CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213972Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	213972 (*NDA Resubmission*)
Applicant Name	Iterum Therapeutics US Limited
Drug Product Name	ORLYNVAH™ (sulopenem etzadroxil and probenecid) tablets
Dosage Form.	Tablet
Proposed Strength(s)	500 mg of sulopenem etzadroxil and 500 mg of probenecid
Route of Administration	Oral
Maximum Daily Dose	1000 mg of sulopenem etzadroxil and 1000 mg of probenecid
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of uncomplicated urinary tract infections caused by designated microorganisms demonstrated to be susceptible to ORLYNVAH in adult women without appropriate alternative oral treatment options.
Drug Product Description	The proposed drug product, sulopenem etzadroxil and probenecid tablets, is a fixed-dose combination of a thiopenem β-beta-lactam antibacterial (sulopenem etzadroxil) and a uricosuric and renal tubular blocking agent (probenecid). Probenecid inhibits the OAT3-mediated excretion of sulopenem, thereby providing increased plasma concentrations of sulopenem. The drug product is an immediate release, bilayer tablet, containing 500 mg sulopenem etzadroxil and 500 mg probenecid, supplied in HDPE bottles (10 and 30 counts) with child-resistant caps. The intended therapeutic dosing regimen is one tablet, twice daily, for 5 days with food.
Co-packaged product information	N/A
Device information:	N/A
Storage Temperature/ Conditions	20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)

	Discipline	Primary	Secondary
Review Team	*Drug Substance*	Karina Zuck	Katherine Windsor
	Drug Product	Akshata Nevrekar	Dorota Matecka
	Labeling	Akshata Nevrekar	David Claffey
	Manufacturing	Iwona Weidlich	Nathan Davis
	Biopharmaceutics	Haodan Yuan	Elsbeth Chikhale
	Microbiology	N/A	N/A
	RBPM	Janell Artis	
	ATL	Dorota Matecka	

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

60 months when stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room temperature]

b. Additional Comments for Action: N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

This NDA was issued a Complete Response (CR) letter on July 23, 2021, due to clinical deficiencies. No CMC/Product Quality deficiencies were identified in the first review cycle and the NDA was recommended for approval from the Product Quality perspective (refer to the OPQ Integrated Quality Assessment dated June 1, 2021, in DARRTS). With the current NDA resubmission (SDN# 71, dated April 25, 2024), several changes have been proposed in Module 3. They include updates to the manufacturing process in the sulopenem etzadroxil drug substance manufacturing process and a (b) (4) *, which resulted in the removal of two manufacturing sites from the original NDA submission. The overall information to support these changes submitted in the NDA resubmission,*

and the updated information submitted in the referenced DMF for probenecid drug substance, were found acceptable. From the drug product perspective, the most significant change includes a removal of (b) (4) *. In addition, during the NDA review, a* (b) (4) *risk assessment was submitted and deemed to be low for this drug product. Several additional issues were resolved, e.g., the description quality attribute for the proposed drug product was revised to accurately reflect the appearance of the tablet in the drug product specification table and the Prescribing Information. All quality related labeling comments were addressed adequately by the Applicant. In addition, based on the overall stability data package, the proposed expiration dating of 60 months for the drug product packaged in HDPE bottles and to be stored at room temperature, was found acceptable. All proposed commercial manufacturing and testing facilities have been found acceptable in this review cycle and an overall "Approve" recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment on September 6, 2024.*

Overall, the NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, sulopenem etzadroxil and probenecid tablets. 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 - Adequate
Microbiology - N/A

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: N/A

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The information included in the PI, carton label and container label is adequate from quality perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	ORLYNVAH	Adequate
Established name(s)	Sulopenem etzadroxil Probenecid tablets	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	ORLYNVAH tablets: 500 mg sulopenem etzadroxil and 500 mg probenecid.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a scored tablet
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.	N/A	Not an Injectable drug product

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

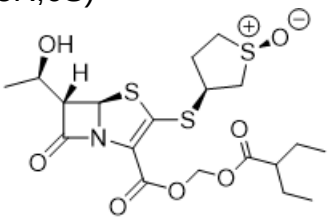
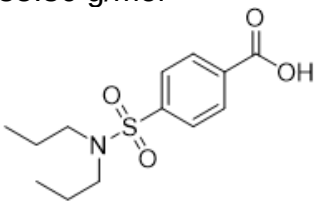
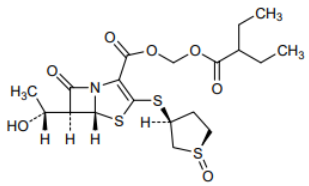
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	No special preparation instructions needed for this oral dosage form

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	ORLYNVAH tablets	Adequate
Strength(s) in metric system	500 mg of sulopenem etzadroxil and 500 mg of probenecid	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	Not a salt form
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Pink, oval-shaped, film-coated, fixed-dose, bilayer combination tablets debossed with SULO on one side and plain on other side	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a scored tablet
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	Not an Injectable drug product

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	ORLYNVAH (sulopenem etzadroxil and probenecid) tablets	Adequate
Dosage form(s) and route(s) of administration	Tablets for oral administration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	Not a salt form
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Microcrystalline cellulose, croscarmellose sodium, magnesium stearate, lactose monohydrate, hydroxypropylcellulose, polyvinyl alcohol, titanium dioxide, talc, lecithin (soy), xanthan gum, and carmine	Adequate. Revised to alphabetize inactive ingredients and separate film coating ingredients. the following inactive ingredients: croscarmellose sodium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The film coating contains carmine, lecithin polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.
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.	N/A	Not an injectable dosage form
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Alcohol is not present.
Statement of being sterile (if applicable)	N/A	Not a sterile dosage form

Pharmacological/ therapeutic class	Sulopenem etzadroxil: [redacted] penem antibacterial drug Probenecid: a [redacted] renal tubular transport [redacted]	Adequate. The adequacy of the pharmacological class will be determined by OCP and non-clinical review team.
Chemical name, structural formula, molecular weight	Sulopenem etzadroxil: 4-Thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-[(1R)-1- hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-, (2-ethyl-1-oxobutoxy)methyl ester, (5R,6S)  Chemical Formula: $C_{19}H_{27}NO_7S_3$ Molecular Weight: 477.61 g/mol Probenecid: 4-[(dipropylamino) sulfonyl] benzoic acid Molecular Weight: 285.36 g/mol  Chemical Formula: $C_{13}H_{19}NO_4S$	Adequate Note: The structure of Sulopenem etzadrozil submitted by the Applicant is not in accordance with the drug substance structure* per USAN. *Structure per USAN: STRUCTURAL FORMULA  The drug product review team has consulted with drug substance reviewer, Dr. Karina Zuck, regarding a correct structure for sulopenem etzadroxil. It was communicated by Dr. Karina Zuck in an email dated 09/11/2024, that "Both structures (the one including the S-O with the charge and the one with the S=O) are correct; there are just two different ways to represent the same molecule. The bolded bond in the structure with the double bond (S=O) is representing also that the O is oriented above the ring structure". No further comments are issued to the Applicant.

If radioactive, statement of important nuclear characteristics.	N/A	Not a radioactive/radiolabeled compound.
Other important chemical or physical properties (such as pKa or pH)	None provided	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	no gluten present
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	No statements added

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	ORLYNVAH tablets	Adequate
Strength(s) in metric system	500 mg of sulopenem etzadroxil and 500 mg of probenecid	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 10 tablets with child-resistant caps Bottles of 30 tablets with child-resistant caps	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Pink, oval-shaped, film-coated bilayer tablets debossed with SULO on one side and plain on the other side	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a scored tablet
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.	N/A	Not an injectable dosage form

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

Item	Information Provided in the NDA	Assessor's Comments

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.)	N/A	No special statements are necessary As per labelling review by Dr. Molly Lee, dated 5/27/2021; Photostability study suggests the product does not need to be protected from light. In-use stability study demonstrates that at long-term storage conditions (25 ºC/60% RH), the product is stable outside of bottle (in open tray) for up to 3 months.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	(b) (4) desiccant bag containing 1 gram (b) (4) (b) (4)	Desiccant is included (b) (4) (b) (4) desiccant bag containing 1 gram (b) (4). The shape (rectangular) and color (white) visibly differentiates the desiccant bag from the drug product. The appearance of the desiccant bag has a cautionary statement “Desiccant Do Not Eat”.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room temperature]	Adequate. In accordance with section 3.2.P.8.1
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.”	N/A	N/A
Include information about child-resistant packaging	Child resistant caps included in packaging	The Applicant states in section 3.2.P.7 of original

		application that the child-resistant caps meet the Consumer Product Safety Commission standards under 16 CFR 1700

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 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	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Iterum Therapeutics U.S. Limited, Chicago, IL 60606	Adequate

2.0 PATIENT LABELING

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

The information in the prescribing information is adequate. No further comments are issued to the applicant.

