CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216165Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	216165
Applicant Name	Allecra Therapeutics SAS
Drug Product Name	EXBLIFEP (cefepime and enmetazobactam) for injection
Dosage Form.	Powder for reconstitution
Proposed Strength(s)	2.5 grams (2 grams cefepime and 0.5 gram enmetazobactam)
Route of Administration	Intravenous
Maximum Daily Dose	7.5 grams (6 grams cefepime and 1.5 grams enmetazobactam)
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of patients 18 years and older with complicated urinary tract infections (cUTI) including pyelonephritis caused by designated susceptible microorganisms.
Drug Product Description	The proposed drug product, cefepime and enmetazobactam for injection, contains 2 grams of cefepime (as cefepime hydrochloride) and 0.5 gram of enmetazobactam, and is supplied as a sterile powder for constitution in a single-dose, clear glass vial. The drug product does not contain any preservatives, and the only excipient is L-arginine, (b) (4) . The finished drug product (a powder in a vial) needs to be constituted and further diluted for intravenous infusion using the following reconstitution agents/diluents: NaCl 0.9% solution for injection (saline), dextrose 5% solution for injection or a combination of NaCl 0.45% and dextrose 2.5% solution for injection. The reconstituted and diluted solutions can be stored for up to (b) (4) hours at 2°C to 8°C (b) (4)
Co-packaged product information	N/A
Device information:	N/A

Storage Temperature/ Conditions	2°C to 8°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sivakoteswara Rao Mandadapu	Katherine Windsor
	Drug Product	Hudson Roth	Dorota Matecka
	Labeling	Hudson Roth	David Claffey
	Manufacturing	Xiumei Ruan	Christine Falabella
	Biopharmaceutics	N/A	N/A
	Microbiology	Sallie Crenshaw	John Metcalfe
	RBPM	Anh-Thy Ly	
	ATL	Dorota Matecka	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

Based on the stability data submitted to date, the expiry dating period for Exblifep (cefepime and enmetazobactam) powder for injection shall be 24 months from the date of manufacture when stored in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

b. Additional Comments for Action: N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug substances and the drug product (cefepime and enmetazobactam for injection). The CMC information for cefepime drug substance (cefepime (b) (4) monohydrate) which was provided via a reference to a Type II DMF (b) (4), and the CMC information for enmetazobactam (provided in the current NDA) was found adequate (*refer to the Drug Substance review, below*). In response to the FDA comment regarding the enmetazobactam name, the Applicant has provided a confirmation in the amendment dated January 31, 2024, that the USAN Council has adopted enmetazobactam as a USAN. In addition, all issues, comments, and requests for additional information, identified during the review by the Microbiology, Drug Product, Manufacturing reviewers, such as the finished drug product and in-process controls associated with the proposed product overfill, have been adequately addressed and resolved (*for details refer to the Microbiology, Drug Product, Manufacturing reviews, below*). Also, the labeling comments (*as outlined in the Labeling review, below*) have been adequately addressed by the Applicant. In addition, the manufacturing and testing facilities have been found acceptable and an overall "Approve" recommendation for this NDA was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on February 6, 2024. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

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

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:
Comparability Protocols (PACMP): No
Comments:
Additional Lifecycle Comments: None

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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	216165
Assessment Cycle Number	1
Drug Product Name	EXBLIFEP (cefepime and enmetazobactam) for injection

Assessment Recommendation: Adequate *pending revisions conveyed to OND*

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Inadequate	
Patient Information	N/A	
Instruction for Use (IFU)	N/A	
Container Labels	Adequate	**28**
Carton Labeling	Adequate	**28**

Brief Description of Outstanding Issues:

Issues in Sections 2, 11, and 16 of the Prescribing Information require revision from the Applicant.

- Section 2: As currently written, the preparation instructions not supported by the withdrawable volume study and in-use stability data in the NDA.
- Section 11: The description, name, molecular formula, and structure of the cefepime active ingredient is incorrect.
- Section 16: Special storage conditions/instructions are not included.

In addition, several recommendations to improve clarity, conciseness, and readability of the Prescribing Information are also described in this review.

