# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 213972Orig1s000

# OTHER REVIEW(S)

# Clinical Inspection Summary (CIS)

| | |
|---|---|
| Date | 10/07/2024 |
| From | John Lee, M.D., Primary Reviewer<br>Good Clinical Practice Assessment Branch<br>Division of Clinical Compliance Evaluation<br>Office of Scientific Investigations |
| To | Angela Kopack, M.D., Medical Officer<br>Ramya Gopinath, M.D., Team Leader<br>Sheel Shah, Regulatory Project Manager<br>Division of Anti-Infectives, Office of Infectious Disease |
| NDA / BLA | NDA 213972 |
| Applicant | Iterum Therapeutics, Inc. |
| Drug | Sulopenem etzadroxil/probenecid (Orlynvah®) |
| NME or Original NDA | Yes |
| Proposed Indication | Treatment of uncomplicated urinary tract infection in women |
| Consult Date | 5/22/2024 |
| CIS Goal Date | 10/07/2024 |
| Review Clock | Priority review |
| Action Goal Date | 10/25/2024 |
| PDUFA Due Date | 10/25/2024 |

# I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigators (CIs) were inspected for Study IT001-310 in support of this original (resubmission) NDA review: (1) Dr. Peyman Banooni (Los Angeles, CA); (2) Dr. Jodi L. Sanson (Hot Springs, AK); and (3) Dr. Moises A. Issa (Hollywood, FL).

Based on the inspectional findings, the data from the inspected CI sites appear to be acceptable in support of the proposed indication for using sulopenem etzadroxil/probenecid (Orlynvah®), for the treatment of uncomplicated urinary tract infection (uUTI). The primary and the key secondary efficacy endpoint data were verifiable (clinical and microbiologic outcome on treatment Day 12). No significant underreporting of adverse events (AEs) was observed.

For Drs. Banooni and Sanson, the study appears to have been conducted in compliance with good clinical practice (GCP) principles and regulations. For Dr. Issa, adequate contraception history and negative pregnancy testing were not consistently documented in as many as one-third of the women enrolled. The clinical and regulatory implications of this apparently systemic and potentially serious GCP deficiency appear to be limited to subject welfare and unlikely to be important to the study data (discussed further in Section III, INSPECTION RESULTS).

# II. BACKGROUND

This NDA from Iterum Therapeutics, Inc. (as amended in this resubmission) supports the marketing approval of sulopenem etzadroxil in combination with probenecid for the treatment of uUTI. According to the review division (DAI), the original application (November 2020) was inadequate to support the then-proposed uses for complicated urinary tract and intra-abdominal infections. This NDA resubmission presents the findings of a new study, IT001-310, in support of the currently proposed use limited to uUTI.

Study IT001-301 was audited on-site at GCP inspections of three CIs. The following study synopsis highlights the major study features examined for GCP compliance at the three pre-approval surveillance inspections; no GCP-related review concerns were identified at NDA review.

IT001-310: *A prospective, Phase 3, randomized, multi-center, double-blind study of the efficacy, tolerability, and safety of oral sulopenem etzadroxil/probenecid versus oral amoxicillin/clavulanate for treatment of uncomplicated urinary tract infections (uUTI) in adult women*

This double-blind randomized controlled trial was conducted over 13 months (October 2022 – November 2023) in 2222 subjects with uUTI randomized at 139 CI sites in the United States. The primary study objective was to compare the overall treatment response (combined clinical and microbiologic) at the test-of-cure (TOC) visit on treatment Day 12 of oral sulopenem etzadroxil + probenecid, relative to that of oral amoxicillin + clavulanate in treating women with uUTI.

*Major Subject Inclusion Criteria*

- Women (age > 18 years) with uUTI signs/symptoms for > 24 and < 96 hours, including two of: (1) urinary frequency, (2) urinary urgency, (3) pain on micturition, or (4) suprapubic pain

- Mid-stream urine: (1) dipstick-positive for nitrite AND leukocyte esterase; OR (2) indicative of pyuria, by: (a) dipstick for leukocyte esterase, or (b) urine microscopy showing > 10 white blood cells per mm3 (unspun urine) or per high-power field in the spun sediment

*Major Subject Exclusion Criteria*

- Pyelonephritis; antibacterial therapy potentially effective for uUTI within 7 days; non-study intervention that complicate uUTI evaluation, including analgesics
- Anatomically abnormal urinary tract, including surgical modification or obstruction (e.g., kidney stones, tumor); history of trauma to pelvis or urinary tract
- On-going urinary retention or neurogenic bladder; residence at a long-term care facility; instrumentation of the urinary tract within 30 days; in-dwelling urinary catheter, ureteral stent, or other foreign body in the urinary tract
- Recent urine culture positive for > two organisms; dialysis/renal transplant; neutropenia < 1000/$mm^3$; alanine/aspartate aminotransferase > 3x normal, total bilirubin > 2x normal
- Malignancy requiring chemotherapy, radiation, or immune therapy within 6 weeks; HIV; corticosteroid therapy equivalent to prednisolone > 40 mg/day for > 5 days within 30 days
- Child-bearing potential without adequate contraception, positive pregnancy test within 24 hours, pregnant, or currently nursing
- Poorly controlled diabetes mellitus (ketoacidosis or hyperosmolar hyperglycemia); history of seizures, currently on valproate; blood dyscrasias; urate kidney stones, acute gout
- Hypersensitivity to carbapenems, β-lactam antibiotics, probenecid, or to any excipient in their formulations; use of any non-study investigational medication within 30 days; prior participation in any sulopenem clinical study

*Randomization, Blinding, and Treatment Regimen*

- Randomization 1:1, oral twice daily for 5 days: (1) bilayer tablet, sulopenem etzadroxil 500 mg + probenecid 500 mg; or (2) capsule, amoxicillin 875 mg + clavulanate 125 mg
- Sulopenem etzadroxil/probenecid: one bilayer tablet, along with one dummy (placebo) capsule for the active control (amoxicillin/clavulanate)
- Amoxicillin/clavulanate: one encapsulated tablet, along with one dummy (placebo) tablet for the investigational medication (sulopenem etzadroxil/probenecid)

*Adjunctive Systemic Antibiotics (Rescue Therapy)*

Adjunctive systemic antibiotics were generally not permitted; any rescue therapy was considered treatment failure, except for the use of (per CI judgment):

- Clostridioides difficile infection: metronidazole, vancomycin, or fidaxomicin
- Treatment-resistant gram-positive co-infection: narrow spectrum coverage

Subjects could continue in study for: (1) worsening uUTI, special evaluation at an unscheduled visit; and (2) microbiologic testing suggestive of treatment resistance

*Major Endpoints*

Routine evaluation for efficacy and safety (visits): at baseline, and on treatment Days 5, 12, and 28 (or at premature discontinuation)

- Primary endpoint: TOC on Day 12, clinical AND microbiologic
  - TOC outcomes: success, failure, or indeterminate
  - Clinical: urinary frequency/urgency, pain/burning on micturition, suprapubic pain
  - Microbiologic: quantitative culture results and sensitivity
- Key secondary endpoint: TOC on Day 12
  - Clinical: success, failure, or indeterminate
  - Microbiologic: eradication, persistence, or indeterminate
- Safety Assessment
  - AE monitoring at every visit: active questioning including interim clinical history
  - Targeted physical exam per CI discretion at each visit
  - Laboratory tests at baseline, Day 12, and/or premature discontinuation

## III. INSPECTION RESULTS

1. Jodi L. Sanson, M.D.

Healthstar Research, LLC
661 Airport Road, Suite D
HOT SPRINGS, AK 71913

Inspection Dates: 8/20 – 21, 2024

Protocol IT001-310, Site 129: 27 subjects were screened, all 27 were enrolled, and all 27 completed the study. The study conduct at this CI site was audited for adherence to the study protocol, institutional review board (IRB) oversight, site monitoring, staff training, study medication disposition, and CI financial disclosure.

