CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216974Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	216974
Applicant Name	Entasis Therapeutics Inc.
Drug Product Name	XACDURO® (sulbactam for injection and durlobactam for injection)
Dosage Form.	Powder for reconstitution
Proposed Strength(s)	1 g and 0.5 g, respectively
Route of Administration	Intravenous
Maximum Daily Dose	6 g
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP), caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex in patients 18 years of age and older.
Drug Product Description	XACDURO is a combination product of two active ingredients, sulbactam, a beta-lactam antibacterial and beta lactamase inhibitor, and durlobactam, a beta lactamase inhibitor. The proposed drug product is an injectable product containing two sterile solid components, sulbactam for injection and durlobactam for injection, filled into separate single-dose glass vials, which need to be reconstituted and further diluted for intravenous infusion. The sulbactam-durlobactam drug product for commercial use will be provided in a carton of three co-packaged vials, one vial of sulbactam for injection (containing 1 g of sulbactam) and two vials of durlobactam for injection (each containing 0.5 g of durlobactam).
Co-packaged product information	The proposed drug product is a kit of three (3) co-packaged vials, one vial of sulbactam for injection (containing 1 g of sulbactam) and two vials of durlobactam for injection (each containing 0.5 g of durlobactam).
Device information:	N/A

Storage Temperature/ Conditions	2-8°C (36°F to 46°F)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance(s)	Karina Zuck	Katherine Windsor
	Drug Product/ Labeling	George Lunn	Dorota Matecka
	Manufacturing	Iwona Weidlich	Nathan Davis
	Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
	Microbiology	Lauren Walling	Erin Wall
	Other (specify):	N/A	
	RBPM	Anh-Thy Ly	
	ATL	Dorota Matecka	

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

3. Action Letter Information

a. Expiration Dating: XACDURO vials should be stored refrigerated at 2°C to 8°C (36°F to 46°F); brief exposure to 8°C to 15°C (46°F to 59°F) permitted [see USP Controlled Cold Temperature]. Do not freeze.

b. Additional Comments for Action:

The following Post Marketing Commitment (PMC) and Post Marketing Requirement (PMR) should be included in the action letter:

PMC:
Conduct studies to update the manufacturing process for each of the drug product components (i.e., durlobactam for injection and sulbactam for injection) to demonstrate that the labeled vial content can be withdrawn at the lower end of the fill weight variation range following reconstitution, and as appropriate to establish suitable in-process and finished drug product controls/specifications.

Draft Protocol Submission: 12/2023

Final Protocol Submission: 03/2024

Interim Report Submission: 12/2024

Final Report Submission: 04/2025

The interim report submission should include results of studies to update manufacturing process, available release/stability data, any interim in-process controls and finished product specification, etc. The final report submission should include data generated under this PMC (including 3-month long-term drug product stability data) and should be submitted to your NDA as a prior approval supplement. The final report submission should be identified as “Final Report Submission for PMC XXX in addition to being identified as a “Prior Approval Supplement”.

PMR:
Conduct studies for durlobactam drug substance and drug product, as identified in the final protocol, to further characterize the safety of their impurity profiles and establish drug substance and drug product impurity controls to ensure that each impurity limit is in accordance with ICH Q3A, Q3B, and M7, as applicable.

Draft Protocol Submission: 12/2023

Final Protocol Submission: 03/2024

Interim Report Submission # 1: 06/2024

(Long term and accelerated stability through 6 months, and in-use stability data using the methods in the NDA)

Interim Report Submission # 2: 07/2024

(Completion of impurity isolation and characterization studies)

Interim Report Submission # 3: 11/2024

(HPLC impurities method optimization/re-validation study data)

Interim Report Submission # 4: 12/2024

(Long term stability through 12 months and in-use stability data using the methods in the NDA)

Interim Report Submission # 5: 03/2025

(Identification and qualification study data, if needed)

Interim Report Submission # 6: 06/2025

(Comparability long term and additional in-use stability data based on a revised regulatory HPLC method and a revised IV-bag method [if needed])

Study completion: 09/2025

Final Report Submission: 12/2025

In the draft and final protocol, these studies should include release and stability testing of three consecutively manufactured drug substance and drug product process validation batches using optimized fully validated methods and identification and qualification studies for impurities found and controlled above applicable ICH identification and qualification thresholds. The final study reports and data generated through the PMR study should be submitted to your NDA in a prior approval supplement.

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 May 18, 2023. In addition, the labeling comments and recommendations, as discussed with other review disciplines including DMEPA, were conveyed to and accepted by the Applicant. There are two outstanding product quality issues identified during the NDA review that will need to be addressed through additional PMC and PMR studies.

The proposed drug product contains two components, sulbactam for injection and durlobactam for injection, as sterile solids filled into separate single-dose glass vials; they include one vial of sulbactam for injection (containing 1 g of sulbactam) and two vials of durlobactam for injection (each containing 0.5 g of durlobactam). The contents of these vials need to be reconstituted and further diluted for intravenous infusion. An injectable drug product supplied in a vial, such as each of the components of the proposed drug product kit, needs to comply with 21 CFR 201.51(g) 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. In addition, the in-process and finished drug products controls described in MAPP 5019.1 (published in January 2022) should be considered for such drug products. In this case, both drug product components include an overfill and a withdrawable study was conducted for each component 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, (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 discussion with the Clinical Team, it was decided that due to the urgency of this product and its potential to satisfy unmet medical need in treating a serious and life-threatening condition, these issues will be further addressed and finalized through a Post Marketing Commitment (PMC) study, described above (*for further details refer to Appendix 1 of the Drug Product Review, below*).