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

10 count pack: HDPE bottle label

30 Count pack: HDPE bottle label

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

10 Count pack: HDPE Bottle

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	ORLYNVAH (sulopenem etzadroxil and probenecid) 500mg/500mg Oral tablets	Adequate pending revisions. Per USP <1121>, the Established nonproprietary name of the drug product should include the dosage form, i.e., [DRUG] [DOSAGE FORM]. Therefore, we recommend revising the drug name on both the container label and carton labeling using one of the following approaches. The established name can appear on the same line following the proprietary name, to read: Tradename (sulopenem etzadroxil and probenecid) Tablets Or, the established name can appear on a separate line, to read: Tradename (sulopenem etzadroxil and probenecid) tablets. (Comment sent to the applicant)
Dosage strength	500 mg/500mg	Adequate

Route of administration	(b) (4)	Adequate pending revisions (b) (4) Applicant could add "For oral use" to another part of the label, although not necessary. (Comment sent to the applicant)
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	10 tablets 30 tablets	Adequate
"Rx only" displayed on the principal display	Rx Only	Adequate
NDC number	10 counts: NDC 81153-100-01 30 counts: NDC 81153-100-03	Adequate
Lot number and expiration date	yes	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at controlled room temperature 20°C to 25°C (68°F to 77°F)	Inclusion of excursions in the carton label recommended per USP controlled room temperature. (comment, To The Applicant, added to the PI)
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	Not an injectable dosage form

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	Not a pharmacy bulk pack
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Alcohol is not present
Bar code	yes	Adequate

Item	Information Provided in the NDA	Assessor’s Comments about Carton Labeling
Name of manufacturer/distributor	Iterum Therapeutics US Limited Chicago, IL 60606	Adequate
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	N/A	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	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: *Adequate*
No deficiencies to be issued to the applicant.

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

The information in the prescribing information (PI, label for carton and container are adequate from quality standpoint. No comments need to be issued to the Applicant.
The labelling review is adequate.

Primary Labeling Assessor Name and Date: Akshata Nevrekar; 09/11/2024

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

Akshata Nevrekar

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David Claffey

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA 213972-SDN-71
Product Information	Fixed-Dose combination (FDC) Immediate-Release Oral Tablet
Assessment Cycle Number	2
Drug Product Name/ Strength	Sulopenem etzadroxil/Probenecid Tablet; 500 mg/500 mg
Route of Administration	Oral
Applicant Name	Iterum Therapeutics US Ltd
Therapeutic Classification/ OND Division	DAI
LD Number	Benemid (probenecid) Tablets [NDA 007898]
Proposed Indication	Uncomplicated urinary tract infections (uUTI)

Assessment Recommendation: **Adequate**

Background:

Iterum Therapeutics US Ltd is seeking approval under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Sulopenem etzadroxil/Probenecid Tablets, 500 mg/500 mg, for the treatment of uncomplicated urinary tract infections (uUTI). Sulopenem etzadroxil is a new molecular entity (NME) and is a prodrug that is rapidly cleaved in the intestinal wall to release the active parent compound, sulopenem, which is a thiopenem beta-lactam antibacterial drug. Probenecid is a uricosuric and renal tubular blocking agent, which is co-administered with sulopenem etzadroxil to reduce renal clearance and increase systemic exposure of sulopenem. (b) (4) (b) (4) The Applicant originally conducted one single phase 3 uUTI trial evaluating the superiority of sulopenem etzadroxil/probenecid to ciprofloxacin in patients with infections due to a quinolone resistant organism. This NDA relies, in part, on the findings of safety and efficacy of the listed drug (LD), Benemid (probenecid) Tablets (NDA 007898), to reduce renal clearance and increase systemic exposure of beta-lactam antibiotics.

Dissolution Data:

The original Biopharmaceutics review (dated April 19, 2021) for the first review cycle was recommending approval from a Biopharmaceutics perspective[2]. The

[1] Common Technical Document Summaries – Introduction:
\\CDSESUB1\evsprod\nda213972\0000\m2\22-intro\ctd-summaries-intro.pdf
[2] Biopharmaceutics Review (April 19, 2021):
https://panorama.fda.gov/task/view?ID=600af430003d4bc7f87ce8f8994545ee

following dissolution method and acceptance criteria were found adequate for the routine quality control testing of Sulopenem etzadroxil/Probenecid Tablets, 500 mg/500 mg, at batch release and during shelf-life.

USP Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion
II (Paddle)	75 rpm	0.05 M phosphate buffer, pH 6.8	900 mL/ 37.0 ± 0.5 °C	**Sulopenem etzadroxil**: Q (b) (4) % in 30 minutes **Probenecid**: Q (b) (4) % in 15 minutes

However, a complete response (CR) letter with a clinical deficiency was issued on July 23, 2021, recommending that the Applicant conducts at least one additional adequate and well-controlled clinical study in uUTI patients due to the lack of substantial evidence of effectiveness based on the single clinical study IT001-301. There were no deficiencies related to Biopharmaceutics in the CR letter.

In the CRL response dated June 15, 2022 (SDN 63), to address the clinical deficiency, the Applicant indicated their plans to conduct further investigation to better understand the PK/PD behavior of sulopenem and to conduct an additional adequate and well-controlled clinical study in uUTI patients (IT001-310). In the current resubmission (SDN 71) dated 4/25/2024, the Applicant submitted the data from clinical study IT001-310. In addition, the Applicant submitted more information including new stability dissolution data to support the extension of the drug product shelf-life[3] for the Agency's review.

Review of the current submission indicates that there have been no changes to the batch formulation, drug substance and drug product specifications, analytical procedures, the drug substance and drug product manufacture facilities and equipment[4] compared to the original submission.

The Applicant provided the updated stability data of the proposed drug product under long term storage and accelerated storage conditions for the primary registration batches, PPQ/commercial batches and the clinical batches using the accepted dissolution method and acceptance criterion.

The 12 units average dissolution data of all the registration batches, PPQ/commercial batches and clinical batches at different stability time points

[3] Stability Summary and Conclusion (SDN 71) \\CDSESUB1\EVSPROD\nda213972\0070\m3\32-body-data\32p-drug-prod\sulopenem-etza-probenecid-tablet-all\32p8-stab\3-2-p-8-1-stability-summary-rff-pub-v-1.pd

[4] Reviewer's Guide: \\CDSESUB1\EVSPROD\nda213972\0070\m1\us\reviewers-guide.pdf

met the acceptance criteria. However, it is noted there are some individual dissolution data for probenecid[5] that are below 80% but higher than 65%. There is no trend observed in these dissolution data to indicate any potential quality issues of the drug product with the storage conditions or time. As per the dissolution acceptance criteria for the stage two dissolution test stated in the USP chapter <711> "the average of 12 units (S1+S2) is ≥Q, and no unit is <Q−15%", the provided dissolution stability data are acceptable. The CMC/drug product review team will review the overall drug product stability data and set the drug product's expiration date.

Bridging:

Comparative probenecid pharmacokinetic data were reviewed by the Office of Clinical Pharmacology (OCP)[6] during the first review cycle. Based on the provided PK/bioavailability data, the OCP review concluded that probenecid plasma exposure following administration of the proposed drug and the LD are comaprable. Therefore, a PK bridge between the proposed drug product and the LD has been established[7], justifying the reliance of the current NDA 213972 on the listed drug, NDA 007898.

Minor differences in color and debossment between the to be marketed drug product and the product used in the clinical studies were bridged by comparative dissolution data, using the above acceptable dissolution method, as documented in the previous Biopharmaceutics review[2].

Overall Review Recommendation:

From a Biopharmaceutics perspective, **NDA 213972** for Sulopenem etzadroxil/Probenecid Tablets, 500 mg/500 mg remains **ADEQUATE** and recommended for **APPROVAL**.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
SDN-71 (Response to CRL)	4/25/2024

Highlight Key Issues from Last Cycle and Their Resolution:

[5] Data example - stability data for batch F10014630001D9: \\CDSESUB1\EVSPROD\nda213972\0070\m3\32-body-data\32p-drug-prod\sulopenem-etza-probenecid-tablet-all\32p8-stab\3-2-p-8-3-stability-data-f10014630001d9.pdf

[6] REV-SUMMARY-13 (Unireview): https://darrts.fda.gov/darrts/faces/ApplicationHistoryContent/viewApplicationHistoryContent?_afrRedirect=1614804476664311&_afrPage=3, Page 104-105

[7] Summary of Biopharmaceutics Studies and Analytical Method: \\CDSESUB1\evsprod\nda213972\0000\m2\27-clin-sum\summary-biopharm.pdf

- N/A - This NDA was found adequate from a Biopharmaceutics perspective in the first review cycle.