Subject case records were reviewed for all subjects, including detailed review for 15 subjects. The major study data were verified against source records for all enrolled subjects, to include treatment assignment, major efficacy endpoints, AEs, PDs, and use of non-study rescue antibiotics or other concomitant medications.

No significant GCP deficiencies or regulatory deviations were observed. Informed consent forms (ICFs) were signed for all subjects. The study records showed complete financial disclosure, adequate AE and PD reporting, and acceptable drug accountability. The primary and the key secondary efficacy and safety endpoint data were verifiable.

2. Peyman Banooni, M.D.

Matrix Clinical Research
1919 West 7th Street
LOS ANGELES, CA 90057

Inspection Dates: 7/29/2024 - 8/1/2024

Protocol IT001-310, Site 115: 41 subjects were screened, 38 were enrolled, and 35 completed the study. The study conduct at this CI site was audited for adherence to the study protocol, IRB oversight, site monitoring, staff training, study medication disposition, and CI financial disclosure.

Subject case records were reviewed for all enrolled subjects. The major study data were verified against source records for all enrolled subjects, to include treatment assignment, major efficacy endpoints, AEs, PDs, and use of non-study rescue antibiotics or other concomitant medications.

The observed GCP deficiencies were minor and isolated (typically recordkeeping), of which the most significant example appeared to be not having performed pregnancy testing in one subject because the testing was deemed unnecessary due to the history of a recent miscarriage (potential clinical outcomes and risks discussed).

Significant GCP deficiencies were otherwise not observed. ICFs were signed for all subjects. The study records showed complete financial disclosure, adequate AE and PD reporting, and acceptable drug accountability. The primary and the key secondary efficacy and safety endpoint data were verifiable.

3. Moises A. Issa, M.D.

Zenith Clinical Research
7050 Taft Street
HOLLYWOOD, FL 33024

Inspection Dates: 7/29/2024 – 8/2/2024.

Protocol IT001-310, Site 251: 81 subjects were screened, 77 were enrolled, and 63 completed the study. The study conduct at this CI site was audited for adherence to the study protocol, IRB oversight, site monitoring, staff training, study medication disposition, and CI financial disclosure.

Subject case records were reviewed for all subjects, including detailed review for 31 subjects. The major study data were verified against source records for all enrolled subjects, to include treatment assignment, major efficacy endpoints, AEs, PDs, and use of non-study rescue antibiotics or other concomitant medications.

The inspection was noteworthy for documentation of subject selection that appeared to be NOT adequately rigorous, typically for Exclusion Criterion 15 (pregnancy potential). Adequate contraception history and negative pregnancy testing were not consistently documented in as many as one-third (26/77) of the women enrolled.

GCP deficiencies important to study data quality were not observed. ICFs were signed for all subjects. The study records showed complete financial disclosure, adequate AE and PD reporting, and acceptable drug accountability. The major efficacy and safety endpoint data were verifiable.

*Reviewer's Comment: Specifically, the following GCP deficiencies were observed. All observations appear unlikely to have any impact on the efficacy or safety of the study results.*

- *Inclusion Criteria 3 (leukocyte esterase): Six subjects were enrolled based on positive leukocyte esterase urine dipstick testing (LE-UDT) not further specified as 4+ positive (large) LE-UDT.*
- *Exclusion Criteria 15 (pregnancy potential): For all subjects, a negative urine pregnancy test result was obtained, and a screening interview was conducted to verbally confirm (and document) adequate contraception during study participation, but: (1) pregnancy testing was not always obtained within the protocol-specified timeframe, and (2) the specific method of on-going contraception was often not recorded. All subjects were contacted as needed to retroactively obtain and record the missing information about the specific contraception method. No subject became pregnant during the study.*
- *Exclusion 13 (neutropenia): One subject was enrolled with an absolute neutrophil count (ANC) of 0.99 x $10^3$/uL, just under (at) the protocol-specified minimum of 1.0 x $10^3$/uL. Repeat testing (Day 12) confirmed an ANC well above the protocol-specified minimum.*

*{See appended electronic signature page}*

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE:

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Phillip Kronstein, M.D., Team Leader
Good Clinical Practice Assessment Branch
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Jenn Sellers, M.D., Ph.D., Branch Chief
Good Clinical Practice Assessment Branch
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CC:

DAI / Team Leader / Ramya Gopinath
DAI / Medical Officer / Angela Kopack
DAI / Project Manager / Shah Sheel

OSI / Office Director / David Burrow
OSI / Office Deputy Director / Laurie Muldowney
OSI / DCCE / Division Director / Kassa Ayalew
OSI / DCCE / GCPAB / Branch Chief / Jenn Sellers
OSI / DCCE / GCPAB / Team Leader / Phillip Kronstein
OSI / DCCE / GCPAB / Clinical Analyst / John Lee
OSI / DCCE / GCPAB Program Analyst / Yolanda Patague
OSI / DCCE / GCPAB Program Analyst / Loreto-Corazon Lim

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

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

# Memorandum

**Date:** September 25, 2024

**To:** Sheel Shah, Regulatory Project Manager
Division of Anti-Infectives (DAI)

Abimbola Adebowale, Associate Director for Labeling, DAI

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

**CC:** Sam Skariah, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for ORLYNVAH™ (sulopenem etzadroxil and probenecid) tablets, for oral use

**NDA**: 213972

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**Background:**
In response to DAI's consult request dated September 09, 2024, OPDP has reviewed the proposed Prescribing Information (PI), and carton and container labeling for the original NDA submission for ORLYNVAH™ (sulopenem etzadroxil and probenecid) tablets, for oral use.

**PI:**
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on September 20, 2024, and our comments are provided below.

**Carton and Container Labeling**:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on April 25, 2024, and we do not have any comments at this time.

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

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LABEL AND LABELING REVIEW

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

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

| | |
|---|---|
| Date of This Review: | July 31, 2024 |
| Requesting Office or Division: | Division of Anti-Infectives (DAI) |
| Application Type and Number: | NDA 213972 |
| Product Name, Dosage Form, and Strength: | Orlynvah (sulopenem etzadroxil and probenecid) Tablets, 500 mg/500 mg |
| Product Type: | Multiple Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant Name: | Iterum Therapeutics US Limited (Iterum) |
| FDA Received Date: | April 25, 2024 |
| TTT ID #: | 2024-9231 |
| DMEPA 1 Safety Evaluator: | Deborah Myers, RPh, MBA |
| DMEPA 1 Team Leader: | Valerie S. Vaughan, PharmD |

# 1 INTRODUCTION

Iterum Therapeutics US Limited submitted a Class 2 resubmission for Orlynvah (sulopenem etzadroxil and probenecid) Tablets to respond to the deficiencies included in the Agency's Complete Response letter (CRL) dated July 23, 2021. Subsequently, the Division of Anti-Infectives (DAI) requested that we review the revised proposed Orlynvah Prescribing Information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

## 1.1 BACKGROUND

Orlynvah (sulopenem etzadroxil and probenecid) is a proposed 505(b)(2) drug product and the reference product is Benemid (probenecid), NDA 007898 for the active ingredient probenecid.