The other outstanding issue relates to the durlobactam component, specifically, to the currently proposed impurity controls in both durlobactam drug substance and drug product specifications, which are not entirely aligned with the recommendations of applicable ICH guidances. Batch analyses (release and stability) for durlobactam drug substance/drug product have indicated high variability and inconsistency in the overall impurity data and revealed levels of unspecified impurities at various/random time points of testing that were higher than ICH identification and/or qualification thresholds. In addition, qualification information for specified impurities (b) (4), for which structures have been only tentative established, was not found adequate by the Pharmacology/Toxicology (P/T) review team. At least one identified impurity contains a structural alert for genotoxicity. Given the large daily dose of drug that would be administered to patients, even a small percentage of impurity results in a relatively large amount of human exposure. However, release and early stability data for newer drug substance batches manufactured using an improved process and tested using modified/improved analytical methods, have shown an improved and more consistent impurity profile, with fewer impurities detected at the lower levels (with some impurities previously reported but undetected in these newer batches). The stability studies for these batches are currently on-going, therefore, the data from these batches and data for the drug product batches manufactured using an

"improved" drug substance, are quite limited at this time. Following detailed review and extensive internal OPQ discussions, it was determined that additional studies and data are needed to further characterize the impurity profile and controls for durlobactam drug substance and drug product. A recently published MAPP 5015.13 (*Quality Assessment for Products in Expedited Programs*) was also considered. Therefore, the durlobactam impurity issue was further discussed at length with the P/T and Clinical Teams, and the DAI, OID (and OND) managements. Considering the urgency and overall risk-benefit profile of the proposed drug product, and its potential to address an unmet clinical need in the treatment of a serious and life-threatening condition (as demonstrated through clinical studies), it was agreed that this issue will be further addressed through Post Marketing Requirement (PMR) study that should include additional CMC and non-clinical (*if needed*) investigations. The steps outlined in this PMR (described above) will include additional work on analytical methods, generating further release and stability testing for batches manufactured using an improved manufacturing process, and identification, and/or qualification studies of impurities (as applicable) in accordance with ICH recommendations. *For further details refer to the Drug Substance Review (Durlobactam Sodium) and Drug Product Review (in particular, Appendix 2), below*.

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

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate with QPAs**
Drug Product	**-**	**Adequate with QPAs**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate with QPAs**
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: N/A

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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

NOTE: Changes to the PI added to shared document on 2/14/23. Suggested changes for vial and carton labels were combined with DMEPA's review dated 3/29/23 and sent to the applicant.

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items 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		
Established name(s)[1]	Adequate	**sulbactam and durlobactam for injection, for intravenous use**
Route(s) of administration	Adequate	IV
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	XACDURO for injection is supplied as a Kit containing 3 single-dose vials each containing sterile powder for reconstitution: 1 vial contains sulbactam 1 g and 2 vials each contain durlobactam 0.5 g.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	

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

For injectable drug products for parental 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.	Adequate	Single-dose vials
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).	Adequate	1 vial contains sulbactam 1 g and 2 vials each contain durlobactam 0.5 g Note that both actives are sodium salts but the weights quoted are those of the free acids

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items 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, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	Preparation of XACDURO: 1. Reconstitute the sulbactam 1 g single-dose vial with 5 mL of Sterile Water for Injection and gently shake to dissolve. Each reconstituted vial contains 1 g of sulbactam per 5 mL of clear, colorless to slightly yellow solution. The reconstituted solution is not for direct injection and must be diluted before intravenous infusion. Dilution must occur within 1 hour of reconstitution. 2.

		Reconstitute each durlobactam 0.5 g single-dose vial with 2.5 mL of Sterile Water for Injection and gently shake to dissolve. Each reconstituted vial contains 0.5 g of durlobactam per 2.5 mL of clear, light yellow to orange solution. The reconstituted solution is not for direct injection and must be diluted before intravenous infusion. Dilution must occur within 1 hour of reconstitution. 3. To prepare the required XACDURO dose, withdraw 5 mL of reconstituted sulbactam and 5 mL (2.5 mL from each vial) of reconstituted durlobactam. Add the withdrawn volume of both sulbactam and durlobactam to a 100 mL infusion bag of 0.9% Sodium Chloride for Injection, USP. Discard unused portion. All statements supported by data in the NDA.
	Adequate	Administer all doses of XACDURO by intravenous (IV) infusion over 3 hours. XACDURO does not contain a bacteriostatic preservative and the prepared solution must be used within 24 hours. Discard unused portion. (Section 2.4) Store the prepared bag in the refrigerator at 2-8 °C (36-46°F) until administration. The time between start of reconstitution of the powders and the conclusion of the infusion should not exceed 24 hours. (Section 2.6) (b) (4)

		(b) (4) [redacted]
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	**Statement in PI:** The prepared XACDURO solution should appear as a clear, light yellow to orange solution, free of particulates. If the XACDURO solution is cloudy or contains particulates, do not administer. **Comments:** Adequate.
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 11).	Adequate	No corresponding USP drug product
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	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items 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	(b) (4) [redacted]
Strength(s) in metric system	Adequate	0.5 g durlobactam per vial; 1 g sulbactam per vial
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 (Tablets: 10 mg of drug-x hydrochloride).	Adequate	In accordance with the salt policy the weights are those of the free base.
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	1 clear single-dose vial of sulbactam for injection 1g (as white to off-white powder) and 2 amber single-dose vials of durlobactam for injection 0.5g (as solid cake or powder) in each vial.
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 parental 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.	Adequate	The term "single-dose" is used throughout.

Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Items 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)	Adequate	XACDURO (sulbactam and durlobactam)
Dosage form(s) and route(s) of administration	Adequate	Suggest adding "for intravenous use": XACDURO (sulbactam and durlobactam) for injection for intravenous use
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)"	Adequate	1 g sulbactam (equivalent to 1.1 g sulbactam sodium) and two amber single-dose vials each contain 0.5 g durlobactam (equivalent to 0.54 g durlobactam sodium)
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	There are no excipients for sulbactam. The excipients for durlobactam are (b) (4) HCl and NaOH used for pH (b) (4)
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.	Adequate	durlobactam sodium) together with sodium hydroxide and hydrochloric acid used for pH adjustment.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	Adequate	three single-dose vials each containing sterile powder for reconstitution
Pharmacological/Therapeutic class	Adequate	Sulbactam sodium is a beta-lactam antibacterial and a beta-lactamase inhibitor. Durlobactam is a beta-lactamase inhibitor antibacterial drug

Chemical name, structural formula, molecular weight	Adequate	Sulbactam sodium is a beta-lactam antibacterial and a beta-lactamase inhibitor. Chemically, sulbactam sodium is sodium penicillinate sulfone; sodium (2S, 5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate 4,4-dioxide. Sulbactam is a white to off-white crystalline powder that is freely soluble in water and its empirical formula is C8H10NNaO5S with a molecular weight of 255.22. Durlobactam is a beta-lactamase inhibitor antibacterial drug. Chemically, durlobactam sodium is sodium (2*S*,5*R*)-2-carbamoyl-3-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate. Durlobactam sodium is the pure (2S,5R)-enantiomer of the trans diastereoisomer. It is a white to yellow amorphous powder that is freely soluble in water. The empirical formula is C8H10N3NaO6S and the molecular weight (sodium salt) is 299.23.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	Sulbactam is a white to off-white crystalline powder that is freely soluble in water Durlobactam…is a white to yellow amorphous powder that is freely soluble in water

2. Section 11 (DESCRIPTION) Continued

Item	Items 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 oral prescription drug products, include gluten statement (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")	Adequate	No promotional statements observed in Section 11.
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).	Adequate	USP Monograph indicates that sulbactam sodium should be labeled as sterile, which it is in Highlights, Section 3, and Section 11

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

Item	Items 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)	Adequate	XACDURO (b) (4) is supplied as a kit (NDC 82792-111-10) containing (b) (4) • 1 g durlobactam in two (b) (4) amber glass vials (0.5 g durlobactam in each via (b) (4) • 1 g sulbactam in one (b) (4) clear glass vial (b) (4)
Strength(s) in metric system	Adequate	• 1 g durlobactam in two (b) (4) amber glass vials (0.5 g durlobactam in each vial (b) (4)) • 1 g sulbactam in one (b) (4) clear glass vial (b) (4)
Available units (e.g., bottles of 100 tablets)	Adequate	XACDURO is a co-packaged product containing sulbactam for injection and durlobactam for injection. XACDURO is supplied as a kit (NDC 68547-111-10) containing the following single-dose vials each containing sterile powder for reconstitution: • 1 g sulbactam in one clear glass single-dose vial • 1 g durlobactam in two amber glass single-dose vials (0.5 g durlobactam in each single-dose vial) This wording has been agreed with DMEPA

Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	XACDURO is a co-packaged product containing sulbactam for injection and durlobactam for injection. XACDURO is supplied as a kit (NDC 68547-111-10) containing the following single-dose vials each containing sterile powder for reconstitution: • 1 g sulbactam in one clear glass single-dose vial • 1 g durlobactam in two amber glass single-dose vials (0.5 g durlobactam in each single-dose vial) (Agreed with DMEPA)
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 parental 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.	Adequate	Term "single-dose" is used

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."	Adequate	See Storage Statement below.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items 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. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	XACDURO vials should be stored refrigerated at 2°C to 8°C (36°F to 46°F); brief exposure to 8°C to 15°C (46°F to 59°F) permitted [see USP Controlled Cold Temperature]. Do not freeze. Store prepared XACDURO solution in the refrigerator
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."*	Adequate	Stoppers not made with natural rubber latex.
Include information about child-resistant packaging	N/A	Not a consumer product.

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.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items 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)
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	(b) (4)

2.0 PATIENT LABELING

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	Xacduro
Special preparation instructions (if applicable)	Adequate	This is an IV product but Patient Counseling Information is provided. "Advise the patient…"
Storage and handling information (if applicable)	Adequate	
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 differs 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	(b) (4)

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Durlobactam Container Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	XacDURO
Strength(s) in metric system	Adequate	(b) (4)
Route(s) of administration	Adequate	For Intravenous Use
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	Not mentioned Not required for reasons of space (21 CFR 201.10(h)(2).)
Net contents (e.g., tablet count, volume of liquid)	Adequate	Durlobactam 0.5 g/vial
"Rx only" displayed on the principal display	Adequate	Present
NDC	Adequate	Present
Lot number and expiration date	Adequate	Present YYYY MM DD
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Not present
For injectable drug products for parental 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.	Adequate	Single-dose applies but is not present on the label
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	(b) (4)
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Present

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Durlobactam Container Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	(b) (4)
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	There is an administration guide but this is for professional use.
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	No text is present
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
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.	N/A	
And others, if space is available.	Adequate	Contains 0.5 g/vial. Reconstitute with 2.5 mL of sterile water for injection in this vial. (b) (4)