Concise Description of Outstanding Issues:

- There are no outstanding issues from a Biopharmaceutics perspective.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

BIOPHARMACEUTICS LIST OF INFORMATION REQUESTS

None.

Primary Biopharmaceutics Assessor's Name and Date: Haodan Yuan, Ph.D. 08/21/2024

Secondary Assessor Name and Date: Elsbeth Chikhale, Ph.D. 08/21/2024

Elsbeth Chikhale

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Haodan Yuan

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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213972
Assessment # 1

Drug Product Name	[TRADENAME]™ (sulopenem etzadroxil and probenecid) tablets
Dosage Form	Tablet
Strength	500 mg of sulopenem etzadroxil and 500 mg of probenecid
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Iterum Therapeutics Ltd
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
0001	November 11, 2020	All
0018	February 23, 2021	Facilities, Drug Substance
0019	March 5, 2021	Biopharmaceutics, Drug Substance, Drug Product, Environmental Analysis
0024	March 15, 2021	Process, Facilities
0027	April 6, 2021	Drug Substance, Drug Product, Process
0030	April 12, 2021	Biopharmaceutics, Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Soumya Mitra	Ali Al Hakim
Drug Product	Molly Lee	Thomas Oliver
Manufacturing	Xiumei Ruan	Steven Frisbee
Biopharmaceutics	Churg Chan	Elsbeth Chikhale
Environmental Analysis	*Refer to the Drug Product Review*	
Laboratory (OTR)	N/A	
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	April 26, 2021	Review by Dr. Soumya Mitra
Type	III	*Several Type III DMFs are listed in the NDA; overall information provided for the container closure system was found acceptable*				

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	129849	Sulopenem etzadroxil/probenecid tablet formulation *IND active since April 1, 2016*

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	Complete	Adequate (*for drug substance and drug product impurity qualification - refer to the Pharm/Tox review*)		Dr. James Wild
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, sulopenem etzadroxil and probenecid tablets. The manufacturing and testing facilities have been found acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on May 4, 2021. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

The review of the labeling was completed by the OPQ team and resulted in several comments and recommendations; however, the labeling has not been finalized by the NDA review team at this time because of the anticipated Complete Response action for this NDA (due to clinical issues).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed drug product, sulopenem etzadroxil and probenecid tablets, is a fixed-dose combination of a thiopenem β-beta-lactam antibacterial drug (sulopenem etzadroxil) and a uricosuric and renal tubular blocking agent (probenecid). Probenecid inhibits the OAT3-mediated excretion of sulopenem, thereby providing increased plasma concentrations of sulopenem.

The drug product is an immediate release, bilayer tablet, containing 500 mg sulopenem etzadroxil and 500 mg probenecid. The intended therapeutic dosing regimen is a twice daily one tablet for 5 days with food.

Proposed Indication(s) including Intended Patient Population	Treatment of uncomplicated urinary tract infections caused by designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone, in adult women (≥ 18 years of age).
Duration of Treatment	Five (5) days
Maximum Daily Dose	1000 mg/1000 mg sulopenem etzadroxil/probenecid (one tablet twice daily)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substances: Adequate

The two drug substances used in the proposed drug product include sulopenem etzadroxil, which is a penem antibacterial prodrug, and probenecid, a renal tubular transport blocking agent.

The CMC information for the sulopenem etzadroxil drug substance, which is considered an NME, has been provided in the NDA. The overall information submitted for the sulopenem etzadroxil drug substance, such as structure elucidation and characterization, a description of the manufacturing process including packaging, a specification, including characterization and controls for impurities in the sulopenem etzadroxil drug substance, stability, etc., was found acceptable. During the NDA review the Applicant withdrew one of the manufacturing sites (b) (4) for which no supporting data was provided in the NDA, and which required a pre-approval inspection. The Applicant (b) (4)

The CMC information for probenecid drug substance was provided via a reference to DMF Type II (b) (4) held by (b) (4) This DMF was previously reviewed and found acceptable in support of other applications and products submitted to CDER. In addition, the recent DMF amendment was also reviewed and found acceptable by the Drug Substance Reviewer of the current NDA.

The retest period of (b) (4) months has been proposed by the Applicant for sulopenem etzadroxil drug substance based on the stability data, including stress testing data, provided in the NDA. For probenecid drug substance, the retest period of (b) (4) months has been proposed in the NDA in accordance with the retest period established by the DMF (b) (4) holder. These respective retest periods were found acceptable by the Drug Substance Reviewer (*for details refer to the Drug Substance Review, below*).

Drug Product: Adequate

The drug product is a pink, oval-shaped, film-coated, an immediate release bilayer tablet, with SULO debossed on one side and plain on the other side. Each tablet contains 500 mg of sulopenem etzadroxil and 500 mg of probenecid. The commercial packaging configurations for the drug product include: (1) 10-count, 40 mL HDPE bottle with 1 g desiccant, induction seal and CR cap, (2) 30-count, 100 mL HDPE bottle with 1 g desiccant, induction seal and CR cap, and, (3) ALU-ALU foil laminate (b) (4) count blister pack (b) (4).

Most of the excipients used in the drug product formulation are compendial and meet USP/NF standards. (b) (4) is not compendial but is comprised of compendial excipients and follows in-house quality standards based on methods provided by the manufacturer. The drug product manufacturing process consists of (b) (4)

The specification includes appropriate for the proposed dosage form quality attributes, such as appearance, identification, assay, related substances, uniformity of dosage form, dissolution, microbial limits, and (b) (4). The results of batch analysis for the drug product representative batches have been found consistent, and the overall drug product specification, including the analytical procedures and acceptance criteria, has been found adequate (refer to the Biopharmaceutics Review and Manufacturing Integrated Assessment, below, regarding the dissolution and microbial limits tests, respectively).

For probenecid, only one crystalline form is known (b) (4) and there is no evidence for polymorphism. However, for sulopenem etzadroxil, there are two known polymorphic forms, (b) (4) in the sulopenem etzadroxil drug substance manufacturing process. In addition, the PXRD patterns of the sulopenem etzadroxil drug substance samples stored under long-term and accelerated conditions demonstrate that the polymorphic form does not change during drug substance storage. Furthermore, the other polymorphic form of sulopenem etzadroxil, (b) (4) is unlikely to be formed in the drug product during manufacturing or on storage. Based on this rationale, the Applicant did not monitor the polymorphism in the drug product batches; the overall information and justification submitted in the original NDA and subsequent amendments provided were found acceptable by the Drug Product Reviewer.

The stability data package provided in the NDA includes 6 months accelerated (40°C/75% RH) and 12 months long term (25°C/60% RH) stability data for three registration drug product batches for each of the (b) (4) packaging configurations. No significant trends have been observed for any of the tests performed in the stability studies, including (b) (4) and assay. All stability results conform with the acceptance criteria set in the proposed drug product specification. Therefore, the proposed 24 months expiration period for the drug product has been granted.

The Applicant is claiming a categorical exclusion from the requirement to prepare an Environmental Assessment based on 21 CFR 25.31(b) and the claim was found acceptable.

The overall information submitted for the drug product in the initial NDA and subsequent amendments was found adequate (*refer to the Drug Product Review for details*).

Labeling: Choose an item.

Several revisions have been recommended in the applicable to the product quality sections of the proposed prescribing information (PI), container labels, and the carton labeling (for details refer to the Labeling Review, below). These labeling recommendations have been communicated to OND Project Manager. However, the labeling review is currently pending and will not likely be finalized by the NDA review team in this review cycle because of the anticipated Complete Response action for this NDA (due to clinical issues).

Manufacturing: Adequate

Process

The drug product manufacturing process involves (b) (4) A number of comments and recommendations regarding the proposed manufacturing process, including in-process controls, were identified and conveyed to the Applicant during the review. After resolution of those issues, the manufacturing process has been found adequate.

Facilities

Eight facilities were listed in the initial 356h Form. Upon initial assessment, most of the facilities listed in the form were found adequate based on previous history. That includes the two manufacturers of the sulopenem etzadroxil drug substance, (b) (4) Also, the manufacturer of the probenecid drug substance, (b) (4) was found acceptable based on previous history.