DMEPA previously reviewed the prescribing information (PI), container labels, and carton labeling for sulopenem etzadroxil and probenecid (NDA 213972).[a]

## 1.2 REGULATORY HISTORY

Iterum Therapeutics US Limited previously submitted NDA 213972 on November 25, 2020,[b] which received a CRL on July 23, 2021, due to lack of substantial evidence consisting of well-controlled investigations.[c] The Agency's CRL included our DMEPA recommendations regarding the proposed container labels and carton labeling.[d]

Thus, Iterum Therapeutics US Limited submitted a Class 2 Resubmission on April 25, 2024.[e] Revised PI, container labels, and carton labeling, were included in this resubmission dated April 25, 2024. These revised PI, container labels, and carton labeling are the subject of this review (see Appendix B). Additionally, we note that included in this resubmission, Iterum states that they do not plan to commercialize and have therefore removed their previously proposed (b) (4) blister packaging presentation that was included in their original NDA.

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[a] Myers, D. Label and Labeling Review for sulopenem etzadroxil and probenecid (NDA 213972). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 22. OSE RCM #: 2020-2499.

[b] Cover Letter: NDA 213972 for sulopenem etzadroxil and probenecid (NDA 213972). Chicago (IL): Iterum Therapeutics U.S., Ltd.; 2020 NOV 25. Available at: \\CDSESUB1\EVSPROD\nda213972\0000\m1\us\cover-letter.pdf.

[c] Smith, C. Communication: Complete Response Letter for sulopenem etzadroxil and probenecid tablets. Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2021 JUL 23. NDA 213972. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80604baa.

[d] Myers, D. Label and Labeling Review for sulopenem etzadroxil and probenecid (NDA 213972). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 22. OSE RCM #: 2020-2499.

[e] Cover Letter: Resubmission of NDA 213972 for Orlynvah (NDA 213972). Old Saybrook (CT): Iterum Therapeutics US Limited; 2024 APR 25. Available at: \\CDSESUB1\EVSPROD\nda213972\0070\m1\us\cover-letter.pdf.

## 2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 213972.

| Table 1. Materials Considered for this Label and Labeling Review | |
|---|---|
| Material(s) Reviewed | Appendix Section |
| Relevant Product Information | A |
| Labels and Labeling | B |
| Previous DMEPA Reviews | C |

## 3 CONCLUSION

Iterum Therapeutics US Limited implemented our applicable container label and carton labeling recommendations included in the CRL dated July 23, 2021, and we have no additional recommendations at this time.

However, we note that our previous recommendations regarding the prescribing information (PI) submitted with the original NDA on November 25, 2020, were not communicated to Iterum. Therefore, we provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Anti-Infectives (DAI) in Section 4.

## 4 RECOMMENDATIONS FOR THE DIVISION OF ANTI-INFECTIVES (DAI)

| Table 2. Identified Issues and Recommendations for the Division of Anti-Infectives (DAI) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| Prescribing Information – General Issues | | | |
| 1. | As currently presented, we note that the section titled, *How Supplied/Storage and Handling* is included in the proposed PI as Section 15 and the section titled, *Patient Counseling Information* is included in the proposed PI as Section 16. | Per 21 CFR 201.56(d)(1) prescription drug labeling must contain the following headings within the "Full Prescribing Information" (FPI); for Section 16 is titled *How Supplied/Storage and Handling* and Section 17 is titled *Patient Counseling Information*. | Revise the Section numbering to align with 21 CFR 201.56(d)(1). |
| Full Prescribing Information – Section 16 *How Supplied/Storage and Handling* | | | |
| 1. | As currently presented, the storage statement is, "… (b) (4) at 20° to | The storage statement should be clearly stated to | To provide clarity and consistency with the storage statement as presented on the |

| Table 2. Identified Issues and Recommendations for the Division of Anti-Infectives (DAI) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F)." The units of measurement following the first numbers in the temperature ranges are missing. | mitigate the risk of storage error. | proposed container labels and carton labeling, add the Centigrade symbol (C) following 20° and 15°, and Fahrenheit symbol (F) following 68° and 59°within the storage statement.<br><br>For example, "… (b) (4) at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)."<br><br>Additionally, we note that the proposed container labels and carton labeling do not include "excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room temperature]*." as part of the storage statement. We defer to the Office of Pharmaceutical Quality (OPQ) to determine if this excursion information should be included in the storage statement on the container labels and carton labeling. |

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 3 presents relevant product information for Orlynvah received on April 25, 2024 from Iterum Therapeutics US Limited.

| Table 3. Relevant Product Information for Orlynvah | |
|---|---|
| Initial Approval Date | N/A |
| Active Ingredient | sulopenem etzadroxil and probenecid |
| Indication | In adult women ≥ 18 years of age for the treatment of uncomplicated urinary tract infections caused by designated susceptible microorganisms. |
| Dosage Form | Tablets |
| Strength | 500 mg/500 mg |
| Route of Administration | oral |
| Dose and Frequency | One tablet twice daily for 5 days, taken with food (b) (4) (b) (4) |
| How Supplied | Bottles of 10 tablets with child-resistant caps<br>Bottles of 30 tablets with child-resistant caps |
| Storage | Store 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]. |
| Container Closure | The drug product is presented in two, conventional, high-density polyethylene (HDPE) bottle container closure systems as follows:<br>• 30-count, 100 mL HDPE bottle with 1 g desiccant bag, induction seal closure, and (b) (4) child-resistant cap (b) (4) (b) (4)<br>• 10-count, 40 mL HDPE bottle with 1 g desiccant bag, induction seal closure, and (b) (4) child-resistant cap (b) (4) (b) (4) |

## APPENDIX B. LABELS AND LABELING

### B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Orlynvah labels and labeling submitted by Iterum Therapeutics US Limited.

- Prescribing Information (PI) (Images not shown) received on April 25, 2024:
  - Clean proposed (Draft) PI, available at the following link: \\CDSESUB1\EVSPROD\nda213972\0070\m1\us\sulopenem-etzadroxil-draft-uspi-draft-17apr2024final.docx.
- Container label(s) received on April 25, 2024
- Carton labeling received on April 25, 2024

### B.2 Container Labels and Carton Labeling Images

Container labels

(b) (4)

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

## APPENDIX C. PREVIOUS DMEPA REVIEWS

On July 10, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, "NDA 213972." Our search identified one previous review[g], and we considered our previous recommendations to see if they are applicable for this current review.

[g] Myers, D. Label and Labeling Review for sulopenem etzadroxil and probenecid (NDA 213972). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 22. OSE RCM No.: 2020-2499.

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07/31/2024 10:38:37 AM

**Clinical Inspection Summary**

| | |
|---|---|
| **Date** | 17 June 2021 |
| **From** | Cheryl Grandinetti, PharmD<br>Clinical Pharmacologist<br>Good Clinical Practice Assessment Branch<br>Division of Clinical Compliance Evaluation<br>Office of Scientific Investigations |
| **To** | Christopher Smith, Pharm.D., RPM<br>Mukil Natarajan, MD, Medical Reviewer<br>Peter Kim, MD, Medical Team Leader<br>Division of Anti-Infectives (DAI) |
| **NDA #** | 213972 |
| **Applicant** | Iterum Therapeutics International, Limited |
| **Drug** | Sulopenem etzadroxil/probenecid |
| **NME** | Yes |
| **Proposed Indication** | For the treatment of uncomplicated urinary tract infections in adult women |
| **Consultation Request Date** | 22 Jan 2021 |
| **Summary Goal Date** | 24 Jun 2021 |
| **Action Goal Date** | 25 Jul 2021 |
| **PDUFA Date** | 25 Jul 2021 |

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Routine PDUFA surveillance inspections were conducted for four clinical investigators, Drs. Fernandez, Sorkin-Wells, Rodriguez de la Torre, and Thomas, and the study sponsor, Iterum Therapeutics International, in support of NDA 213972. In addition, the results of a combined PDUFA/for-cause inspections of two clinical investigators, Drs. Oporta and Terrelonge are included in this Clinical Inspection Summary (CIS). All of the inspections covered one clinical study, IT001-301.

