicant's proposed labeling to rely on safety, efficacy and/or PK information obtained using any of the three formulations. From a Biopharmaceutics perspective, NDA 218275 for Ceftobiprole medocaril for Injection, 646 mg, is adequate and recommended for Approval.

B. 13 BIOWAIVER REQUEST

Assessment:
N/A

Comparability Protocols

Assessment: N/A

Post-Approval Commitments

Assessment: N/A

BIOPHARMACEUTICS LIST OF DEFICIENCIES

N/A

Primary Biopharmaceutics Assessor's Name and Date: Payal Agarwal, Ph.D. 01/21/2024
Secondary Assessor Name and Date: Elsbeth Chikhale, Ph.D. 01/21/2024

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	218275
Assessment Cycle Number	1
Drug Product Name / Strength	Zevtera (Ceftobiprole medocaril) / 646 mg/vial
Route of Administration	IV
Applicant Name	Basilea Pharmaceutica International, Ltd, Allschwil
Manufacturing Site	Nipro Pharma Corporation – Odate Plant 5-7, Niida Aza Maedano Odate-Shi, Akita 018-5751 Japan
Method of Sterilization	(b) (4), lyophilization

Assessment Recommendation: **Adequate**

Theme:

☐ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:* **Justification Statements**

N/A
Other (Requires Division Director Approval) – *Assessor writes-in justification here if "other" selected as theme.*

Assessment Summary:

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
ORIG-1 (SD# 1)	08/03/2023
ORIG-1 (SD# 3)	08/22/2023
ORIG-1 (SD# 4)	08/28/2023
ORIG-1 (SD# 23)	11/06/2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is a sterile lyophilized powder for injection provided in a single-dose glass vial. The drug product is indicated in the treatment of adults with *Staphylococcus aureus* bloodstream infections (bacteremia). Note that during late cycle discussions, labeling was changed to state that the drug product consists of 646 mg ceftobiprole medocaril per vial, rather than 500 mg, reflecting a change in the definition of the active pharmaceutical ingredient.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): *N/A*

Supporting Documents: N/A

Select Number of Approved Comparability Protocols: Choose an item.
N/A

S DRUG SUBSTANCE

This section will not be assessed, as the drug substance is rendered sterile in the drug product manufacturing process.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**
  Section: 3.2.P.1, p. 1 of 2
  The drug product is a sterile lyophilized powder for IV injection, provided in a single-dose glass vial.

- **Drug product composition –**
  Section: 3.2.P.1, p. 1 of 2

Ingredient	Quantity per vial	Function
Ceftobiprole medocaril sodium	666.6 mg (equivalent to 646mg Ceftobiprole medocaril)	API
Citrc acid monohydrate, USP	26.3 mg	Buffer

Sodium hydroxide, USP	Q.S. to pH	(b) (4)	pH adjustment
(b) (4)			

- **Description of container closure system –**
  Section: 3.2.P.1, p. 2 of 2

Component	Description	Manufacturer
Glass Vial	20 mm, clear, 20 mL tubular, (b) (4) glass vial	(b) (4)
Rubber Stopper	20 mm (b) (4) elastomer stopper	
Seal	Aluminum seal with plastic (b) (4) flip-off	Not given

Assessment: ***Adequate***
The applicant has provided a sufficient description of the drug product composition and container closure system. While the manufacturer of the aluminum seals was not provided, as this is a non-drug product contact component, this information will not be requested.

Note that during late cycle discussions, the labeling was changed to reflect that a vial of drug product consists of 646 mg of ceftobiprole medocaril, rather than 500 mg.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

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Lauren Walling

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Erin Wall

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M E M O R A N D U M

DATE: March 25th, 2024

TO: NDA 218275 Amendment (IR response)

FROM: Erin A. Wall, Ph.D.
Senior Pharmaceutical Quality Assessor
CDER/OPQ/OPMA/DPMAV

THROUGH: Erika A. Pfeiler, Ph.D.
Unit Supervisor
CDER/OPQ/OPMA/DPMAVI

SUBJECT: **NDA 218275 Label update**
Submission Date: 3/21/2024
Drug Product: Ceftobiprole medocaril 500mg for injection
Applicant: Basilea Pharmaceutica International Ltd. Allschwil