Pre-Approval Inspection (PAI) was recommended for the drug product manufacturer, (b) (4) and the manufacturer of the drug substance intermediate (b) (4)

The existing manufacturer of [redacted] (b) (4) and the production, testing and release activities will be transferred to [redacted] (b) (4) Since this facility does not have any FDA inspection history, on-site PAI was recommended. However, upon further consideration, the Applicant withdrew this facility from the current NDA via the March 15, 2021 amendment and stated [redacted] (b) (4)

The drug product manufacturer, [redacted] (b) (4) did not have any FDA inspection record on tablet manufacturing and, therefore, it was recommended for inspection. Due to travel restrictions related to the COVID-19 pandemic, a 704(a)(4) based review was conducted for this facility. Based on the review of various documents, including the firm's responses to several FDA information requests, this facility was found adequate to manufacture tablets, the proposed drug product dosage form.

The overall recommendation of "Approve" was for this NDA entered in Panorama on May 4, 2021. *For further details refer to the Manufacturing Integrated Assessment, below*.

Biopharmaceutics: Adequate

The biopharmaceutics review focused on the assessment of the proposed dissolution test (analytical procedure and acceptance criterion), to be used for release and stability testing of the drug product. For the routine quality control testing of sulopenem etzadroxil/probenecid tablets, 500 mg/500 mg, the following dissolution method and acceptance criteria were found to be adequate:

USP Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criteria
II (Paddle)	75 rpm	0.05 M phosphate buffer, pH 6.8	900 mL/ 37.0 ± 0.5 °C	**Sulopenem etzadroxil:** Q= (b) (4) % in 30 minutes **Probenecid:** Q= (b) (4) % in 15 minutes

In addition, bridging of formulations was also part of the biopharmaceutics assessment. The commercial drug product contains a different color film-coat (pink versus white) and debossment that was not present on the pivotal clinical batches. The composition of tablet core, tablet shape, dimensions, and weight have remained identical. The in vitro dissolution studies conducted by the Applicant have demonstrated the similarity between the registration and clinical batches; thus, the bridging between the clinical and the commercial drug product was found adequate. *For additional details refer to the Biopharmaceutics Review, below*.

Microbiology (if applicable): Adequate

The drug product is an oral dosage form; therefore, a separate microbiology review chapter was not created. However, the evaluation of the drug product microbiology controls is included in the Manufacturing Integrated Assessment. The Applicant proposed to exclude monitoring of the microbial limits in the routine drug product testing (both release and stability) based on the release results, available stability data and water activity assessment for the developmental, clinical and registration drug product batches. These data and justification were found adequate by the Process Reviewer (*refer to the Manufacturing Integrated Assessment*, below).

C. Risk Assessment

From Initial Risk Identification			**Assessment**		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	Formulation Raw materials Process parameters Scale/equipment Site	Low	(b) (4)	Acceptable	
Content uniformity	Formulation Raw materials Process parameters Scale/equipment Site	Low		Acceptable	
Physical stability	Formulation Raw materials Process parameters Scale/equipment Site	Medium		Acceptable	

			(b) (4)		
Microbial limits	Formulation Raw materials Process parameters Scale/equipment Site	Low		Acceptable	
Dissolution	Formulation Raw materials Process parameters Scale/equipment Site	Medium		Acceptable	

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

NDA 213972

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	n/a	
Established name(s)	sulopenem etzadroxil and probenecid tablets	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	[TRADENAME] tablets: 500 mg sulopenem etzadroxil and 500 mg probenecid (**Error! Reference source not found.**)	Revised to remove TRADENAME: Tablets: 500 mg of sulopenem etzadroxil and 500 mg of probenecid (**Error! Reference source not found.**)
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.	n/a	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
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)	n/a	No special preparation instructions needed for this oral dosage form

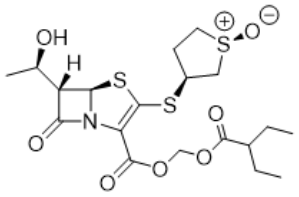
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

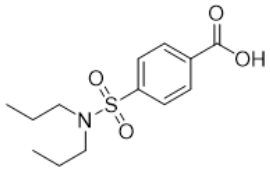
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	500 mg sulopenem etzadroxil and 500 mg probenecid	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	n/a	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	[TRADENAME] tablets are supplied as pink, oval-shaped, film-coated, fixed-dose, bilayer combination tablets debossed with SULO on one side, containing 500 mg of sulopenem etzadroxil and 500 mg of probenecid.	Revise to add "plain on other side" [TRADENAME] tablets are supplied as pink, oval-shaped, film-coated, fixed-dose, bilayer tablets debossed with SULO on one side and plain on other side, containing 500 mg of sulopenem etzadroxil and 500 mg of probenecid.
Assess if the tablet is scored. If product meets guidelines and criteria	n/a	n/a

for a scored tablet, state "functionally scored"		
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	n/a	n/a

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	**[TRADENAME]** (sulopenem etzadroxil and probenecid) tablets	Adequate
Dosage form(s) and route(s) of administration	Tablet for oral use	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	n/a	n/a
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Inactive ingredients are not listed in alphabetical order.	Revised to alphabetize inactive ingredients and separate film coating ingredients. the following inactive ingredients: croscarmellose sodium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The film coating contains carmine, lecithin polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.
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.	n/a	n/a
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Statement of being sterile (if applicable)	n/a	n/a

Pharmacological/ therapeutic class	sulopenem etzadroxil, (b) (4) penem antibacterial drug and probenecid, a (b) (4) renal tubular transport (b) (4)	Adequate
Chemical name, structural formula, molecular weight	The chemical name of sulopenem etzadroxil is 4-Thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-[(1*R*)-1-hydroxyethyl]-7-oxo-3-[[(1*R*,3*S*)-tetrahydro-1-oxido-3-thienyl]thio]-, (2-ethyl-1-oxobutoxy)methyl ester, (5*R*,6*S*)-. See Figure 1 for sulopenem etzadroxil chemical structure and chemical formula. The molecular weight of sulopenem etzadroxil is 477.61 g/mol.  Chemical Formula: $C_{19}H_{27}NO_7S_3$ Figure 1. Sulopenem Etzadroxil Chemical Structure and Formula The chemical name for probenecid is 4-[(dipropylamino) sulfonyl] benzoic acid. See Figure 2 for probenecid chemical structure and chemical formula. The molecular weight of	The chemical name, structures and molecular weight were compared with the USP Dictionary for both active ingredients. Both molecular weights match USP Dictionary file. After evaluating the USAN names in the USP Dictionary for both actives, the following changes were recommended: • Revised probenecid chemical name to match the USP Dictionary's chemical name #2: 4-(Dipropylsulfamoyl)benzoic acid • Revise sulopenem etzadroxil chemical name to match the USP Dictionary's chemical name #2 and structure.

	probenecid is 285.36 g/mol.  Chemical Formula: $C_{13}H_{19}NO_4S$ Figure 2. Probenecid Chemical Structure and Formula	
If radioactive, statement of important nuclear characteristics.	n/a	n/a
Other important chemical or physical properties (such as pKa or pH)	None provided	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	n/a	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	n/a

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	500 mg of sulopenem etzadroxil and 500 mg of probenecid	Adequate

Available units (e.g., bottles of 100 tablets)	Bottles of 30 tablets with child-resistant caps (NDC#####-####-##) Bottles of 10 tablets with child-resistant caps (NDC#####-####-##) (b) (4)	Revise to include desiccant and (b) (4) (b) (4) Bottles of 30 tablets with desiccant and child-resistant caps (NDC number pending) Bottles of 10 tablets with desiccant and child-resistant caps (NDC number pending) (b) (4)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	pink, oval-shaped, film-coated bilayered tablets debossed with SULO on one side.	Revise bilayered to bilayer and add plain on other side: pink, oval-shaped, film-coated bilayer tablets debossed with SULO on one side and plain on other side.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	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.	n/a	n/a

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

Item	Information Provided in the NDA	Assessor's Comments
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.)	n/a	Photostability study suggests the product does not need to be protected from light. In-use stability study demonstrates that at long-term storage conditions (25 ºC/60% RH), the product is stable outside of bottle (in open tray) for up to 3 months.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	Sponsor provided pictures of both the product and desiccant in the cover letter of amendment on 3/5/2021 (b) (4)	Tablet and desiccant differ in shape/size and desiccant has "Do not eat" printed on it
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	[TRADENAME] tablets (b) (4) at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) *[see USP Controlled Room temperature]*.	Language revised slightly to match OPPQ's recommended storage statements: [TRADENAME] tablets (b) (4) 20° to 25°C (68° to 77°F); brief exposure to 15° to 30°C (59° to 86°F) permitted *[see USP*

		Controlled Room Temperature].
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."	n/a	n/a
Include information about child-resistant packaging	Bottles of 30 tablets with child-resistant caps (NDC#####-####-##) Bottles of 10 tablets with child-resistant caps (NDC#####-####-##) (b) (4)	Bottles- adequate (b) (4)