1 Page of Draft Labeling has been Withheld in Full as B4(CCI/ TS) Immediately Following this Page

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Sulbactam Container Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[4], (font size and prominence)	Adequate	Xacduro
Strength(s) in metric system	Adequate	1 g/vial
Route(s) of administration	Adequate	For intravenous use
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	Not mentioned Not required for reasons of space (21 CFR 201.10(h)(2).)
Net contents (e.g., tablet count, volume of liquid)	Adequate	Sulbactam 1 g/vial
"Rx only" displayed on the principal display	Adequate	Present
NDC	Adequate	Present
Lot number and expiration date	Adequate	Both present, expiration is YYYY MM DD
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Not present but acceptable for reasons of space
For injectable drug products for parental 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.	Adequate	Single-dose applies but is not present on the label
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	There are no inactive ingredients (drug substance is sterile filled into a vial).
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Present

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Sulbactam Container Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	(b) (4) [redacted]
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	There is an administration guide but this is for professional use.
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	No text is present
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	
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.	N/A	
And others, if space is available.	Adequate	Contains 1 g/vial. Reconstitute with 5 mL of sterile water for injection in this vial. (b) (4) [redacted]

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

3.2 Carton Labeling

Note that the application contains a conventional carton to hold the vials and instructions for the preparation of the infusion solution. From the CMC point of view the instructions seem reasonable seem reasonable.

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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[5], (font size and prominence)	Adequate	Xacduro (sulbactam-durlobactam) for injection Comment: Should be sulbactam-durlobactam because durlobactam boosts the efficacy of sulbactam
Strength(s) in metric system	Adequate	1 g/1 g (b) (4)
Route(s) of administration	Adequate	For intravenous use
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	"Each durlobactam vial contains 0.5 g durlobactam (equivalent to 0.54 g durlobactam sodium) and each sulbactam vial contains 1 g sulbactam (equivalent to 1.1 g sulbactam sodium)."
Net contents (e.g., tablet count, volume of liquid)	Adequate	1 g/1 g
"Rx only" displayed on the principal display	Adequate	Present
NDC	Adequate	Present
Lot number and expiration date	Adequate	Present. Expiration is YYYY MM DD format
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Store in refrigerator at 2°C to 8°C (36°F to 46°F)
For injectable drug products for parental 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.	Adequate	Single-dose kit 3 Vials Does not say "Not for direct infusion" but one panel contains a brief description of the preparation process and this describes dilution with saline.

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

For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	(b) (4)
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Present

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	(b) (4) [redacted]
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	There is a preparation guide but that is for professional use.
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	No text present
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	USP requires sulbactam to be labeled as sterile. Sterile is on the carton.
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.	N/A	
And others, if space is available.	Adequate	See below for a copy of the preparation procedure on the carton. This seems reasonable from a CMC point of view but is really DMEPA's call.

(b) (4)

Assessment of Carton and Container Labeling: *{Adequate/Inadequate}*

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3. ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Overall Assessment and Recommendation:

The following comments concerning the vial and carton labels were conveyed to the applicant. Note that a number of points discussed above have been omitted because the issue has been taken care of in the DMEPA review.

Vials

Each vial should be labeled as sterile.

Instructions for Use

There is a separate Instructions for Use. This is generally acceptable but we would recommend the following change (on 2 occasions):

Change: (b) (4)

To: After reconstituting, ensure there are no visible particles in the solution

Carton

Add some indication that this is a sterile product.

(b) (4)

Add: "Each durlobactam vial contains 0.5 g durlobactam (equivalent to 0.54 g durlobactam sodium) and each sulbactam vial contains 1 g sulbactam (equivalent to 1.1 g sulbactam sodium)."

The applicant subsequently made these changes.

(b) (4)

[redacted]

Primary Labeling Assessor Name and Date: George Lunn, Ph.D., 19-5-23

Secondary Assessor Name and Date (and Secondary Summary, as needed): Dorota Matecka, Ph.D., 19-5-23

George Lunn

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Date: 5/22/2023 08:18:00AM
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Dorota Matecka

Digitally signed by Dorota Matecka
Date: 5/22/2023 08:19:30AM
GUID: 508173530000859092c69506374d0011

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	216974; 505(b)(2) Type 1 NME and Type 4 New Combination
Assessment Cycle	1
Drug Product	Xacduro™ (sulbactam and durlobactam) for injection, 1 g/1 g
Dosage Form	Lyophilized Powder For Solution
Proposed Indication	XACDURO is indicated in adults for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex.
Dosage and Administration	• Administer 1.0 g sulbactam and 1.0 g durlobactam every 6 hours by intravenous infusion (IV) over 3 hours in patients with creatinine clearance (CLcr) of 45 to 129 mL/min for 7-14 days. • Dose adjustments are required for patients with CLcr <45 ml/min and for patients with CLcr ≥130 mL/min. • Administer all doses over 3 hours.
Applicant Name	Entasis Therapeutics Inc.
OND Division	OND/OID/DAI
Associated INDs	IND 131330
Primary Assessor	Qi Zhang, Ph.D.
Secondary Assessor	Elsbeth Chikhale, Ph.D.

Assessment Recommendation: Adequate

The proposed drug product (DP), XACDURO for injection is a combination drug product consisting of two separate chemical entities, durlobactam sodium and sulbactam sodium, co-packaged in separate vials. Durlobactam sodium is a new molecular entity (NME), and sulbactam sodium has previously been approved in combination with ampicillin sodium, as a powder for injection, for the treatment of *Acinetobacter* infections [Unasyn® (ampicillin sodium/sulbactam sodium) for Injection, NDA 050608].