Summary: Adequate

Background: Basilea originally proposed a label in which the drug product was reconstituted and diluted with various solutions with in-use hold times requiring microbiological challenge studies. The applicant provided adequate microbiological challenge study data for WFI-reconstituted product in normal saline and 5% dextrose. However, the proposed label states that the drug product can be reconstituted in 5% dextrose and subsequently diluted in normal saline or dextrose. Quality Microbiology considered that the data provided covered the (b)(4) hour room temperature and (b)(4)-hour refrigerated holds for all admixtures except drug product reconstituted in dextrose and diluted in saline. Prior to the QDD2, Quality Microbiology was informed that the Drug Product assessors were concerned about the product's chemical stability and were therefore limiting all admixture holds to 4 hours at room temperature and 24 hours under refrigeration. Quality Microbiology concluded the NDA assessment stating that these in-use hold time values would be written into the label prior to QDD2 (1/26/2024).

However, after that date it was determined that the drug product assessor and pharmacology/toxicology disciplines would allow the reconstituted and diluted drug product to be stored for NMT 6 hours at room temperature, and NMT 94 hours at 2-8°C. The microbiology data supported this duration of storage for all admixtures except reconstitution in glucose and dilution in saline. Therefore, the following tables appeared in the label:

Table 6 Storage Time for Diluted ZEVTERA Infusion Solutions for Adult and Pediatric Patients 12 Years to Less than 18 Years Old (2.67 mg/mL)

Reconstitution solution diluent (vial)	**Infusion solution diluent**	**Infusion solutions stored at 25°C** NOT protected from light	**Infusion solutions stored at 2°C to 8°C** Protected from light
5% Dextrose solution for injection	5% Dextrose solution for injection	6 hours	94 hours
	0.9% Sodium chloride solution for injection	4 hours	24 hours
Sterile water for injection	5% Dextrose solution for injection or 0.9% Sodium chloride solution for injection	6 hours	94 hours

Table 7 Storage Time for Diluted ZEVTERA Infusion Solutions for Pediatric Patients < 12 years (5.33 mg/mL)

Reconstitution solution diluent (vial)	**Infusion solution diluent**	**Infusion solutions stored at 25°C** NOT protected from light	**Infusion solutions stored at 2°C to 8°C** Protected from light
5% Dextrose solution for injection	5% Dextrose solution for injection	6 hours	24 hours

Assessment: **Adequate**. Existing quality microbiology data supports the label-indicated reconstitution and dilution times.

END

Erin Wall

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Erika Pfeiler

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OPPQ Memorandum

To: George Lunn, Quality Assessor, CDER/OPQ/OPQA1
Dorota Matecka, Quality Assessment Lead, CDER/OPQ/OPQA1
Tom Oliver, Division Director, CDER/OPQ/OPQA1

From: Jibril Abdus-Samad, Policy Lead, CDER/OPQ/OPPQ/COSS

Date: March 21, 2024

Subject: Established Name and Strength determination for NDA 218275

BACKGROUND

The purpose of this memo is to document OPQ/OPPQ/COSS recommendation for the established name and strength for the Applicant's, Basilea Pharmaceutica, Ltd., New Drug Application (NDA) 218275. The active pharmaceutical ingredient (API), ceftobiprole medocaril sodium, is a salt in which the neutral form is a prodrug ceftobiprole medocaril, and the active metabolite is ceftobiprole. The dosage form is *for Injection*.

- API (salt) ceftobiprole medocaril sodium 666.6 mg/vial
- Prodrug (neutral form) ceftobiprole medocaril 646 mg/vial
- Active metabolite ceftobiprole 500 mg/vial

Earlier in the application review cycle, OPQ/OPQA1 recommended the Applicant revise the strength from 500 mg/vial to 646 mg/vial to express the amount of the prodrug neutral form. In response, the Applicant requested exemption from the USP Salt Policy to align with a similar salt prodrug product CRESEMBA (isavuconazonium sulfate) available in *for Injection* and *Capsules* dosage form. OPQ/OPQA1 reached out to OPQ/OPPQ/COSS for policy assistance to address the Applicant's request.

The following considerations were discussed during multiple meetings involving OPQ/OPPQ/COSS, OPQ/OPQA1, OND/DAIP, and OSE/DMEPA.