1.2.5 Other Sections of Labeling

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Iterum Therapeutics US Limited, Chicago, IL 60606	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):
None provided

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

[redacted]

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Tradename (sulopenem etzadroxil and probenecid)	Per USP <1121>, the established nonproprietary name of the drug product should include the dosage form, i.e., [DRUG] [DOSAGE FORM]. Therefore, we recommend revising the drug name on both the container label and carton labeling using one of the following approaches. The established name can appear on the same line following the proprietary name, to read: Tradename (sulopenem etzadroxil and probenecid) tablets Or, the established name can appear on a separate line, to read: Tradename (sulopenem etzadroxil and probenecid) tablets
Dosage strength	500 mg/500 mg	Adequate
Route of administration	(b) (4)	(b) (4) Applicant could add "For oral use only" to another part of the label, although not necessary
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	n/a	n/a
Net contents (e.g. tablet count)	10 or 30 tablets	Adequate

“Rx only” displayed on the principal display	Rx Only on container and carton labels	Adequate
NDC number	NDC number not provided	Validation and verification of NDC #s is covered by the Office of Unapproved Drugs and Labeling Compliance. Labels should state “NDC number pending” and comment to be sent to applicant with language from Office of Unapproved Drugs and Labeling Compliance regarding the verification of NDC number with separate submission.
Lot number and expiration date	Lot and expiration date on each container and carton	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at controlled room temperature 20°C -25°C (68°F-77°F). (b) (4)	Per OPPQ’s latest recommendations, revise to: Store at 20°C -25°C (68°F-77°F), see insert. (b) (4)
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	n/a	n/a

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	n/a	n/a
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Bar code	Present	DMEPA comments regarding barcode position were sent to sponsor.

Item	Information Provided in the NDA	Assessor’s Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Iterum Therapeutics US Limited, Chicago, IL 60606	Adequate
Medication Guide (if applicable)	n/a	n/a
No text on Ferrule and Cap overseal	Yes	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	n/a
And others, if space is available	n/a	n/a

Assessment of Carton and Container Labeling: *Adequate, pending recommended revisions from applicant*

The bottle and carton labels will comply with all regulatory requirements from a CMC perspective once the recommended edits have been included.

Overall Assessment and Recommendation: Adequate

Recommendations from the product quality perspective have been conveyed to OND for incorporation as labeling is finalized.

Primary Drug Product Assessor Name and Date:
Molly Lee, Ph.D., Branch 2, ONDP Division of New Drug Products I, 5/27/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Thomas Oliver, Ph.D., ONDP Division of New Drug Products I, 5/27/2021

Molly Lee

Digitally signed by Molly Lee
Date: 5/27/2021 03:16:32PM
GUID: 5e2b04c70029e7c7580982b0a5cb16be

Thomas Oliver

Digitally signed by Thomas Oliver
Date: 5/27/2021 03:20:16PM
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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	213972
Product Information	Fixed-Dose combination (FDC) Immediate-Release Oral Tablet
Assessment Cycle Number	1
Drug Product Name/ Strength	Sulopenem etzadroxil/Probenecid Tablet; 500 mg/500 mg
Route of Administration	Oral
Applicant Name	Iterum Therapeutics US Ltd
Therapeutic Classification/ OND Division	DAI
LD Number	Benemid (probenecid) Tablets [NDA 007898]
Proposed Indication	Uncomplicated urinary tract infections (uUTI)

Assessment Recommendation: **Adequate**

Background:
Iterum Therapeutics US Ltd is seeking approval under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Sulopenem etzadroxil/Probenecid Tablets, 500 mg/500 mg, for the treatment of uncomplicated urinary tract infections. Sulopenem etzadroxil is a new molecular entity (NME) and is a prodrug that is rapidly cleaved in the intestinal wall to release the active parent compound, sulopenem, which is a thiopenem beta-lactam antibacterial drug. Probenecid is a uricosuric and renal tubular blocking agent, which is co-administered with sulopenem etzadroxil to reduce renal clearance and increase systemic exposure of sulopenem. (b) (4) [1]

This NDA relies on the findings of safety and efficacy of the listed drug (LD), Benemid (probenecid) Tablets (NDA 007898), to reduce renal clearance and increase systemic exposure of beta-lactam antibiotics. Comparative probenecid pharmacokinetic data provide a bridge between the proposed drug product and the LD.[2] The Applicant conducted a single phase 3 uUTI trial evaluating the superiority of sulopenem etzadroxil/probenecid to ciprofloxacin in patients with infections due to a quinolone resistant organism.

Bridging:
The commercial drug product contains a different color film-coat (pink vs. white) and debossment that was not present on the pivotal clinical batches. The composition of tablet core, tablet shape, dimensions, and weight have remained identical. The Applicant conducted *in vitro* dissolution studies to demonstrate the similarity between the registration and clinical batches.

[1] \\CDSESUB1\evsprod\nda213972\0000\m2\22-intro\ctd-summaries-intro.pdf
[2] \\CDSESUB1\evsprod\nda213972\0000\m2\27-clin-sum\summary-biopharm.pdf

Assessment Summary:
For the routine quality control testing of Sulopenem etzadroxil/Probenecid Tablets, 500 mg/500 mg, at batch release and during shelf-life, the following dissolution method and acceptance criterion were found to be adequate.

USP Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criteria
II (Paddle)	75 rpm	0.05 M phosphate buffer, pH 6.8	900 mL/ 37.0 ± 0.5 °C	**Sulopenem etzadroxil:** Q (b) (4) % in 30 minutes **Probenecid:** Q (b) (4) % in 15 minutes

Overall Review Recommendation:
From a Biopharmaceutics perspective, **NDA 213972** for Sulopenem etzadroxil/Probenecid Tablets, 500 mg/500 mg is **adequate** and recommended for **approval**.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
SDN-1 (Original NDA Submission)	11/25/2020
SDN-20 (Response to Information Request)	3/5/2021
SDN-31 (Response to Information Request)	4/12/2021

Highlight Key Issues from Last Cycle and Their Resolution:

- N/A, this is the first review cycle

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

- None

B.1 BCS DESIGNATION

Assessment:
The Applicant did not request a BCS designation for the proposed drug product. Sulopenem etzadroxil exhibits solubility and permeability characteristics consistent with BCS Class IV drugs, and probenecid is consistent with BCS Class II.

Solubility:
Per BCS criteria, sulopenem etzadroxil and probenecid are considered to have low solubility (Table 1) given that the calculated dose solubility volume is greater than 250 mL.[3,4]

Table 1. Solubility of sulopenem etzadroxil and probenecid in aqueous buffers at 37 °C

pH	Solubility (mg/mL)	
	Sulopenem etzadroxil	Probenecid
1.2	1.49	0.06
3.4	1.90	
4.4	1.81	
4.7		0.15
5.4	1.57	
6.8	1.31	4.08

Permeability:[5]
The Applicant studied the permeability of sulopenem and sulopenem etzadroxil with and without probenecid across Caco-2 cell monolayers. Sulopenem and its prodrug were found to be low permeability compounds with P_{app} values < 1 x 10^{-6} cm/s in the A-B and B-A directions. Efflux ratios were < 2, indicating absence of involvement of apical efflux transporters. Probenecid did not affect sulopenem or sulopenem etzadroxil permeability or efflux ratio.

Dissolution:
The formulation of the proposed drug product is designed to be an immediate-release drug product.

B.2 DISSOLUTION METHOD

Assessment: *Adequate*
The dissolution method for Sulopenem etzadroxil/Probenecid Tablets, 500 mg/500 mg, uses USP Apparatus 2 (Paddle) at 75 RPM in 900 mL of 0.05 M phosphate buffer, pH 6.8 at 37 ± 0.5 °C. The selected dissolution method parameters were identified based on dissolution method development studies, as summarized in the Dissolution Method Development Report (Module 3.2.P.2).[6]

[3] \\CDSESUB1\evsprod\nda213972\0000\m3\32-body-data\32s-drug-sub\sulopenem-etzadroxil-all\32s1-gen-info\general-properties.pdf
[4] \\CDSESUB1\evsprod\nda213972\0000\m3\32-body-data\32p-drug-prod\sulopenem-etza-probenecid-tablet-all\32p2-pharm-dev\pharmaceutical-development-substance-probencid.pdf
[5] \\CDSESUB1\evsprod\nda213972\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5323-stud-other-human-biomat\xenogesis-report-4\xenogesis-report-4.pdf
[6] \\CDSESUB1\evsprod\nda213972\0000\m3\32-body-data\32p-drug-prod\sulopenem-etza-probenecid-tablet-all\32p2-pharm-dev\dissolution-report-rep2019005.pdf

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Discriminating ability of the dissolution method

The dissolution method was tested for its discriminating ability with respect to changes in critical material attributes (particle size), critical process parameters ((b) (4)), and critical formulation variables ((b) (4)).