Throughout the labeling, the strength of the drug product is designated as 2.5 g, the sum of the individual strengths of 2 g of cefepime and 0.5 g of enmetazobactam. This approach is acceptable from the Product Quality perspective based on input from OND and DMEPA that combining the strengths will help avoid dosing errors that have previously occurred with other β-lactam and β-lactamase inhibitor combination products.

Recommendations and required revisions have been conveyed to OND.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
eCTD 0001, SDN 1	06/22/2023	Prescribing Information Labeling Container Labels Carton Labeling
eCTD 0017, SDN 17	09/27/2023	Prescribing Information Labeling
eCTD 0023, SDN 23	10/11/2023	Container Labels Carton Labeling
eCTD 0028, SDN 28	10/26/2023	Container Labels Carton Labeling
eCTD 0029, SDN 29	10/30/2023	Prescribing Information Labeling

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

Deficiencies and recommendations for Sections 1, 2, 3, 11, and 16 of the Prescribing Information are discussed in this review. Implementation of these revisions is needed in order for the Prescribing Information to be adequate from the product quality perspective.

(b) (4)

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	

[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)

[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).

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)
Route(s) of administration	Adequate	
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	
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	
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	

Assessment: *Adequate pending the following revisions which have been conveyed to OND*

[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>

[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>

Recommend revising the dosage forms and strength as follows to improve readability and clarity:

(b) (4)

[redacted]

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

[redacted]

[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).	Inadequate	Step 3 of the preparation instructions indicates only 0.9% sodium chloride injection can be used for the final dilution. This step should be revised to indicate the same injection solution should be used for both reconstitution and dilution.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Inadequate	Step 4 of the preparation instructions does not clearly indicate how long the reconstituted and diluted drug product solution can be stored prior to administration. This step should be revised to more clearly state the

[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

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)
		storage conditions and time supported by the in-use stability data in the NDA.
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]	Inadequate	This verbatim statement is not present. Step 5 of the preparation instructions should be revised to include this statement.
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 practitioner(s) who administer the drug	N/A	
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 pending the following revisions which have been conveyed to OND*

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

(b) (4)

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

(b) (4)

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	

[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)
Strength(s) in metric system	Adequate	
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.	Adequate	
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	
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>).	N/A	

Assessment: *Adequate pending the following revisions which have been conveyed to OND*

Recommend revising as follows to improve readability and clarity and remove unnecessary information:

(b) (4)

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

[redacted]

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

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	
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency 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)].	Inadequate	The salt equivalency statement is missing from Section 11.
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	
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	
If alcohol is present, must provide the amount of alcohol in	N/A	

[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).

[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.

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)
terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].		
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	Adequate	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Inadequate	Not clearly stated that the active ingredient is cefepime (b) (4) monohydrate. Molecular formula and structure are incorrect.
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)].	N/A	
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	

[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.

[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)

Assessment: *Adequate pending the following revisions which have been conveyed to OND*

(b) (4)

[redacted]

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

(b) (4)

[redacted]

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

(b) (4)

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	
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	
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	
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	
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 terms include pharmacy bulk package and imaging bulk package (see USP <659>).	Adequate	

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)
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)]	Inadequate	Missing a statement about protection from light. Missing a reference to Section 2.3 for storage information on the constituted and diluted drug product.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	
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]	N/A	
Include information about child-resistant packaging[22] (if chosen by manufacturer).	N/A	

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

Assessment: *Adequate pending the following revisions which have been conveyed to OND*

(b) (4)

1.2.5 Other Sections of Labeling

Not Applicable

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

(b) (4)

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	

Assessment: *Adequate*

2.0 PATIENT LABELING

Not Applicable

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

3.0 CONTAINER AND CARTON LABELING[24]

(b) (4)

[redacted]

[24] Carton and Container Labeling Resources

[25] 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.

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[26], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[27]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
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	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[28]	Adequate	Yes	
"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	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	

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

[27] 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)

[28] § 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)
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	
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	Yes	
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	Yes	
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.	
Linear Bar code [§ 201.25(c)(2)].[29]	Adequate	Choose an item.	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Choose an item.	