The source records documenting the overall response criteria (i.e., survival status, concomitant non-study antibacterial therapy, urine culture and susceptibility testing results, and PSAQ responses) and investigator's assessment of clinical response (i.e., resolution of pre-therapy signs and symptoms of the index infection and whether additional antibiotics were required) were reviewed and verified against the sponsor's data line listings, with only minor discrepancies noted. The data generated by Site 219 (Dr. Fernandez), Site 103 (Dr. Sorkin-Wells), Site 150 (Dr. Rodriguez de la Torre), and Site 200 (Dr. Thomas) appear acceptable in support of the respective indication.

However, data reliability concerns were identified during the routine PDUFA inspection of the sponsor as follows:

1. The statistical analysis plan (SAP) was amended after a pre-planned interim analysis conducted by an unblinded statistician. The SAP amendment specifically changed overall response criteria to state that the genus/species and susceptibility profiles of the urinary isolate needed to match [to incorporate results from whole genome sequencing (WGS) and pulse-field gel electrophoresis (PFGE)]
2. WGS and PFGE test results (which were used to place subjects in subgroups of susceptible and resistant populations and to determine overall response) were incorporated after the study was unblinded (i.e., study was unblinded on 19 June 2019; WGS and PFGE were incorporated on 29 June 2019).

This is concerning because there was a potential for bias to be introduced to the study results because the sponsor's statisticians and data management staff had prior knowledge of the subjects' treatment assignment and overall response. Despite these concerns, the reanalysis of study data (generated in Protocol IT001-301) as requested by the review division adequately addresses our concerns regarding the changes to the SAP and use of WGS and PFGE results after unblinding of the study. Please see the inspection summary below for more details.

In addition, the combined PDUFA/for-cause inspection of Drs. Terrelonge (Site 202) and Oporta (Site 218) were conducted to address the sponsor's specific data reliability concerns that, for example, PFGE analysis of a high percentage of urinary isolates identified from the baseline urine bacterial cultures at these sites were either genetically indistinguishable or closely related). The sponsor used these data reliability concerns as a basis to exclude the patient data from these two sites from all efficacy analyses.

The sponsor's data reliability concerns regarding the possible use of urine samples from one subject to enroll multiple subjects (possible explanation for the PFGE analysis results seen at these two sites) and other significant protocol noncompliance issues could not be confirmed during the for-cause inspections of Drs. Terrelonge and Oporta because a full picture of the conduct of the trial at these two site could not be reconstructed (i.e., significant knowledge gaps remain). Moreover, at Dr. Oporta's site, all study-related source records were found to be missing in their entirety. Therefore, to assess the impact of the data reliability concerns at Sites 202 (Dr. Terrelonge) and 218 (Dr. Oporta) on the efficacy and safety endpoints, post hoc sensitivity analyses should be conducted, excluding all the subjects from these two sites to determine the robustness of the study results.

## II. BACKGROUND

NDA 213972 was submitted in support of the use of oral sulopenem etzadroxil/probenecid for the treatment of adult women with uncomplicated urinary tract infections (uUTI). The key study supporting the application was the following:

- IT001-301, "A prospective, Phase 3, randomized, multi-center, double-blind study of the efficacy, tolerability, and safety of oral sulopenem etzadroxil/probenecid versus oral ciprofloxacin for treatment of uncomplicated urinary tract infections in adult women."

This was a prospective, phase 3, randomized, multicenter, double-blind, double-dummy, controlled study that compared oral sulopenem etzadroxil/ probenecid to oral ciprofloxacin for the treatment of patients with uUTI. The study was designed to determine whether oral sulopenem etzadroxil/probenecid is non-inferior to oral ciprofloxacin for the outcome measure of overall response (combined clinical and microbiologic success) at Day 12 (± 1 day) in the microbiologic modified intent-to-treat ciprofloxacin susceptible (micro-MITTS) population and/or whether oral sulopenem etzadroxil/probenecid was superior to oral ciprofloxacin for overall success at Day 12 (± 1 day) in the microbiologic modified intent-to-treat ciprofloxacin resistant (micro-MITTR) population.

- ***Subjects:*** A total of 1671 subjects were randomized; data from 1071 subjects were analyzed for efficacy (286 subjects comprised the micro-MITTR population), and data from 1660 subjects were analyzed for safety
- ***Sites:*** 142 sites in 4 countries: Italy (5), Russia (20), Ukraine (15), and the United States (US; 102)
- ***Study initiation and completion dates:*** 23 August 2018 (first subject, first visit) to 20 January 2020 (last subject, last visit)
- ***Database lock date:*** 17 Jun 2020
- ***Unblinding of study:*** 19 Jun 2020

Eligible subjects were randomized in a 1:1 ratio using an Interactive Web Response System (IWRS) to receive one of the following:

- **Sulopenem etzadroxil/probenecid:** A bilayer tablet with sulopenem etzadroxil 500 mg/probenecid 500 mg, administered orally twice daily for 5 days and matching placebo for ciprofloxacin capsules, administered orally twice daily for 3 days
- **Ciprofloxacin:** Oral ciprofloxacin 250 mg capsules, administered orally twice daily for 3 days and matching placebo for sulopenem etzadroxil/probenecid tablets, administered orally twice daily for 5 days

Urinalysis and urine culture and sensitivity testing were performed at Baseline (Day -1 to Day 1), Day 3, End of Treatment Visit (EOT, Day 5), Test of Cure Visit (TOC, Day 12) and the Follow-Up Visit (FV, Day 28). Investigator sites collected urine specimens at the specified visits (i.e., Baseline, Day 3, EOT, TOC and FV).

The ***primary efficacy endpoint*** was overall response (percentages of patients with combined clinical and microbiologic response [success, failure or indeterminate]) in the micro-MITTS and micro-MITTR populations on Day 12 (± 1 day), the TOC visit.

A subject was to be defined as a success [responder] at a given timepoint (Day 3, EOT, TOC and FV) if all of the following criteria were met:

- The subject was alive
- The subject had received no non-study antibacterial therapy for uUTI

    - If an antibiotic active against the urinary tract pathogen was given for non-uUTI reasons, then the patient was to be considered indeterminate
- The subject had resolution of the symptoms of uUTI present at trial entry and no new UTI symptoms based on the Patient Symptom Assessment Questionnaire [PSAQ]
    - Missing PSAQ questions were to be treated as missing thus the outcome was indeterminate
- Urine culture collected at the TOC visit demonstrated $<10^3$ CFU/mL of the baseline uropathogen

A subject was to be defined as a failure [non-responder] if at least one of the following criteria was met:

- The subject died due to uUTI
- The subject received non-study antibacterial therapy for uUTI
- The subject had no resolution or worsening of symptoms of uUTI present at trial entry and/or had new uUTI symptoms
- Missing PSAQ questions were to be considered missing and the outcome was to be indeterminate
- Urine culture at the TOC visit demonstrated $\geq 10^3$ CFU/mL of the baseline uropathogen

Subjects were to be defined to have an indeterminate outcome if any data needed to determine whether the outcome was a success or failure were missing. Patients who died due to other reasons than the uUTI were to have an indeterminate outcome.