DISCUSSION

This section discusses the various policies and concerns applicable to name and strength determination.

USP Salt Policy

For DPs with salt drug substance (DS), CDER applies Guidance: Naming of Drug Products Containing Salt Drug Substances, June 2015 (Salt Guidance). The basic principle of the Salt Guidance is to express the name and strength of the DP on the active moiety (or neutral form). There are exceptions to this naming approach, when the name of the salt conveys vital information from a clinical perspective, for

the safety, or historical conditions. Thus, in this scenario for NDA 218275, we should express the name and strength of the DP on the neutral form which is the prodrug, ceftobiprole medocaril.

Note the Salt Policy does not directly discuss prodrugs that are salts. The Salt Guidance discusses esters -which in some cases are prodrugs. The Guidance states that esters should be named as the entire existing covalent entity. Although the API is not a simple ester, but rather a carbamate, this statement supports the principle of naming the DP based on the prodrug entity that is covalently bound, ceftobiprole medocaril, and not the salt, ceftobiprole medocaril sodium.

The Salt Guidance provides instances of when the name of the salt should be retained for the safety or historical conditions. For this DP, there is consideration to not apply the USP Salt Policy because there are relevant documented safety reasons (e.g., medication error concerns) in a closely related product, CRESEMBA. Both the Applicant and OND/DAI noted the similarities with NDA 218275 and a similar prodrug salt drug product CRESEMBA (isavuconazonium sulfate) for Injection and Capsules. Within both CRESEMBA and NDA 218275, there are concerns with medication errors associated with labeling three expressions of strength (e.g., Each vial contains ceftobiprole medocaril sodium 666.7 mg (equivalent to 646 ceftobiprole medocaril, provides 500 mg ceftobiprole).

Prodrugs

The Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors; May 2022, (Medication Error Guidance) within the subsection that discusses Product Strength and Prodrug states the following:

> For prodrugs, the product strength should be expressed in terms of the established or proper name of the prodrug. For example, Fosaprepitant for Injection is a prodrug for aprepitant. After administration, fosaprepitant is converted to aprepitant. The strength of this product is based on fosaprepitant rather than aprepitant.

Thus, in this scenario for NDA 218275, we should express the name and strength of the DP in terms of the prodrug neutral form, ceftobiprole medocaril, rather than the active metabolite, ceftobiprole.

Food, Drug, and Cosmetic Act (FDCA) section 502(e)
FDCA section 502(e) requires the label state the name and amount of the active ingredient. Thus, for NDA 218275, the label must state ceftobiprole medocaril sodium 666.7 mg. This statement must appear on the container label, carton labeling, and section 11 DESCRIPTION of the PI. Considering the API is a salt and DP name and strength will be expressed in terms of the neutral form, we can include this amount in the salt equivalency statement.

OND preference for linking the NDA to ceftobiprole 500 mg,
OND prefers the labeling include information to link the DP to ceftobiprole 500 mg, which represents the active metabolite.

- Medical literature expresses the DP name, strength, and dosage in terms of the active metabolite, 500 mg.
- Ex-USA (e.g., Canada, Europe) DPs express name and strength in terms of the active metabolite, ceftobiprole 500 mg.

- Concerns for medication errors if the other expressions of strength are used due to the unusual numerals and decimals required when calculating doses.
- Avoid three expressions of strength in the labeling (e.g., Each vial contains ceftobiprole medocaril sodium 666.6 mg (equivalent to 646 ceftobiprole medocaril, provides 500 mg ceftobiprole)

Options

Here are the list of options for the name and strength determination.

1. Name and Strength expressed in terms of Neutral Form: Ceftobiprole Medocaril for Injection 646 mg/vial.

   This option aligns with both the FDCA section 502(e), Salt Guidance, and Medication Error Guidance. This also aligns with the majority of prodrug DPs in Appendix A.

2. Name and Strength expressed in terms of the Salt: Ceftobiprole Medocaril Sodium for Injection 666.7 mg/vial.

   This mimics CRESEMBA (isavuconazonium sulfate) for Injection precedent that sought to avoid labeling three expressions of name and strength that may lead to confusion and medication errors.