APPEARS THIS WAY ON ORIGINAL

[29] 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)
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Choose an item.	APPEARS THIS WAY ON ORIGINAL
"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>).	N/A	Choose an item.	
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 criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[30]	N/A	Choose an item.	
And others if space is available.	N/A	Choose an item.	

[30] USP General Notices 3.20 Indicating Conformance

Assessment of Carton Labels and Container Labeling: *Adequate*

On September 28, 2023, the following comments were conveyed to the Applicant:

1. On the carton labeling and container labels, include the name and quantity of each inactive ingredient in the drug product (i.e., XX g of L-arginine).
2. Include the full salt equivalency statement on the carton labeling and container labels, i.e., "Each vial contains cefepime 2 g (equivalent to XX g of cefepime [redacted]^(b)(4))". See FDA Guidance *Naming of Drug Products Containing Salt Drug Substances.*

The Applicant responded on October 11, 2023, but did not adequately revise the salt equivalency statement. The following comment was conveyed on October 24, 2023:

1. According to current best labeling practices, the [redacted]^(b)(4) should not be included in the salt equivalency statement. Revise the salt equivalency statement on the container label rear panel and the carton labeling to "Each vial contains 2 g of cefepime (equivalent to 2.3 g of cefepime [redacted]^(b)(4)) and 0.5 g of enmetazobactam". See the FDA Guidance *Naming of Drug Products Containing Salt Drug Substances* for additional information).

The Applicant responded on October 26, 2023, with revised carton and container labeling. As the requested revision was implemented, the carton and container labeling are now adequate from the product quality perspective.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

Recommended revisions have been conveyed to OND. After implementation, the labeling will be adequate from the product quality perspective.

Primary Labeling Assessor Name and Date:
Hudson Roth, Ph.D.

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

Hudson Roth

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Date: 1/19/2024 09:39:02AM
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David Claffey

Digitally signed by David Claffey
Date: 1/19/2024 09:42:21AM
GUID: 508da71e00029e20b201195abff380c2

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	216165
Assessment Cycle Number	MR01
Drug Product Name/Strength	EXBLIFEP (cefepime (2g)-enmetazobactam (0.5g), powder for concentrate for solution)
Route of Administration	Intravenous infusion
Applicant Name	Allecra Therapeutics SAS
Therapeutic Classification/ OND Division	CDER/OND/OID/DAI
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Original Submission SD#0001	**6/22/2023**
"Resp-fda-ir-dated-13jul2023.pdf" document	**7/18/2023**
"Resp-fda-cmc-ir6-dated-30aug2023.pdf"	**9/20/2023**

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

Remarks: The drug product is a sterile powder for reconstitution intended for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis.

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

Supporting Documents:

- Microbiology review of DMF (b) (4) (D (b) (4) M05R01.docx dated 9/29/2022 and deemed adequate) for the manufacture of the sterile DS Cefepime for Injection ((b) (4)).
- Microbiology review of DMF (b) (4) (" (b) (4) mic1a3.doc dated 12/14/2015 and deemed adequate) for the manufacture of the sterile DS Cefepime for Injection ((b) (4)).
- Microbiology review of DMF (b) (4) (D (b) (4) M06R01.docx dated 8/3/2023 and deemed adequate) for the manufacture of the sterile DS Cefepime for Injection ((b) (4)).

S DRUG SUBSTANCE

S.2. MANUFACTURE

(b) (4)

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MICROBIOLOGY LIST OF DEFICIENCIES: N/A

Primary Microbiology Assessor Name and Date: Sallie Crenshaw, Ph.D., 10/12/2023

Secondary Assessor Name and Date: John Metcalfe, Ph.D., 10/12/2023

Sallie Crenshaw

Digitally signed by Sallie Crenshaw
Date: 10/12/2023 02:15:19PM
GUID: 5d5aac41000e95e6384dc64515b1eda3

John Metcalfe

Digitally signed by John Metcalfe
Date: 10/12/2023 02:26:17PM
GUID: 503451f000004f68b7145543c615dbba
Comments: I concur with the primary reviewer's assessment.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DOROTA M MATECKA
02/15/2024 02:37:15 PM