The following Central Laboratories were used for processing and analyzing urine specimens:

1. Covance Central Laboratory Services
2. (b) (4)
3. (b) (4)
4. International Health Management Associates, Inc (IHMA)
5. (b) (4)
6. (b) (4)

**U.S. sites:** The sites sent screening urine specimens to their local/regional Covance Central Laboratory Services and also to the IHMA (i.e., Central Laboratory) for culture and sensitivity testing (i.e., primary testing). At post-screening visits (Day 3, EOT, TOC, and FU), the sites sent urine specimens to Covance for culture and sensitivity testing. In addition, urinary isolates identified by Covance were sent by (b) (4) to IHMA-US for re-identification at all visits (i.e., confirmatory testing). Covance sent the urine culture results (minus the sensitivity testing results) at screening and post-screening visits directly to all investigators; however, site personnel did not enter these results in the EDC system. Covance sent the isolate's sensitivity testing results (to quinolones and carbapenem) to sites after TOC Visit.

**Foreign sites:** The sites sent screening and post-screening urine specimens to (b) (4) (b) (4) which served as the local/regional laboratory in (b) (4) respectively. At (b) (4) the urine culture results from all visits were sent directly to the site and entered in the EDC by the site. Sites were unable to see isolate's sensitivity to quinolones and carbapenems until after TOC. Urinary isolates were sent by (b) (4) to IHMA-US (via (b) (4) for re-identification, and a backup isolate was stored at (b) (4)

**IHMA-US** performed gram stain, culture, and susceptibility testing with a customized MIC panel on the screening urine samples. Post-screening samples were sent to IHMA for isolate re-identification and custom MIC testing. IHMA-US testing results were not sent to investigators during the conduct of the study but rather certified copies of these testing results were sent to all investigators (U.S. and ex-U.S.) at the end of the study. To help determine whether a post-screening (EOT and TOC visits) isolate was the same or different from the screening isolate (same genus and species), (b) (4) performed whole genome sequencing (WGS) testing of the pairs upon request from the Sponsor. (b) (4) study results were transferred to the (b) (4) contract research organization (CRO) and sponsor via (b) (4).

The protocol also required that all subjects in the US use AiCure, an artificial intelligence application (App), to confirm medication ingestion and monitor their medication adherence. Subjects either downloaded the AiCure App onto their personal mobile device or were provided mobile devices by the site with the App installed on the device. Subjects were instructed to use the App to record themselves ingesting the medication at each dosing time. If subjects had difficulty using the App, they had the option to self-report in the App that they took the medication. To assist in assessing treatment adherence, the AI software read the pixelated dosing videos (submitted by the subjects) and classified doses as follows:

- Green Flag: video captured expected/typical dosing behavior and is not missing visual information that would impact the ability to determine adherence
- Yellow Flag: video is missing visual information necessary in order to confirm adherence (e.g., subject leans out of field of view)
- Orange Flag: video captures the dosing process and it contains highly likely behavior of intentional non-adherence
- Red Flag: video captures the dosing process and it shows strong visual proof of intentional non-adherence behavior (e.g., removing study drug from the mouth, "cheeking," spitting out the drug)

The site would receive an automated email notification (generated from the AiCure Platform) if the subject missed a dose or when the dose was classified as orange or red. The site staff was supposed to follow-up with the subject to verify whether the subject had taken the missed dose or the dose classified as orange or red and then document the dose in the source records and in the AiCure platform.

**Rationale for Site Selection**

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, protocol deviations, complaints/reports of protocol nonadherence, and prior inspectional history.

## III. RESULTS (by site):

**1. Inti Fernandez, MD**
Site #219
Valencia Medical & Research Center
9804 SW 40th Street
Miami, FL 33165
***PDUFA Inspection Dates:*** 16 to 19 Feb 2021

At this site for Protocol IT001-301, 72 subjects were screened and randomized, and 70 subjects completed the study. One subject withdrew consent for unspecified reasons and the second subject withdrew consent due to an adverse event (i.e., vomiting).

A full audit of the study records for 20 of the 72 randomized subjects was conducted. Of note, these 20 subjects were included in the micro-MITTR population as identified in the sponsor's initial analysis dataset submitted to FDA. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data related to overall response (i.e., survival status, concomitant non-study antibacterial therapy, urine culture and susceptibility testing results, and PSAQ responses), including the investigator's assessment of clinical response; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records documenting the overall response criteria (i.e., survival status, concomitant non-study antibacterial therapy, urine culture and susceptibility testing results, and PSAQ responses) and investigator's assessment of clinical response were reviewed and verified against the sponsor's data line listings for 20 of the 72 randomized subjects. Urine culture and susceptibility testing results performed by Covance, the local/regional laboratory, could not be verified during the inspection for any of the enrolled subjects at this site because these test results were not available at the site. In addition, IHMA urine culture and susceptibility test results for Subject (b) (6) were missing and therefore could not be verified during inspection. Otherwise, no discrepancies were noted when comparing the source records that were available against the sponsor's data line listings.

***Reviewer's comment****: In a 1 April 2021 response to an IR, the sponsor submitted certified copies of the urine culture and susceptibility test reports from both the local/regional and central laboratories (i.e., Covance and IHMA laboratories) to the NDA. Certified copies of these reports were reviewed and verified against the sponsor's data listings for (1) the same 20 subjects audited during the inspection, including verification of the IHMA test reports that were missing at the site for Subject* (b) (6) *and (2) an additional 20 randomly selected subjects in the ITT population. No discrepancies were noted.*

**2. Valerie Sorkin-Wells, MD**
Site #103
Precision Trials AZ, LLC
3805 E. Bell Road
Phoenix, AZ 850032
***PDUFA Inspection Dates:*** 22 to 26 Feb 2021

At this site for Protocol IT001-301, per the sponsor's data line listings, 97 subjects were screened, 81 were randomized, and 77 subjects completed the study. Four subjects were discontinued from the study: one subject withdrew consent and one subject was withdrawn by the investigator for unspecified reasons and two subjects withdrew from the study due to adverse events (i.e., diarrhea and dizziness).

A full audit of the study records for 32 of the 81 randomized subjects was conducted. Of note, five of the 32 subjects were included in the micro-MITTR population as identified in the sponsor's initial analysis dataset submitted to FDA. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data related to overall response (i.e., survival status, concomitant non-study antibacterial therapy, urine culture and susceptibility testing results, and PSAQ responses), including the investigator's assessment of clinical response; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records documenting the overall response criteria (i.e., survival status, concomitant non-study antibacterial therapy, urine culture and susceptibility testing results, and PSAQ responses) and investigator's assessment of clinical response were reviewed and verified against the sponsor's data line listings for these 32 (out of 81) randomized subjects. Two discrepancies were noted. The investigator assessment of clinical response in both the source record and the eCRFs at the TOC visit was clinical cure for Subjects (b) (6) (randomized to sulopenem etzadroxil) and (b) (6) (randomized to ciprofloxacin), while the sponsor reported clinical response in these subjects as indeterminant and failure, respectively.

***Reviewer's comment:*** *The two discrepancies were discussed with Dr. Sorkin-Wells at the inspection close-out. She acknowledged the discrepancies and explained that for both subjects, she made her assessment at the TOC visit (Study Day 12) with the information that was available to her at the time. According to source records, Subject* (b) (6) *was prescribed Bactrim by her primary care physician and received the non-study antibacterial from Study Day 9 to Study Day 15; however, the investigator was not even aware that the subject received Bactrim until Study Day 28. Also, the primary care physician's reason for prescribing Bactrim was not clear in the source records. In addition, for Subject* (b) (6)*, the PSAQ responses noted mild burning and dysuria symptoms at the TOC visit.*

*It is important to note that the investigator's assessments of clinical response for both of these subjects were changed by the sponsor without ensuring that the investigator updated the source records and the eCRFs with the corrected clinical response assessments. Although this practice for making changes to the study data is concerning because it is unclear who made the change, and when, and if the changes were discussed with and/or authorized by the clinical investigator, it should be noted that the changes made for both of these subjects were found to represent accurate assessments of clinical response.*

**3. Jesus Rodriguez de la Torre, MD**
Site #150
Health and Life Research Institute, LLC
7801 Coral Way, Suite #115
Miami, FL 33155
***PDUFA Inspection Dates:*** 25, 26, 29, 30, 31 Mar 2021 and 2 Apr 2021

At this site for Protocol IT001-301, 23 subjects were screened, 22 were randomized, and 21 subjects completed the study. One subject withdrew consent because they did not want to take the study drug.