A batch of sulopenem etzadroxil drug substance was produced with a larger range of PSD (D_{90} =(b) (4)µm, lot 088#150) compared to the target PSD (D_{90} = (b) (4)µm, lot 088#146). The dissolution profiles demonstrate no impact from varying the sulopenem etzadroxil PSD. Batches of probenecid drug substance that cover the upper and lower PSD (D_{90} range (b) (4) µm) also showed no influence on drug product dissolution (Figure 4). Therefore, the proposed dissolution method is unable to discriminate against the studied changes in PSD.

Figure 3. Dissolution profile from drug product containing sulopenem etzadroxil with different PSD (N=12)

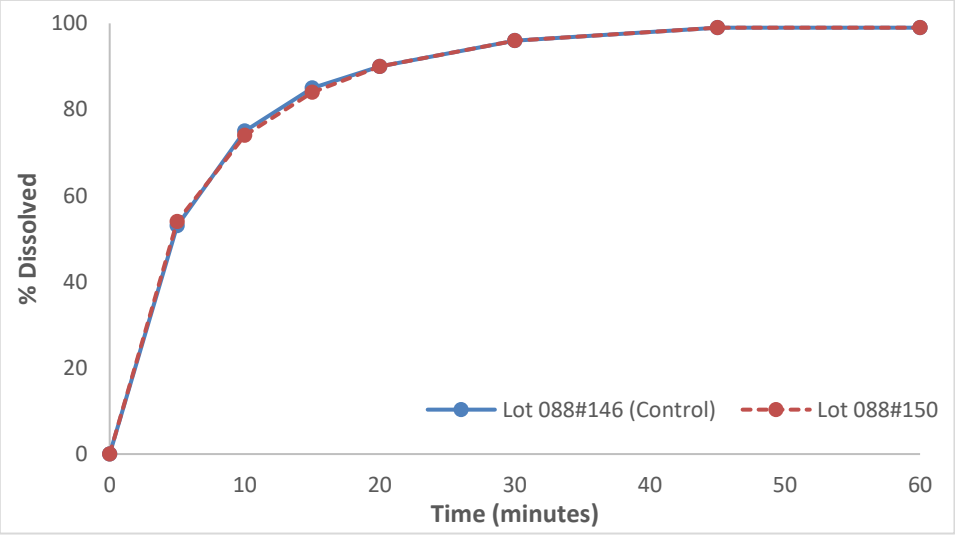
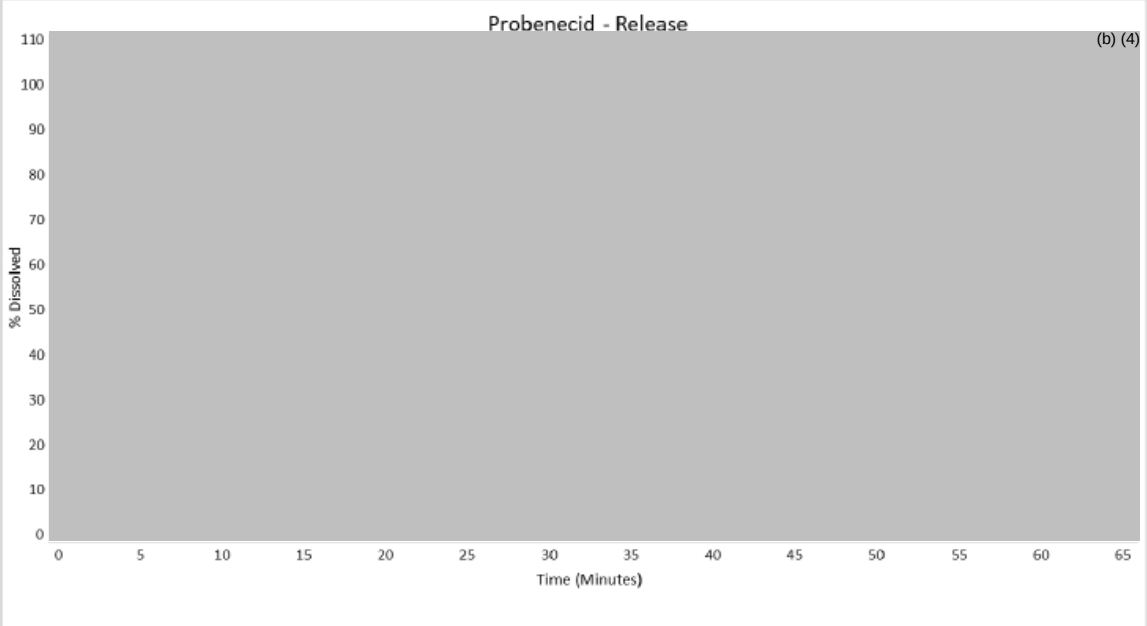


Figure 4. Dissolution profiles of drug product containing probenecid with a range of PSD



Dissolution profiles of batches manufactured with higher tablet total (b) (4) (lot 088#146 T1D) and removal of (b) (4) from either the sulopenem etzadroxil (b) (4) (lot 088#146 T3) or probenecid (b) (4) (lot 088#146 T5) were compared to a control batch (lot 088#146 T5) (Table 4). Figure 5Figure 6 demonstrate that the proposed dissolution method can discriminate between batches that were not manufactured according to standard process for all three of the assessed parameter changes.

Table 4. Process and/or formulation component changes manufactured for discriminating ability studies

Component change	088#146 T1A (target)	088#146 T1D	088#146 T3	088#146 T5
(b) (4)				
Similarity factors (f2) Sulopenem etzadroxil, probenecid	--	37, 33	8, 49	79, 3

Figure 5. Sulopenem etzadroxil Dissolution Discrimination Study (N=12)

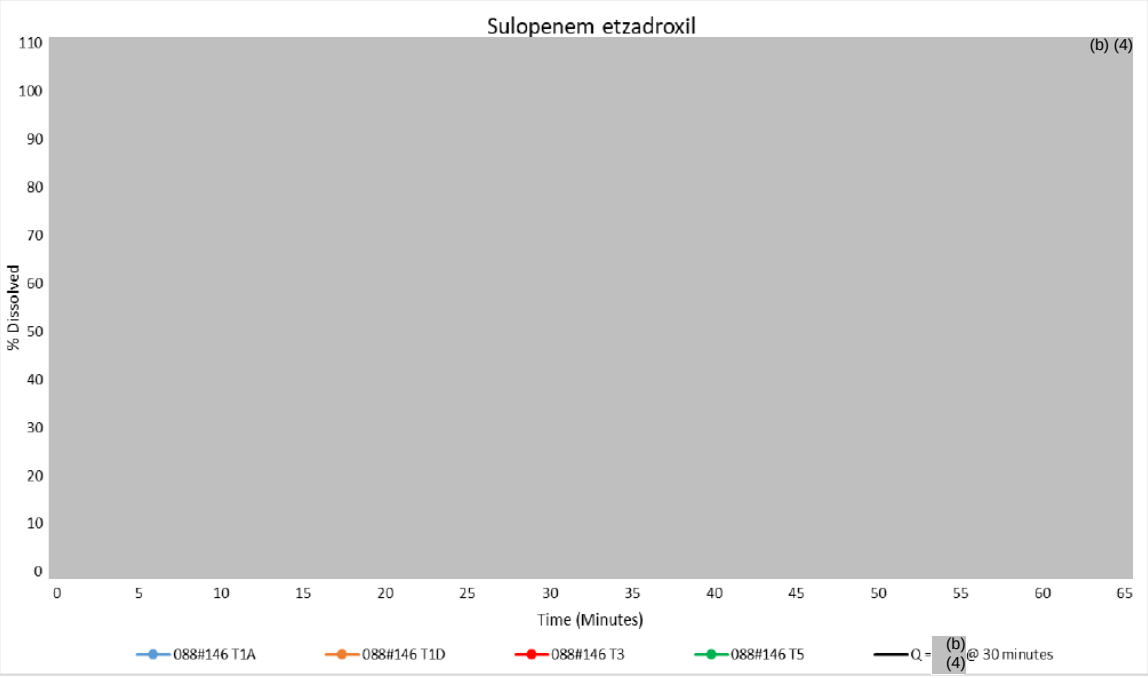
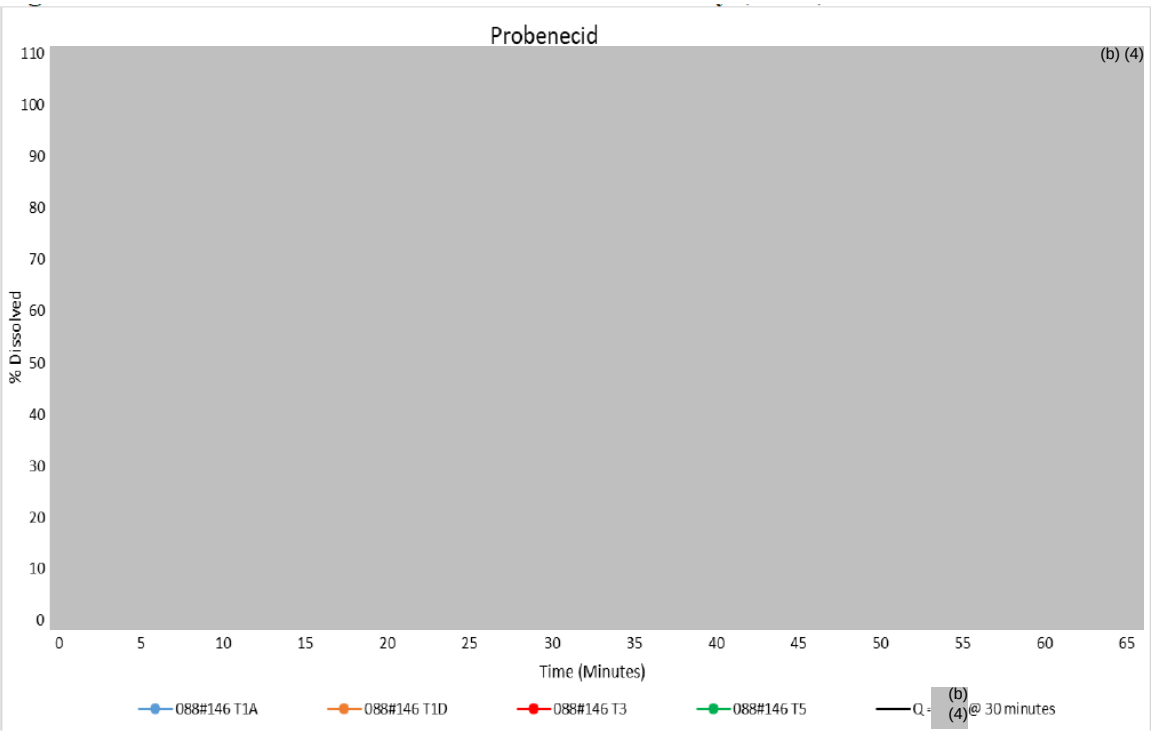