The Applicant is relying, in part, on the safety of the Listed Drug (LD), Unasyn® (see **APPENDIX 1**). In addition, the Applicant has evaluated the safety and efficacy of the proposed DP in phase 1, 2, and 3 clinical trials (refer to the Clinical Pharmacology and Clinical reviews). This Biopharmaceutics review is focused on the data and information supporting the bridging between the proposed DP and the LD.

Product Information:

The commercial drug product will be provided in a carton of co-packaged vials of durlobactam for injection (2 single use vials containing 0.5 g durlobactam each) and sulbactam for injection (1 single use vial containing 1.0 g sulbactam). Each of the 3 vials contains sterile powder that must be reconstituted and further diluted using aseptic technique prior to intravenous infusion. The prepared XACDURO reconstituted and diluted infusion solution should appear as a clear, light yellow to orange solution, free of particulates as indicated in the Preparation of XACDURO for Intravenous Administration section of the proposed product's label.

The formulation composition proposed for the commercial drug product is identical to the product formulation used throughout clinical development (Phase 1 through Phase 3). The drug product manufacturing site of the clinical batches is also the proposed commercial drug product manufacturing site. Therefore, bridging between the clinical and the proposed commercial drug products is not needed.

Sulbactam

Sulbactam for injection contains 1 (b) (4) g of sterile sulbactam sodium salt, equivalent to 1.1 g of sulbactam (free acid) with no other excipients. The vial contents include (b) (4) overfill of sulbactam sodium to enable the accurate withdrawal volume (5.0 mL) equivalent to 1.0 g of sulbactam (free acid) upon reconstitution.

Durlobactam

Durlobactam for injection contains (b) (4) sterile durlobactam sodium salt, equivalent to 0.5 (b) (4) g of durlobactam (free acid) with small amounts of pH adjusters (b) (4) sodium hydroxide solution (b) (4) hydrochloric acid solution) added, if necessary. The vial content includes approximately (b) (4) overfill of durlobactam to allow for an accurate withdrawal volume (2.5 mL) equivalent to 0.5 g of durlobactam (free acid) upon reconstitution. No changes were made to durlobactam for injection formulation composition throughout clinical development (phase 1 through phase 3), (b) (4) after the first lot (B16070043) was manufactured for the phase 1 clinical study.

Bridging Between Proposed Drug Product and Listed Drug:

The Applicant conducted clinical safety and effectiveness trials with the proposed combination drug product (durlobactam and sulbactam), as well as pharmacokinetic and nonclinical studies, to support this application, which supports the proposed indication: treatment of pneumonia caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex. The application relies on the LD Unasyn® for the following specific labeling information that are relevant to the drug substance sulbactam: Contraindications, Warnings & Precautions, Pregnancy, Lactation and Overdosage, Pharmacokinetics (for sulbactam protein binding and renal excretion data), and Patient Counseling. Refer to the Table

entitled "Content in proposed XACDURO label derived from Reference Listed Drug (Unasyn)" in the Applicant's response (SN-37) and copied in **APPENDIX 1**. The Applicant indicated that the Adverse Reactions, and the rest of the Clinical Pharmacology, and Clinical Studies sections consist of information that are derived from the existing studies conducted on Xacduro.

As shown in **Table 1** below, the difference between the proposed DP, Xacduro, and the LD, Unasyn®, is the infusion time, the drug combination, the co-packaging, the indication, and the possible routes of administration. Unasyn, after dilution, is infused for 15-30 minutes, whereas the proposed DP is infused for 3 hours. Refer to **Table 1** below.

Table 1. Comparison of The Proposed Drug Product and Listed Drug

Parameters	**Listed Drug Unasyn**		**Proposed Drug Product Xacduro**	
Indication and Usage	Indicated for the treatment of infections due to susceptible strains of the designated microorganisms.		Indicated in adults for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex	
Active ingredient	Ampicillin sodium	Sulbactam sodium	Sulbactam sodium	Durlobactam sodium
Inactive ingredient	None		None	pH adjusters as needed
Dosage form	Parenteral combination, powder for reconstitution		Co-packaged product, sterile powder for reconstitution	
Route of Administration	Intramuscular or IV		IV	
Strength	1 g	0.5 g	1 g	0.5 g
	2 g	1 g		
Dose	1 g	0.5 g	1 g	1 g
	2 g	1 g		
Infusion Time	Every six hours; 15–30 minutes		Every six hours; 3 hours	
Diluent for reconstitution/volume/ concentration	For IV: May be reconstituted directly to the desired concentrations using any of the compatible diluents described in the label insert including sterile water.		5 mL of sterile water 1g/5 mL	2.5 mL of sterile water 0.5 g/2.5 mL
Diluent for dilution/volume/ concentration	For IV: 100 mL and 250 mL of 0.9% Sodium Chloride for 3 g dose		100 mL of 0.9% Sodium Chloride ~10 mg/mL	
	100 mL: ~20 mg/mL	100 mL: ~10 mg/mL		

How supplied	Supplied as a sterile off-white dry powder in glass vials and piggyback bottles. • Vials containing 1.5 equivalent of UNASYN (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt) • Vials containing 3 g equivalent of UNASYN (2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt).	Supplied as a kit containing 3 single-dose vials each containing sterile powder for reconstitution: • 1 g sulbactam in one clear glass single-dose vial • 1 g durlobactam in two amber glass single-dose vials (0.5 g durlobactam in each single-dose vial)
Storage	Stored at or below 30°C. The final diluted solution should be completely administered within 8 hours	Stored refrigerated at 2°C to 8°C (36°F to 46°F); brief exposure (b) (4) Store prepared solution in the refrigerator.