3. Name and Strength expressed in terms of the Prodrug: Ceftobiprole 500 mg/vial.

   We are unaware of any precedent for expressing the DP name and expression in terms of active metabolite. This conflicts with USP Nomenclature Guidelines, FDA Guidance for name and strength determination for prodrugs, FDA general practice of naming DP in terms of the active ingredient/active moiety/prodrug contained in the vial as packaged without consideration of what occurs after administration.

4. Name expressed in terms of Salt and Strength expressed in terms of active metabolite: Ceftobiprole Medocaril Sodium for Injection *500 mg/vial.

   This conflicts with USP Nomenclature Guidelines, FDA practice of DP name and strength matching. In other words, FDA/CDER avoids name and strength mismatches. There are historical examples. However, FDA discourages this practice due to potential for confusion. The Salt Guidance mentions:

   > CDER's application of the USP Salt Policy should help avoid medication errors that could result from a mismatch of established name and strength (e.g., the name includes the salt but the strength is based on active moiety).

   This name and strength mismatch naming convention contributed to medication errors for the CEREBYX (fosphenytoin sodium) Injection DP that expressed the strength in terms of phenytoin equivalents rather than fosphenytoin. This influenced the current recommendation inf the Medication Error Guidance to the express the strength of prodrugs in terms of the established name of the prodrug.

Recommendation

To ensure OPQ aligns with FDCA, Salt Guidance, and Medication Error Guidance while addressing OND's preference, here is OPPQ recommendation. OPQ/OPPQ/COSS agreed with OPQ/OPQA1 initial recommendation to express the name and strength in terms of the prodrug neutral form, Ceftobiprole Medocaril for Injection 646 mg/vial (option #1). OPQ/OPPQ/COSS provided detailed labeling text example that strategically located the three expressions of name and strength to limit their occurrence within the PI, container label, and carton labeling (see Appendix B).

OND expressed concerns with the recommendation because there was still three expressions of name and strength in the labeling. Additionally, OND expressed preference for following the CRESEMBA example that expresses the name and strength expressed in terms of the salt: Ceftobiprole Medocaril Sodium for Injection 666.7 mg/vial (option #2).

After additional internal discussion within OPQ, OPQ/OPPQ/COSS agrees to align with OND's request to mimic CRESEMBA and proceed with Option #2 – express the name and strength in terms of the salt: Ceftobiprole Medocaril Sodium for Injection 666.7 mg/vial.

Note there is ongoing additional discussion on the appropriate strength regarding 666.6 mg vs. 666.7 mg vs. 667 mg as OPQ/OPPQ/COSS recommends the OPQ/OPQA1 ensure that if rounding of the strength does not have negative implications on the API Q1/Q2 determination for ANDAs.

CONCLUSION

The name and strength should be expressed in terms of the API, Ceftobiprole Medocaril Sodium for Injection 666.7 mg/vial[1] (option #2).

[1] OPQA1 will determine the appropriateness of the strength presentation of 666.6 mg/vial, 666.7 mg/vial, or 667 mg/vial.