Figure 6. Probenecid Dissolution Discrimination Study (N=12)



Reviewer's Assessment

Given the incomplete dissolution observed with a paddle speed of (b) (4) rpm and rapid dissolution (≥ 85% in 30 minutes) observed with a paddle speed of 75 rpm for sulopenem etzadroxil, the Applicant was recommended via an Information Request dated February 22, 2021 to investigate whether an intermediate paddle speed of 60 or 65 rpm is more suitable for the dissolution method of their proposed drug product.

In a Response dated March 5, 2021, the Applicant responded with dissolution data for sulopenem etzadroxil and probenecid from batch F2000728 0001 D9 (23 months old; stored at 25 °C/60% RH) using a slower paddle speed of 60 rpm and 65 rpm (Figures Figure 7Figure 8).[7] The data show that 60 rpm result in incomplete drug release of sulopenem etzadroxil at 60 minutes (mean 87%); 65 rpm results in borderline incomplete drug release of sulopenem etzadroxil at 60 minutes (mean 90%). Therefore, the originally proposed dissolution method [USP Apparatus II (Paddle) at 75 rpm in 900 mL of 0.05 M phosphate buffer, pH 6.8] is found acceptable for quality control testing of the proposed drug product.

[7] \\CDSESUB1\evsprod\nda213972\0019\m1\us\fda-ir-questions-and-responses-biopharm-and-drug-product.pdf

Figure 7. Sulopenem etzadroxil Dissolution Data of batch F2000728 0001 D9 using USP Apparatus II at 60 vs. 65 RPM in 900 mL of 0.05 M phosphate buffer, pH 6.8

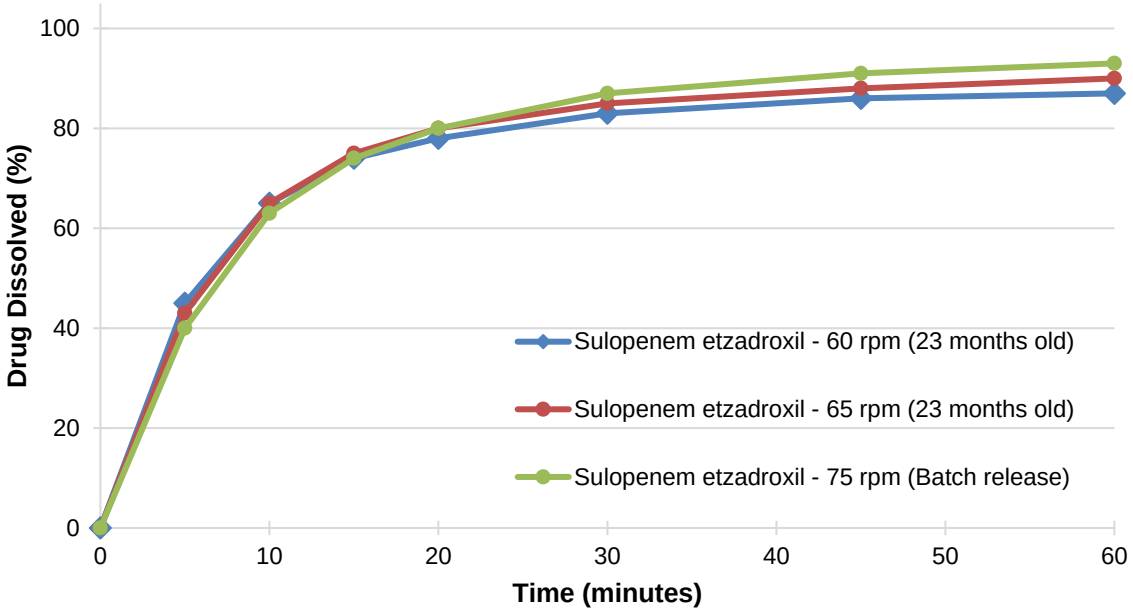
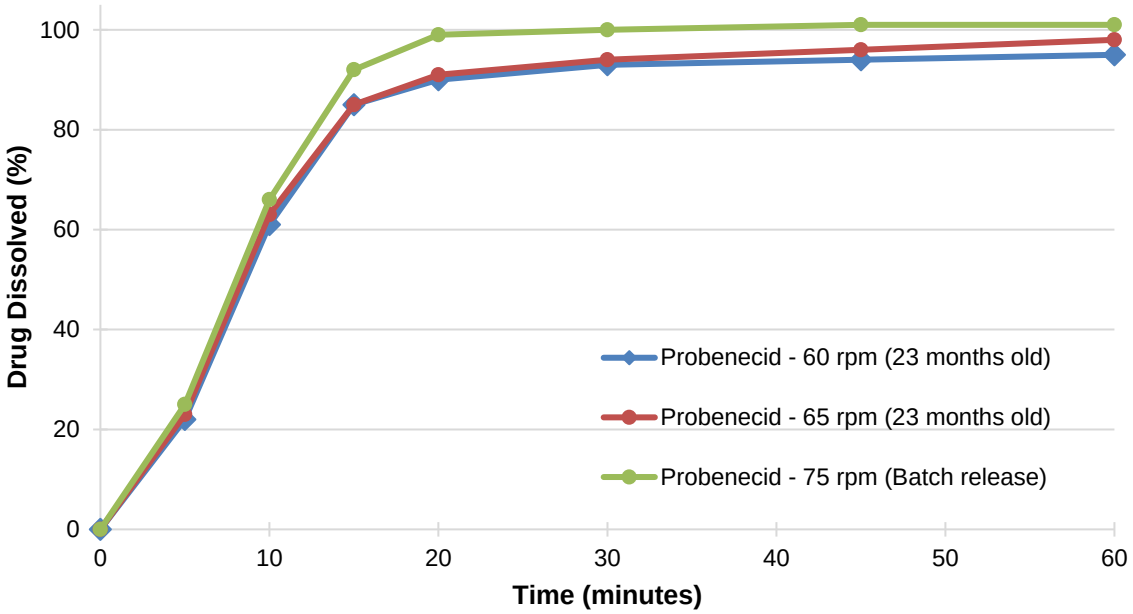