The specific relied upon information from the label of Unasyn (see **APPENDIX 1**) for sulbactam is not affected by the differences between Xacduro and Unasyn based on the following data/information:

- Both products are supplied as powder for reconstitution and dilution and contain the same amount and form of sulbactam (sulbactam sodium) with the same sulbactam drug concentration after reconstitution and dilution in a 100 mL infusion bag of 0.9% Sodium Chloride (10 mg/mL) when comparing the proposed drug product to the 3 g dose of Unasyn (1 g sulbactam).
- Neither product contains excipients or inactive ingredients that impact the solubility, stability, or PK of sulbactam.
- There is no drug-drug interaction between sulbactam and ampicillin, nor between sulbactam and durlobactam.
- As shown in Table 2 of the SN-37 IR Response, the sulbactam PK parameters, specifically, the systematic exposure, half-life, volume of distribution, and clearance of 1.0 g sulbactam were comparable (as confirmed by the Clinical Pharmacology Reviewers Dr. Wei, Xiaohui and Chilukuri, Dakshina), when administered by IV infusion, based on the published and existing PK studies. The C_{max} is different, as expected, because of the difference in the infusion rate, 15 – 30 minutes vs 3 hours. As Xacduro is administered with a longer infusion time of 3 hours (as opposed to Unasyn's 15-30 minutes infusion), a lower sulbactam Cmax was achieved with Xacduro than with Unasyn, implying a higher safety margin. In addition, the Applicant conducted their own PK studies for Xacduro (sulbactam and durlobactam) and provided important safety data for sulbactam.

Recommendation:

Based on the provided information, it is scientifically justified that the Applicant relies, in part, on the safety of the listed drug, Unasyn® (ampicillin sodium/sulbactam sodium) for Injection, NDA 050608. From a Biopharmaceutics perspective, NDA 216974 for Xacduro™ (sulbactam for injection and durlobactam for injection) is recommended for approval.

List of Submissions Being Assessed:

Document(s) Assessed	Date Received
Original Submission	2022-09-29 (SN-1)
IR Response	2023-03-15 (SN-37)

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

Concise Description of Outstanding Issues: None.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Primary Biopharmaceutics Assessor's Name and Date: Qi Zhang, Ph.D. (March 17, 2023)

Secondary Assessor Name and Date: Elsbeth Chikhale, Ph.D. (March 17, 2023)

APPENDIX 1

Content in proposed XACDURO label derived from Reference Listed Drug (Unasyn)

Labeling Section	XACDURO label	Unasyn Label
Contraindications	XACDURO is contraindicated in patients with a history of known severe hypersensitivity to the components of XACDURO, sulbactam or other beta-lactam antibacterial drugs.	The use of UNASYN is contraindicated in individuals with a history of serious hypersensitivity reactions (e.g., anaphylaxis or Stevens-Johnson syndrome) to ampicillin, sulbactam or to other beta-lactam antibacterial drugs (e.g., penicillins and cephalosporins). UNASYN is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with UNASYN.
Warnings & Precautions	5.1 Hypersensitivity Reactions Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam [(b) (4)] These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity and/or a history of sensitivity to multiple allergens. [(b) (4)] Hypersensitivity was observed in patients treated with XACDURO in clinical trials. Before initiating therapy with XACDURO, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta lactams, and other allergens. Discontinue XACDURO if an allergic reaction occurs.	Hypersensitivity Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or hypersensitivity reactions to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, UNASYN should be discontinued and the appropriate therapy instituted.
	5.2 *Clostridioides difficile*-Associated Diarrhea (CDAD) *Clostridioides difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XACDURO, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.	*Clostridium difficile*-Associated Diarrhea *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including UNASYN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD.

Content in proposed XACDURO label derived from Reference Listed Drug (Unasyn)

Labeling Section	XACDURO label	Unasyn Label
Contraindications	XACDURO is contraindicated in patients with a history of known severe hypersensitivity to the components of XACDURO, sulbactam or other beta-lactam antibacterial drugs.	The use of UNASYN is contraindicated in individuals with a history of serious hypersensitivity reactions (e.g., anaphylaxis or Stevens-Johnson syndrome) to ampicillin, sulbactam or to other beta-lactam antibacterial drugs (e.g., penicillins and cephalosporins). UNASYN is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with UNASYN.
Warnings & Precautions	5.1 Hypersensitivity Reactions Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam (b) (4) These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity and/or a history of sensitivity to multiple allergens. (b) (4) Hypersensitivity was observed in patients treated with XACDURO in clinical trials. Before initiating therapy with XACDURO, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta lactams, and other allergens. Discontinue XACDURO if an allergic reaction occurs.	Hypersensitivity Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or hypersensitivity reactions to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, UNASYN should be discontinued and the appropriate therapy instituted.
	5.2 *Clostridioides difficile*-Associated Diarrhea (CDAD) *Clostridioides difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XACDURO, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.	*Clostridium difficile*-Associated Diarrhea *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including UNASYN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD.