APPENDIX

Appendix A: Examples of name and strength expression for approved prodrugs

Table 1. Name and strength expressed in terms of prodrug or prodrug salt

DP	Active Ingredient in DP	Prodrug	What's used in labeling
EMEND (Fosaprepitant) for Injection	fosaprepitant dimeglumine (salt)	Fosaprepitant is a prodrug of aprepitant	Each vial of fosaprepitant for injection for administration as an intravenous infusion contains 150 mg of fosaprepitant (equivalent to 245.3 mg of fosaprepitant dimeglumine)
TAVALISSE (fostamatinib) tablets	fostamatinib disodium hexahydrate (salt)	Fostamatinib is a tyrosine kinase inhibitor with demonstrated activity against spleen tyrosine kinase (SYK). The major metabolite of fostamatinib is R406. **Note R406 is tamatinib	Each TAVALISSE oral tablet contains 100 mg or 150 mg fostamatinib, equivalent to 126.2 mg or 189.3 mg fostamatinib disodium hexahydrate, respectively.
AKYNZEO (fosnetupitant and palonestron) oral capsule, injection solution	Fosnetupitant Chloride Hydrochloride and Palonosetron Hydrochloride (salt)	Fosnetupitant is a prodrug of netupitant	Each vial of AKYNZEO for injection contains 235 mg of fosnetupitant (equivalent to 260 mg fosnetupitant chloride hydrochloride)…
RUKOBIA (fostemsavir) extended-release tablets	Fostemsavir tromethamine (salt)	Fostemsavir tromethamine is a prodrug of temsavir, its active moiety [sic].	Each RUKOBIA extended-release tablet contains 600 mg of fostemsavir (equivalent to 725 mg of fostemsavir tromethamine).
TEFLARO (ceftaroline fosamil) for injection, for intravenous use	Ceftaroline fosamil monoacetate monohydrate (salt)	Ceftaroline fosamil is the water-soluble prodrug of the bioactive ceftaroline	All references to ceftaroline activity are expressed in terms of the prodrug, ceftaroline fosamil. Teflaro vials contain either 600 mg or 400 mg of anhydrous ceftaroline fosamil (equivalent to 668 mg and 446 mg, respectively, of ceftaroline fosamil monoacetate monohydrate).
MONOPRIL Fosinopril sodium tablets, USP	Fosinopril sodium (salt)	Fosinopril sodium tablets, USP are the sodium salt of fosinopril, the ester prodrug of an angiotensin-converting enzyme (ACE) inhibitor, fosinoprilat.	Fosinopril sodium is the sodium salt of fosinopril, the ester prodrug of an angiotensin-converting enzyme (ACE) inhibitor, fosinoprilat.
VASOTEC Enalapril Maleate Tablets, USP	Enalapril Maleate (salt)	Enalapril maleate is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat.	Each tablet, for oral administration, contains 2.5 mg, 5 mg, 10 mg or 20 mg of enalapril maleate. Approved prior to salt policy.

		Enalapril is a pro-drug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin converting enzyme inhibitor. (ACE) in human subjects and animals.	
VALTREX Valacyclovir Tablets	Valacyclovir Hydrochloride (salt)	After oral administration, valacyclovir hydrochloride is rapidly absorbed from the gastrointestinal tract and nearly completely converted to acyclovir and L-valine by first-pass intestinal and/or hepatic metabolism. Clinical data over several decades with valacyclovir and its metabolite, acyclovir, in pregnant women…	Each tablet contains valacyclovir hydrochloride USP equivalent to 500 mg or 1 g valacyclovir
BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) tablets	Bictegravir Sodium; Emtricitabine; Tenofovir Alafenamide Fumarate (TAF)	TAF is a phosphonamidate prodrug of tenofovir.	50 mg/200 mg/25 mg tablet containing 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 200 mg of FTC, and 25 mg of tenofovir alafenamide (equivalent to 28 mg of tenofovir alafenamide fumarate).
DELSTRIGO (doravirine, lamivudine, and tenofovir disoproxil fumarate) tablets	Doravirine; Lamivudine; Tenofovir Disoproxil Fumarate (TDF)	TDF (a prodrug of tenofovir) is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir.	Each tablet contains 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of TDF (equivalent to 245 mg of tenofovir disoproxil) as active ingredients.
SYMFI (efavirenz, lamivudine and tenofovir disoproxil fumarate) tablets	Efavirenz; Lamivudine; Tenofovir Disoproxil Fumarate (TDF)	TDF (a prodrug of tenofovir), a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir.	Each film-coated tablet contains 600 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil…

Table 2: Name expressed in terms of prodrug/prodrug salt, strength expressed in terms of active metabolite

DP	Active Ingredient in DP	Prodrug	What's used in labeling
Cefpodoxime proxetil for oral suspension, tab	Cefpodoxime proxetil	Cefpodoxime proxetil is a prodrug; its active metabolite is cefpodoxime.	All doses of cefpodoxime proxetil in this insert are expressed in terms of the active cefpodoxime moiety. (NDAs are discontinued)
Cerebyx (fosphenytoin sodium) Injection	Fosphenytoin sodium (salt)	Fosphenytoin is a prodrug of phenytoin	Fosphenytoin Sodium Injection, USP is a prodrug… its active metabolite is phenytoin. 1.5 mg of fosphenytoin sodium is equivalent to 1 mg phenytoin sodium, and is referred to as 1 mg phenytoin sodium equivalents (PE) **Note: This approach resulted in adverse events that required revised labeling. FDA determined this was error-prone and influenced policy on naming prodrugs that appears in Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors; May 2022

Table 3: Name expressed in terms of prodrug/prodrug salt; but equivalency statement includes the amount of active metabolite.