A full audit of the study records for 12 of the 22 randomized subjects was conducted. Of note, these 12 subjects were included in the micro-MITTR population as identified in the sponsor's initial analysis dataset submitted to FDA. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data related to overall response (i.e., survival status, concomitant non-study antibacterial therapy, urine culture and susceptibility testing results, and PSAQ responses), including the investigator's assessment of clinical response; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records documenting the overall response criteria (i.e., survival status, concomitant non-study antibacterial therapy, urine culture and susceptibility testing results, and PSAQ responses) and investigator's assessment of clinical response were reviewed and verified against the sponsor's data line listings for all 22 randomized subjects. Two discrepancies were noted. The investigator assessment of clinical response in the source records at the TOC visit was failure for Subjects (b) (6) (randomized to ciprofloxacin) and (b) (6) (randomized to ciprofloxacin) while the sponsor reported clinical response in these two subjects as successes.

***Reviewer's comment:*** *The investigator's assessment of clinical response for these two subjects should have been classified as successes at the TOC visit as investigators were supposed to base their clinical response assessment only on resolution of pre-therapy*

*signs and symptoms of the index infection and whether additional antibiotics were required. Source records available at the site indicated that pre-therapy signs and symptoms had resolved, and subjects had not received additional antibiotics at the TOC visit.*

*Again, it is important to note that the sponsor changed the assessments without ensuring that the investigator updated the source records with the corrected clinical response assessments. Although this practice for making changes to the study data is concerning because it is unclear who made the change, and when, and if the change was discussed with and/or authorized by the clinical investigator, it should be noted that the changes made for both of these subjects, who were randomized to ciprofloxacin, were found to represent accurate assessments of clinical response.*

In addition, Subject (b) (6) was enrolled without verification that the subject met eligibility criterion 3b, which states that the subject must have a mid-stream urine specimen with evidence of pyuria, defined by either a dipstick analysis positive for leukocyte esterase and/or at least 10 white blood cells (WBC) per cubic millimeter on microscopic analysis of unspun urine and/or WBC count ≥10 cells/HPF in the sediment of a spun urine. This subject's machine-read urine dipstick was not positive for leukocyte esterase. In addition, the site relied only on a positive result for leukocyte esterase on a machine-read dipstick and did not perform any additional microscopic analysis of the unspun or spun urine to confirm that WBC count in the urine met the minimum requirement for enrollment in the trial.

***Reviewer's comments:*** *This protocol deviation was not documented during routine monitoring visits (RMV) or in the protocol deviation listing reported to FDA. Enrolling a single ineligible subject is unlikely to affect the overall efficacy and safety results of the study.*

**4. Flavia Thomas, MD**
Site #200
Excel Clinical Research LLC
14019 Southwest Freeway, Suite 201
Sugar Land, TX 77478
***PDUFA Inspection Dates:*** 16 to 22 Mar 2021

At this site for Protocol IT001-301, 41 subjects were screened and 40 were randomized, all of whom completed the study. A full audit of the study records for 15 of the 40 randomized subjects was conducted. Of note, these 15 subjects were included in the micro-MITTR population as identified in the sponsor's initial analysis dataset submitted to FDA. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data related to overall response (i.e., survival status, concomitant non-study

antibacterial therapy, urine culture and susceptibility testing results, and PSAQ responses), including the investigator's assessment of clinical response; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records documenting the overall response criteria (i.e., survival status, concomitant non-study antibacterial therapy, urine culture and susceptibility testing results, and PSAQ responses) and investigator's assessment of clinical response were reviewed and verified against the sponsor's data line listings for 15 (of the 40) randomized subjects. No discrepancies were noted.

***Reviewer's comment****: In a 1 April 2021 response to an IR, the sponsor submitted certified copies of the urine culture and susceptibility test results from both the local and central laboratories (i.e., Covance and IHMA laboratories) to the NDA. Covance and IHMA urine culture and susceptibility test results were reviewed and verified against the sponsor's data line listings for the remaining 25 subjects in the ITT population. No discrepancies were noted.*

**5. Antonio Terrelonge, MD**
Site #202
Ocean Blue Medical Research Center, Inc.
286 Westward Drive
Miami Springs, Florida 33166
***PDUFA/For-cause Inspection Dates:*** 14 to 16, 20 to 23, 26 and 28 Apr 2021

At this site for Protocol IT001-301, 77 subjects were screened, 68 were randomized, and 65 subjects completed the study. Three subjects withdrew consent, one for unspecified reasons and two for adverse events (i.e., nausea and diarrhea).

A full audit of the study records for 23 of the 68 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data related to overall response (i.e., survival status, concomitant non-study antibacterial therapy, urine culture and susceptibility testing results, and PSAQ responses), including the investigator's assessment of clinical response; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records documenting the overall response criteria (i.e., survival status, concomitant non-study antibacterial therapy, urine culture and susceptibility testing results, and PSAQ responses) and investigator's assessment of clinical response were reviewed and verified against the sponsor's data line listings for the 65 of 68 randomized subjects. No discrepancies were noted; however, there were many missing microbiology laboratory reports at the site from the IHMA central laboratory for the 65 subjects whose data were verified.

***Reviewer's comment**: In a 1 April 2021 response to an IR, the sponsor submitted to the FDA certified copies of the urine culture and susceptibility test results from both the local and central laboratories (i.e., Covance and IHMA laboratories). IHMA urine culture and susceptibility test reports that were missing at the site for verification during the inspection were reviewed and verified against the sponsor's data line listings. No discrepancies were noted.*

In addition, two out of 68 randomized subjects who met exclusion criteria were enrolled. Subject (b) (6) (randomized to sulopenem) met exclusion criterion #11 (Version 7 June 2018), which excludes patients with a known history of creatinine clearance (CrCl) less than 50 mL/min as calculated by Cockcroft-Gault equation. The subject, who had a CrCl of 33 mL/min, was enrolled and randomized despite her CrCl being less than 50 mL/min at screening. Although this protocol deviation was identified during a RMV by the CRO and was reported to FDA in the listing of protocol deviations for this site, the site did not have any documentation that enrollment and randomization of the ineligible subject was discussed with the medical monitor. In addition, this subject completed the study, and there were no adverse events reported.

Subject (b) (6) (randomized to sulopenem) met exclusion criterion #15 (Version 7 June 2018), which excludes patients with uncontrolled diabetes mellitus (defined as the presence of ketoacidosis, hyperosmolar hyperglycemia, or glycosuria, with a random or fasting fingerstick or serum glucose ≥250 mg/dL at screening). The medical history for Subject (b) (6) included type II diabetes mellitus, and she had glucose levels >250 mg/dL at the screening, TOC (Day 12), and FV (Day 28). In addition, this subject completed the study, and there were no adverse events reported.

***Reviewer's comment:** The enrollment of these two ineligible subjects (out of 68 randomized) is an isolated incident and unlikely to affect the overall safety and efficacy results of the trial. Of note, the protocol deviation that occurred in Subject (b) (6) was not reported to the FDA in the listing of protocol deviations.*

**For-cause Inspection**

In addition, a for-cause inspection was conducted in response to a report from the sponsor, Iterum Therapeutics, informing FDA of their concerns (identified below) about the reliability and removal of the efficacy data generated by this site from their efficacy analysis for the following reason:

1) Pulse-field gel electrophoresis (PFGE) analysis of 17 isolates identified from the baseline urine bacterial cultures for 15 of 68 subjects obtained on 6 separate dates showed that the organisms were either genetically indistinguishable or closely related (1-2 band differences).
2) High contamination rates of urine samples during a certain period of enrollment, presumably due to problems with the urine collection and processing techniques.
3) There were 27 of 68 subjects who had red/orange flags as noted by AiCure. Orange and red flags indicated behavior which is highly likely or strong visual proof of intentional non-adherence behavior.