Labeling Section	XACDURO label	Unasyn Label
		(b) (4) [redacted]
Lactation	Risk Summary (b) (4) [redacted] The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XACDURO and any potential adverse effects on the breastfed child from XACDURO or from the underlying maternal condition.	**Nursing Mothers** Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.
Overdosage	There is no information on clinical signs and symptoms associated with an overdose of XACDURO. Neurological adverse reactions, including convulsions, may occur with the attainment of high CSF levels of beta-lactams. (b) (4) [redacted] (b) (4) [redacted] (b) (4) Sulbactam and durlobactam are removed by hemodialysis [see Clinical Pharmacology (12.3)]. No clinical information is available on the use of hemodialysis to treat overdosage.	Neurological adverse reactions, including convulsions, may occur with the attainment of high CSF levels of beta-lactams. Ampicillin may be removed from circulation by hemodialysis. The molecular weight, degree of protein binding and pharmacokinetics profile of sulbactam suggest that this compound may also be removed by hemodialysis.
Pharmacokinetics	(b) (4) [redacted] (b) (4) [redacted]	Ampicillin has been found to be approximately 28% reversibly bound to human serum protein and sulbactam approximately 38% reversibly bound. Approximately 75 to 85% of both ampicillin and sulbactam are excreted unchanged in the urine during the first 8

Labeling Section	XACDURO label	Unasyn Label
	The binding of sulbactam and to human plasma proteins is approximately 38% and independent of drug concentration. *Excretion* Approximately 75 to 85% of sulbactam is excreted unchanged in the urine during the first 8 hours after administration of ampicillin/sulbactam to individuals with normal renal function. (b) (4) (b) (4)	hours after administration of UNASYN to individuals with normal renal function. Somewhat higher and more prolonged serum levels of ampicillin and sulbactam can be achieved with the concurrent administration of probenecid.
Patient Counselling	Serious Allergic Reactions Advise the patient, their families, or caregivers that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. Ask them about any previous hypersensitivity reactions to XACDURO, other beta-lactams (including cephalosporins) or other allergens [see Warnings and Precautions (5.1)]. Potentially Serious Diarrhea Advise the patient, their families, or caregivers that diarrhea is a common problem caused by antibacterial drugs. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, tell them to contact their healthcare provider [see Warnings and Precautions (5.2)]. Antibacterial Resistance Patients (b) (4) should be counseled that antibacterial drugs, including XACDURO, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). (b) (4) (b) (4) patients should be told that (b) (4) (b) (4) (b) (4) the medication should be administered exactly as directed. (b) (4) (b) (4)	Information for Patients Patients should be counseled that antibacterial drugs including UNASYN should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When UNASYN is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by UNASYN or other antibacterial drugs in the future. Diarrhea is a common problem caused by antibacterials which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterials, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial. If this occurs, patients should contact their physician as soon as possible.

Labeling Section	XACDURO label	Unasyn Label
	(b) (4) (b) (4) [see Warnings and Precautions (5.3)].	

Elsbeth Chikhale

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Qi Zhang

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CHAPTER VII: MICROBIOLOGY

For more details about the items in this template, please see Chapter VII (Microbiology) of the NDA IQA Guide

Product Information	
NDA Number	216974
Assessment Cycle Number	1
Drug Product Name/ Strength	Sulbactam sodium – Durlobactam sodium (Xacduro) / Sulbactam – 1.0 g/vial, Durlobactam – 0.5 g/vial
Route of Administration	IV
Applicant Name	Entasis Therapeutics Inc.
Therapeutic Classification/ OND Division	DAI
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
0001	**9/29/2022**
0004	**10/20/2022**
0019	**12/29/2022**

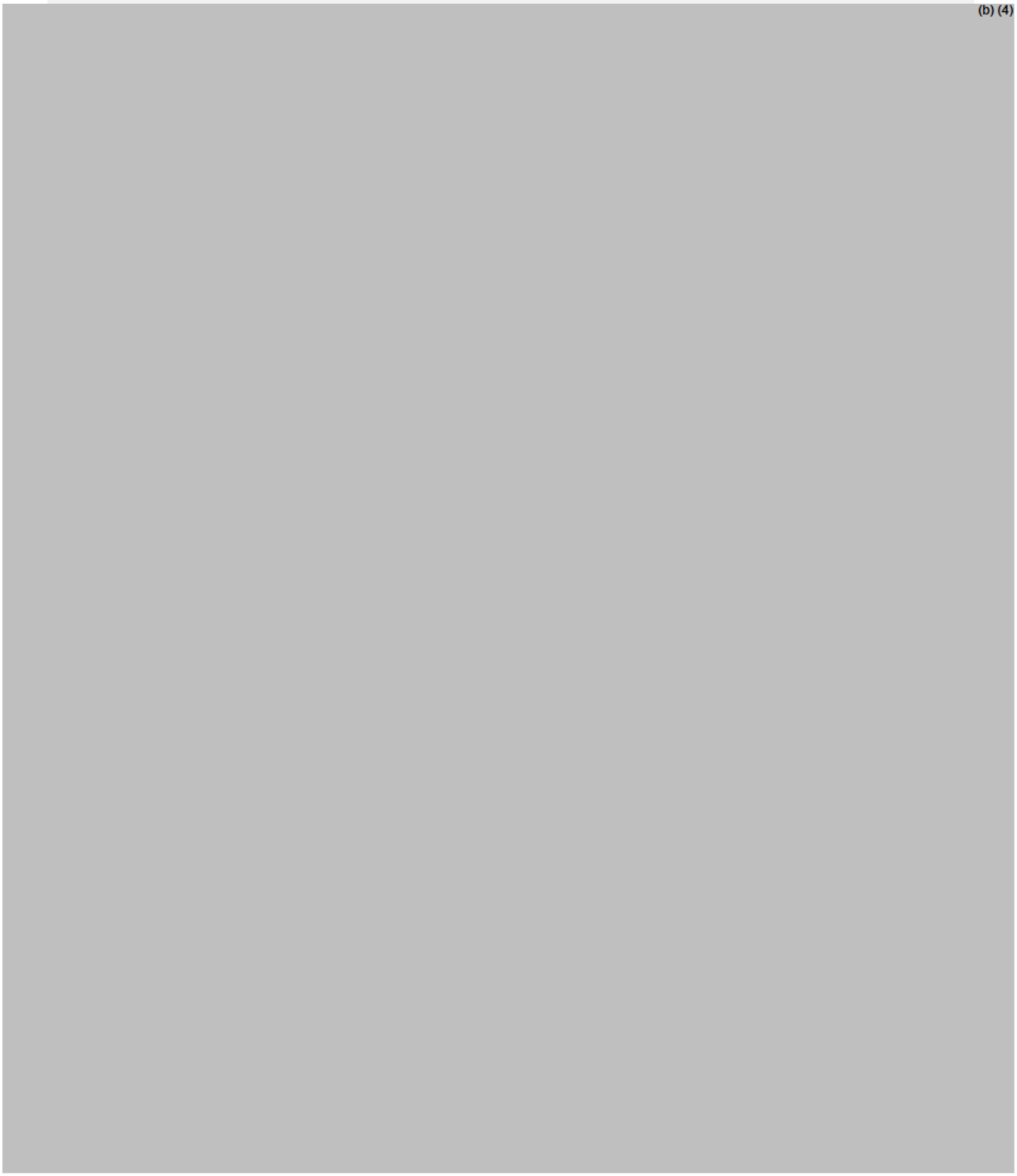
Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: Sulbactam sodium – Durlobactam sodium consists of two drug products, which consist of one vial of Sulbactam sodium (sterile powder) and two vials of Durlobactam sodium (lyophilized) packaged together in a single carton. These drug products are powders for solution for IV injection. The drug