Figure 8. Probenecid Dissolution Data of batch F2000728 0001 D9 using USP Apparatus II at 60 vs. 65 RPM in 900 mL of 0.05 M phosphate buffer, pH 6.8



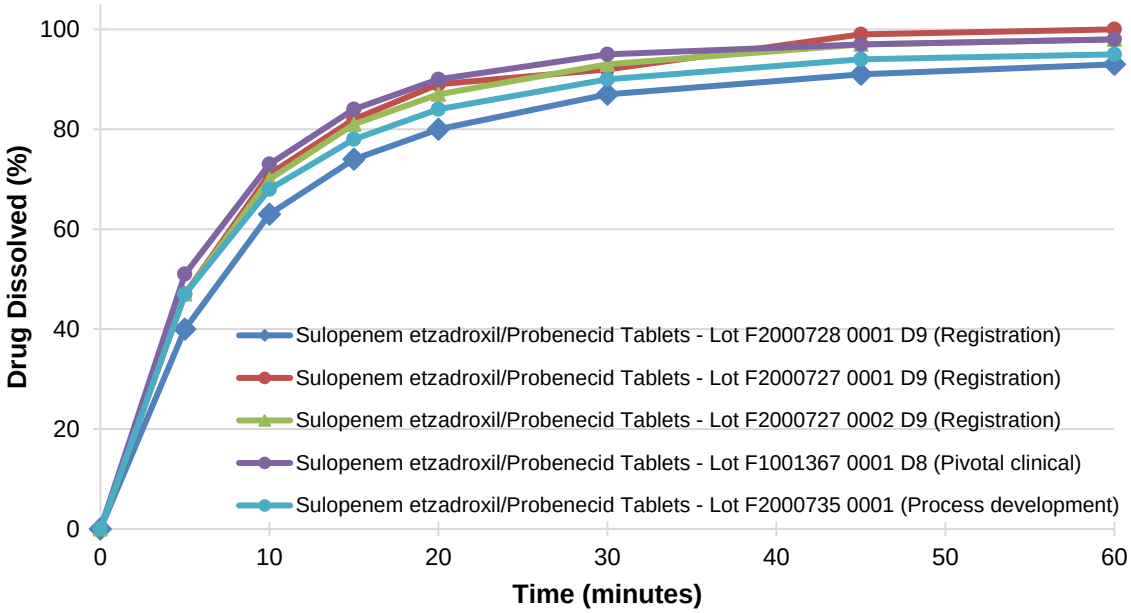
B.3 DISSOLUTION ACCEPTANCE CRITERIA

Assessment: *Adequate*

Based on the dissolution data shown in Figure 9 Figure 10 below, (b) (4) (b) (4) (b) (4) Based on the provided dissolution data of the registration batches, the dissolution acceptance criteria of "Q (b) (4)% of sulopenem etzadroxil in 30 minutes" and "Q (b) (4)% of probenecid in 15 minutes" was recommended via an Information Request dated April 6, 2021. In a Response dated April 12, 2021, the Applicant updated their drug product specifications to implement the recommended dissolution acceptance criteria of "Q (b) (4)% of sulopenem etzadroxil in 30 minutes" and "Q (b) (4)% of probenecid in 15 minutes."[8]

Dissolution Data[9]

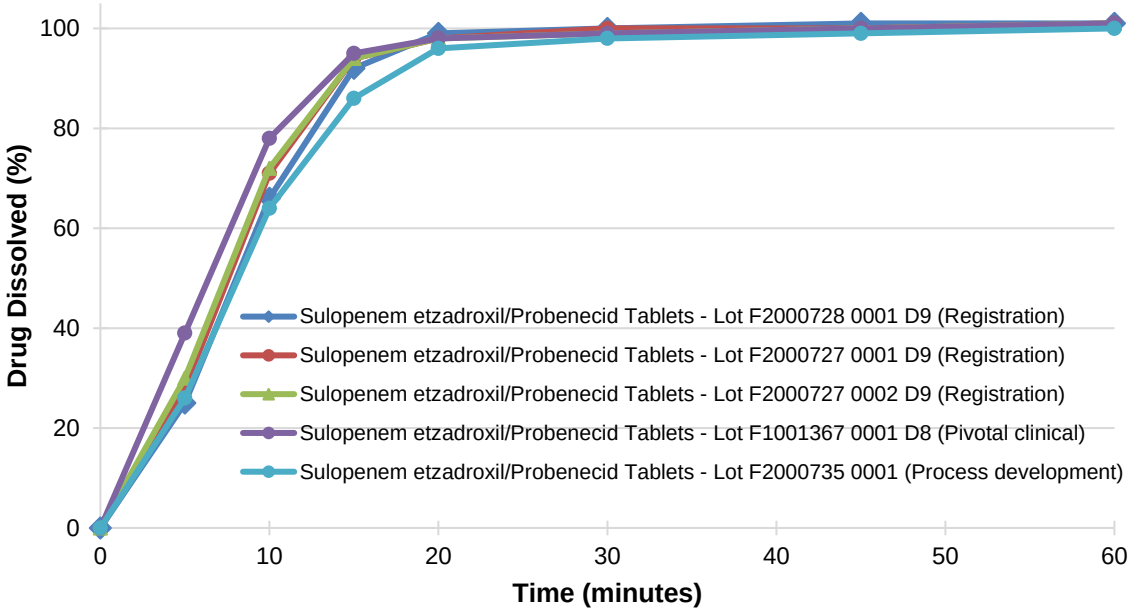
Figure 9. Summary of mean *in vitro* dissolution data for Sulopenem etzadroxil (n=12) using proposed dissolution method



[8] \\CDSESUB1\evsprod\nda213972\0030\m3\32-body-data\32p-drug-prod\sulopenem-etza-probenecid-tablet-all\32p5-contr-drug-prod\32p51-spec\3-2-p-5-1-specifications-clean.pdf

[9] \\CDSESUB1\evsprod\nda213972\0000\m3\32-body-data\32p-drug-prod\sulopenem-etza-probenecid-tablet-all\32p2-pharm-dev\rep-2019-005-dissolution-release-data.xpt

Figure 10. Summary of mean *in vitro* dissolution data for Probenecid (n=12) using proposed dissolution method



B.4 STABILITY

The Applicant conducted dissolution stability studies on the registration batches in long term stability (25°C/60% RH), intermediate stability (30°C/75% RH), and accelerated stability (40°C/75% RH). No significant changes in dissolution of sulopenem etzadroxil and probenecid at 30 minutes during stability testing in accelerated conditions up to 6 months, and intermediate and long-term conditions up to 12 months were observed.[10] Although the stability data currently provided for probenecid does not include the 15-minute timepoint, the dissolution data of Batch F2000728 0001 D9 at 23 months old using USP Apparatus II (Paddle) at 65 rpm in 900 mL of 0.05 M phosphate buffer passed Stage 3 testing using the recommended dissolution acceptance criterion of "Q (b) (4) % of probenecid in 15 minutes." Therefore, the other registration batches at 23-months are expected to meet Stage 2 testing when using the accepted dissolution method with a higher paddle speed of 75 rpm.

B.5 BRIDGING

Assessment: *Adequate*

The to-be-marketed drug product is not the same product as the drug product used in the pivotal clinical studies. The commercial drug product contains a different color film-coat (pink vs. white) and includes a debossment. The tablet core composition of the pivotal clinical batch and the to-be-marketed product

[10] \\CDSESUB1\evsprod\nda213972\0000\m3\32-body-data\32p-drug-prod\sulopenem-etza-probenecid-tablet-all\32p8-stab\stability-data.pdf

are the same. The Applicant submitted comparative dissolution data to demonstrate the similarity between the pivotal clinical batch (F1001367 0001 D8, white film-coat with no debossment), process development batch (F2000735 0001, pink film-coat with debossment), and registration batches (F2000728 0001 D9, F2000727 0001 D9, and F2000727 002 D9) which have white color coating with 'SULO' debossment on one side (Figure 9Figure 10). This Reviewer calculated the similarity factors for sulopenem etzadroxil between the dissolution profiles of the pivotal clinical batch and the three registration batches (f_2 = 50.22, 78.49, 73.25) and between the process development batch and the pivotal clinical batch (f_2 = 63.59), indicating that the dissolution profiles are similar (f_2 > 50). Because probenecid releases > 85% at 15 minutes, f_2 calculations are not needed and the dissolution profiles may be considered similar. Therefore, the provided comparative dissolution data support the change in color and debossment.

B.5 BIOWAIVER REQUEST

Assessment: *Not Applicable*

A biowaiver is not included nor required.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

BIOPHARMACEUTICS LIST OF INFORMATION REQUESTS

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