4) Five of 31 subjects enrolled in the pharmacokinetic (PK) component of the trial had no measurable drug in either the blood or urine.

**The for-cause part of the inspection found the following:**

1) **PFGE analysis results suggesting the use of urine samples from one subject to enroll multiple subjects:** Documentation was available in the subjects' source records for review related to the urine collection, handling, processing, and shipping, and dosing of the study drug. However, it was not possible to confirm whether urine samples sent to the laboratory belonged to the subject identified on the sample. Attempts were also made to contact 10 subjects during the inspection to confirm their participation in the study (i.e., Subjects (b) (6) . Two of the 10 subjects (i.e., (b) (6)) participated in the PK part of the study and were reported by the sponsor to have no measurable drug in their urine or blood. Three of the 10 subjects (i.e., (b) (6)) confirmed their participation in the trial. Seven subjects did not answer the phone call. Of the 7 subjects who did not answer the phone, 5 subjects had a voice mailbox set up with 2 of the 5 subjects' voicemail stating their name.

***Reviewer's comment:*** *Based on the results of this inspection, it could not be confirmed that urine samples from one subject were used to enroll multiple subjects.*

2) **High contamination rates of urine samples:** There were issues identified during the conduct of the study with the collection, handling, processing, and shipping of the urine samples. For example, numerous samples were contaminated, urine samples were possibly sent on dry ice instead of at ambient temperature, urinalyses were not run by the central laboratory, and samples were not received by the central laboratory. Based on the microbiology urine culture and susceptibility reports, these issues appear to have started as early as October 2018. RMV reports reviewed during the FDA inspection showed that the CRO reviewed the site's laboratory processes and procedures in November and December 2018 and January 2019 and found no deficiencies. In addition, during the RMVs, the monitor noted that the site appeared to have appropriately collected, processed, labeled, and shipped all necessary biospecimen samples in a timely manner to the central laboratories as outlined in the current Covance, (b) (4) and IHMA study central laboratory manuals. Furthermore, RMVs conducted in February and March 2019 began to address some issues with the urine samples; however, the reports further stated that monitors found no deficiencies in the site's laboratory processes and procedures. The CRO retrained the site staff on the collection, handling, and processing of urine samples on 12 Dec 2018. Despite the retraining, the issues continued, and the sponsor placed the site on enrollment hold on 4 Apr 2019. Two audits of the site were conducted in June and October 2019 by the CRO and sponsor, respectively.

***Reviewer's comment:*** *Both Dr. Terrelonge and the Executive Director of the Research Center provided written statements during the inspection acknowledging the challenges they experienced with the central laboratories and the contaminated urine samples. They further provided their detailed standard operating procedures (SOPs) for urine collection, sample*

*processing, and sample shipping. No issues were noted in review of their SOPs.*

*Furthermore, the site did not have any formal documentation from the sponsor informing them of their enrollment hold, nor did they have documentation regarding the results of the June 2019 audit, which appears to not have been communicated or provided to the site. Only the final report of the second audit conducted in October 2019 was communicated and provided to the site, and this report did not address the issue of contaminated urine samples. It also does not appear that the sponsor and CRO conducted a formal root-cause analysis and implemented a sufficient corrective and preventative action (CAPA) plan (other than the re-training that occurred in December 2018 and the subsequent enrollment hold). Thus, it was difficult to find a concise summary of the all actions taken by the CRO and sponsor prior to placing the site on enrollment hold. Based on the lack of a formal root cause analysis of these issues and a lack of a formal letter informing the site of their enrollment hold, it was not clear which issues were the result of problems at the site and which were the result of potential problems at the central laboratory.*

*Most importantly, it should be noted that these high contamination rates, whatever the cause (site vs. laboratory), would not necessarily justify removing all of the efficacy data from this site from the primary analysis. The specific subjects with contaminated samples (and without a repeat sample) can be addressed by statistics.*

3) **AiCure red flags:** The sponsor reported to FDA that the dosing of 27 out of 68 subjects was classified with red and/or orange flags (i.e., red flag means strong visual proof of intentional non-adherence behavior and orange flag means intentional non-adherence behavior is highly likely). In an email correspondence to the study site's research coordinator from the sponsor, the sponsor identified the following 10 subjects for follow-up by the site staff as having their dosing classified as red: Subjects (b) (6)

   Documentation was available in the source records that confirmed that all of these 10 subjects subsequently took the dose that was classified as red by AiCure after initially spitting the dose out. The reasons noted in the source records for subjects taking the medication out of their mouth included the large size of the tablet and capsule, the medication made them feel nauseous, and difficulty using the AiCure application while at the same time trying to take the medication. This information in the source record was verified against printouts of the compliance information in the AiCure platform. The site-reported doses reflected the information that was found in the AiCure platform for all but 3 of the 10 subjects, i.e., Subjects (b) (6). For these 3 subjects, the investigator failed to record the dosing information from the source record in the AiCure Platform.

***Reviewer's comment:*** *Based on the inspection observations regarding the AiCure App noted above, the high rate of red and/or orange flags (27 out of 68 subjects) as reported by the sponsor appears to misrepresent the actual number of subjects who intentionally did not take the medication as directed. Although many subjects may have initially spit out the medication during the recording of the AiCure videos for various reasons (e.g., difficulty using the application, tablets/capsules were too large, study medication causing nausea), at least 10 of*

*the 27 subjects later confirmed that they took the medication after initially spitting out or removing the tablet or capsule from their mouth, with the dosing information being well-documented in the source records at the site (e.g., in the drug accountability records, medical notes, and other written notes in the subject's regulatory binder, including the RMV reports). The dosing of the remaining 17 subjects with either orange or red flags could not be assessed during inspection because the identifying subject numbers and the respective AiCure dosing classifications (i.e., red or orange) were not available.*

*In summary, use of urine samples from one subject to enroll multiple subjects and other GCP noncompliance issues that may impact data reliability at this site could not be confirmed because a full picture of the conduct of the trial at this site could not be reconstructed (i.e., significant knowledge gaps remain). Therefore, a post hoc sensitivity analysis should be conducted, excluding all the subjects from this site to determine the robustness of the study results. Of note, in the sponsor's 22 March 2021 response to an IR, the sponsor has already conducted a reanalysis of the study data as requested by FDA, both with and without the subjects from Site 202.*

**4) Alejandro Oporta, MD**
Site #218
D & H National Research Centers
7775 SW 87th Avenue, Suite 1201
Miami, FL 33173
***PDUFA/For-cause Inspection Dates:*** 14 to 19 Apr 2021

At this site for Protocol IT001-301, per the sponsor's data line listings, 15 subjects were screened, 13 were randomized, and 12 subjects completed the study. A for-cause inspection was conducted in response to a report from the sponsor, Iterum Therapeutics, informing FDA of their concerns about the reliability and removal of the efficacy data generated by this site from their primary analysis. Specifically, the sponsor deemed the data from this site unreliable because 13 patients at the site had a positive baseline culture for both *Escherichia coli* and *Klebsiella pneumoniae*, and PFGE analysis showed that the *Escherichia coli* and *Klebsiella pneumoniae* were either genetically indistinguishable or closely related (1-2 band differences) in 12 of 13 and 13 of 13 patients, respectively. The sponsor also reported that urine leukocyte esterase and nitrite dip stick results differed from central lab results in 10 of the 13 patients.