DP	Active Ingredient in DP	Prodrug	What's used in labeling
CRESEMBA for Injection, (372 mg of isavuconazonium sulfate per vial)	Isavuconazonium Sulfate	CRESEMBA contains isavuconazonium sulfate, which is the prodrug of isavuconazole, an azole antifungal drug	372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole
LEXIVA (fosamprenavir calcium) tab 700 mg on carton label LEXIVA (fosamprenavir calcium) oral suspension	fosamprenavir calcium	Fosamprenavir calcium is a prodrug of amprenavir	LEXIVA tablets are available for oral administration in a strength of 700 mg of fosamprenavir as fosamprenavir calcium (equivalent to approximately 600 mg of amprenavir). LEXIVA oral suspension is available in a strength of 50 mg per mL of fosamprenavir as fosamprenavir calcium equivalent to approximately 43 mg of amprenavir.

Appendix B: Option 1 explanation with detailed labeling text that strategically locates the three expressions of name and strength.

1. Express the DP name and strength in terms of the prodrug neutral form, ceftobiprole medocaril 646 mg/vial.
2. Include a salt equivalency statement "Each vial contains ceftobiprole medocaril 646 mg (equivalent to 666.7 mg ceftobiprole medocaril sodium), citric acid monohydrate 26.3 mg and sodium hydroxide."
3. The reference to 500 mg appears mainly to allow prescribers familiar with the ex-US product dosing to link their familiarity of 500 mg of active metabolite ceftobiprole to the dosing within this US PI. Therefore, place this information in the dosage section of labeling to avoid conflating it with the product-quality requirements of strength presentation. The goal is to assure them that if HCPs follow the dosing instructions based on this "new 646 mg", it provides the "500 mg" they are familiar with. Consequently, we recommend including information in the section 2 DOSAGE AND ADMINISTRATION section of the PI that ceftobiprole medocaril 646 mg provides 500 mg ceftobiprole, its active metabolite.

4. Here is detailed example of how the labeling should appear with suggested text in green font.:
    a. DP Name and strength
    TRADENAME (ceftobiprole medocaril) for injection 646 mg/vial

    b. Contain Label and Carton Labeling
        i. Principal Display Panel
        TRADENAME
        (ceftobiprole medocaril) for injection
        646 mg/vial

        ii. Side Panel
        Each vial contains ceftobiprole medocaril 646 mg (equivalent to 666.7 mg ceftobiprole medocaril sodium), citric acid monohydrate 26.3 mg and sodium hydroxide as a pH adjuster.

    c. PI Product Title within Highlights
    TRADENAME (ceftobiprole medocaril) for injection, for intravenous use

    d. PI Section 2 DOSAGE AND ADMINISTRATION
    All dosing information is based on prodrug ceftobiprole medocaril 646 mg. Similar CRESEMBA, include a notation that ceftobiprole medocaril 646 mg provides 500 mg ceftobiprole, its active metabolite.
        i. **Important dosing information. TRADENAME is a prodrug. The strength and dosing are expressed in terms of the prodrug. TRADENAME 646 mg provides 500 mg of ceftobiprole, its active metabolite.

    e. PI Section 3 DOSAGE FORMS AND STRENGTHS
    The Highlights can be similar except form omission of identifying characteristics.
        i. For Injection: 646 mg ceftobiprole medocaril as a white, yellowish to slightly brownish, lyophilized cake or powder for reconstitution in a single-dose vial.

f. PI Section 11 Description

i. Each vial contains ceftobiprole medocaril 646 mg (equivalent to 666.7 mg ceftobiprole medocaril sodium), citric acid monohydrate 26.3 mg and sodium hydroxide as a pH adjuster.

g. PI Sections 6 and 14

The Review Team should consider how to adjust the other areas of the PI such as Clinical Studies that discuss patients received ZEVTERA 500 mg. Options include revising to be consistent with the expression of strength for this US product and including a statement showing the relationship.

i. "…, patients received ZEVTERA 646 mg (provided 500 mg ceftobiprole)…"

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/s/

JIBRIL ABDUS-SAMAD
03/21/2024 05:03:45 PM

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/s/

DAVID J CLAFFEY
03/28/2024 03:14:47 PM
For Dorota Matecka