product is indicated for the treatment of infections due to *Acinetobacter baumannii-calcoaceticius* complex, including multidrug-resistant and carbapenem-resistant strains, in adults.

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

(b) (4)



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(b) (4)

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Durlobactam:

- **Description of drug product –**
  Section 3.2.P.1, p. 1 of 2. Lyophilized solid, reconstituted for IV administration. Single-dose vial. Commercially provided in a carton of co-packaged vials containing 1 vial sulbactam and 2 vials durlobactam.

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

Ingredient	Quantity per 2.5 mL	Function
Durlobactam Sodium	(b) (4)	Active ingredient
Sodium Hydroxide	q.s.	pH adjustment as needed
Hydrochloric Acid	q.s.	pH adjustment as needed

(b) (4)

(b) (4)

- **Description of container closure system –**
  Section 3.2.P.1, p. 1-2 of 2; Section 3.2.P.7, p. 2 of 7.

Component	Description	Manufacturer
Vial	10 mL, USP (b) (4) amber glass vial	(b) (4)
Stopper	20 mm (b) (4) rubber stopper	
Seal	20 mm (b) (4) flip-off seal	

Assessment: *Adequate*
The applicant appropriately describes the durlobactam drug product composition and container closure system.

Sulbactam:

- **Description of drug product –**
  Section 3.2.P.1, p. 1 of 1. Sterile solid, reconstituted for IV administration. Single-dose vial. Commercially provided in a carton of co-packaged vials containing 1 vial sulbactam and 2 vials durlobactam.

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

Ingredient	Quantity per Vial	Function
Sulbactam Sodium	1 (b) (4) g	Active ingredient

- **Description of container closure system –**
  Section 3.2.P.1, p. 1 of 1; Section 3.2.P.7, p. 2 of 7

Component	Description	Manufacturer
Vial	30 mL clear, USP (b) (4) glass vial	(b) (4)
Stopper	20 mm (b) (4) rubber stopper	
Seal	20 mm (b) (4) flip-off crimp seal	

Assessment: *Adequate*
The applicant appropriately describes the sulbactam drug product composition and container closure system.

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(b) (4)

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

(b) (4)

Section: 1.14.1.3
Study Report #: Not given
Route of administration: IV
Container: Single dose

Reconstituted/Further Diluted Drug Product

Reconstitution: Reconstitute the sulbactam vial (1.0 g) with 5 mL sterile water for injection and reconstitute two durlobactam vials (0.5 g each) with 2.5 mL sterile water for injection. Use reconstituted solutions immediately.

Further product dilution: Add 5.0 mL each of reconstituted sulbactam and durlobactam to a 100 mL infusion bag of 0.9% Sodium Chloride for Injection. This dosage may be altered depending on renal function of the patient and a table is included indicating these recommendations. The prepared infusion bag can be stored in the refrigerator at 2-8°C for NMT 24 hours.

Assessment: *Adequate*
The applicant has adequately described the drug product reconstitution, dilution, and storage of the diluted product prior to administration. The post-dilution storage time is NMT 24 hours at 2-8°C, which poses minimal risk to patient safety and is acceptable from a product quality microbiology standpoint.

MICROBIOLOGY LIST OF DEFICIENCIES
N/A

Primary Microbiology Assessor Name and Date: Lauren Walling, PhD, 01/25/2023

Secondary Assessor Name and Date (and Secondary Summary, as needed): Erin A. Wall, Ph.D. 1/25/2023

Lauren Walling

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Date: 1/25/2023 01:06:16PM
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Erin Wall

Digitally signed by Erin Wall
Date: 1/25/2023 01:05:37PM
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