(b) (7)(A)

***Reviewer's comment:*** *In the 22 March 2021 response to an IR, the sponsor has already conducted a reanalysis of the study data as requested by FDA, without the efficacy data from the subjects at Site 218.* (b) (7)(A) *a post hoc sensitivity analysis should be conducted, excluding all the subjects from this site to assess the impact of the data*

*reliability concerns and determine the robustness of the study results.*

**5) Iterum Therapeutics US Ltd**
20 Research Pky, STE G
Old Saybrook, CT 06475
***PDUFA Inspection Dates:*** 19 to 23 Apr 2021

The inspection of the sponsor, Iterum Therapeutics, focused on:

- Oversight of Protocol IT001-301 in general and of their CROs
- The collection, handling, and management of urine culture and susceptibility testing
- The processes and procedures for categorizing subjects in the susceptible and resistant populations and determining overall response

The sponsor transferred regulatory obligations to (b) (4) (b) (4). Among other study-related activities, (b) (4) was responsible for selecting qualified investigators, study conduct, clinical trial monitoring, medical monitoring, data management, and statistics. (b) (4) was responsible for trial conduct and monitoring at specific sites in the US.

The inspection covered roles and responsibilities; the organization and its personnel; registration of studies on clinicaltrials.gov; monitoring procedures and activities; quality management; adverse event reporting; process for managing protocol deviations; data collection, handling, and management; record retention; statistical analysis processes and procedures; financial disclosure; and test article accountability. Records reviewed during the inspection included investigator agreements; vendor agreements and contracts; written standard operating procedures; documentation of protocol deviations; validation and other documentation related to the operational use of eSystems and AiCure compliance software used in the trial; AiCure dosing classified as red at Site 202; adverse event reporting; drug accountability; relevant communication and correspondence; and monitoring activities.

The sponsor explained that the following challenges occurred in interpreting the susceptibility testing results, which led them to perform WGS on 149 subjects and change the overall response outcome in 8.4% (90/1071) of subjects:

1) **Discrepant testing results in baseline samples among the central laboratories (e.g., Covance, IHMA):** For example, two cultures of the same urine sample demonstrated the same genus/specified with different quinolone susceptibilities. The sponsor noted that 1.7% (18/1071) of subjects had discrepant susceptibilities at screening.
2) **Different susceptibility profiles between baseline and TOC**: For example, standard susceptibility testing implied that the TOC isolate was not the same as the baseline isolate. Results of standard susceptibility testing were confirmed by WGS.
3) **Reliability of urine culture results among patients at Sites 202 and 218**: See inspection summary for these two sites presented earlier in Section III of this CIS.

The statistical analysis plan (SAP) was finalized on 30 Sep 2019 prior to the pre-planned

interim analysis conducted by an unblinded statistician for sample size re-adjustment. The SAP was further amended on 11 March 2020 to specifically change overall response criteria, stating that the genus/species and susceptibility profiles needed to match (i.e., to incorporate results from PFGE and WGS). The study was unblinded on 19 Jun 2020, and PFGE and WGS testing results were incorporated into the study results on 29 Jun 2020.

***Reviewer's comment:*** *It is very concerning that the WGS results were incorporated into the study results after unblinding of the study, as these results were used to place subjects in subgroups of susceptible and resistant populations and to determine overall response. There was a potential for bias to be introduced to the study results because the sponsor's statisticians and data management staff had prior knowledge of the subjects' treatment assignment and overall response.*

*Moreover, the sponsor was also unable to provide documentation (i.e., meeting minutes for calls or any relevant email between the sponsor, IHMA,* (b) (4) *and Covance laboratories, and/or data management and statistics groups) that contemporaneously documented the discussions and rationale for key decisions made relating to the microbiology analysis decisions and changes to the SAP after the interim analysis. The lack of contemporaneously generated documentation possibly points to a larger issue of inadequate sponsor oversight of the trial and of their CROs.*

*In a 22 March 2021 response to an IR, the sponsor, at the request of the review division, conducted a re-analysis for the EOT, TOC, and FV timepoints using the IHMA primary or confirmatory culture and ciprofloxacin susceptibility of local isolates based on MIC broth microdilution assay only. In addition, a subject with a urinary bacterial pathogen found post-baseline with $>10^3$ CFU/mL that was the same genus and species as that found at baseline was considered a microbiological failure/persistence. Differences in antibacterial drug susceptibility or WGS profiles of post-baseline isolates were not considered to justify a different strain of the baseline pathogen. Of note, this re-analysis addresses our concerns, as described above, regarding the changes to the SAP and incorporation of WGS and PFGE results after unblinding of the study.*

The sponsor also deemed the data generated at Site 202 and Site 218 unreliable for issues previously noted in this CIS. For more detailed information on these issues, please see the inspection summaries for Site 202 and Site 218 above.

For Site 202, it was noted during the sponsor inspection that RMV were conducted approximately every month starting in October 2018 until May 2019. The site was further audited by the CRO in June 2019 and then again by the sponsor in October 2019. The sponsor states that they notified the site of an enrollment hold on 4 Apr 2019 and deemed the data to be unreliable on 20 May 2020. However, neither the sponsor (during the sponsor inspection) nor Site 202 (during the site inspection) were able to provide a formal notice/letter of enrollment hold. The only documentation that the sponsor was able to provide was a telephone contact report, dated 16 May 2019, reportedly documenting their discussion with the site of their enrollment hold. In addition, the June and October 2019 audit reports were not available for review during the inspection. Also, the sponsor did not provide documentation of any formal

root cause analysis that was conducted and CAPA that was implemented to address the urine sample contamination issues.

The sponsor also stated that there was a high rate of red and/or orange flags (in 27 out of 68 subjects) from use of the AiCure software at Site 202. During the sponsor inspection, the sponsor provided an Excel listing of all subjects at all sites (including Site 202) whose dosing was classified as red by AiCure. Although 14 of the 68 subjects at Site 202 had their dosing classified as red (as reported on the Excel listing), there were discrepancies found in the Excel listing when it was compared against information and source records collected during the inspection of Site 202. Specifically, there was documentation in the source records at Site 202 that noted that 10 of these 14 subjects had later taken the red flagged doses after first intentionally spitting them out.

***Reviewer's comments:*** *Based on the documentation provided during the sponsor inspection, it does not appear that the sponsor and the CRO conducted a sufficient root cause analysis of the urine sample contamination problem or implemented a sufficient CAPA, other than retraining (that occurred in December 2018 and which was ineffective) and placing the site on enrollment hold.*

*In addition, the high rate of red/orange flags at this site as reported by the sponsor appears to misrepresent the actual number of subjects who intentionally did not take the medication as directed. Source records indicate that subjects had difficulty using the application, had issues with swallowing the tablets and capsules because they were too large, or experienced nausea, and this explains in part the high number of doses that were classified as red by the AiCure software. It was well-documented in the source records at the site (e.g., drug accountability records, medical notes, and written notes in the subject's regulatory binder, including the RMV reports) that at least 10 subjects confirmed that they subsequently took the dose after initially spitting out or removing the tablet or capsule from their mouth. It is unclear why this dosing information was not communicated or available to the sponsor as there was adequate follow-up on these issues during the RMV.*

*As previously stated in this CIS, use of urine samples from one subject to enroll multiple subjects and other GCP noncompliance issues that may impact data reliability could not be confirmed because a full picture of the conduct of the trial at this site could not be reconstructed (i.e., significant knowledge gaps remain. Therefore, a post hoc sensitivity analysis should be conducted, excluding all the subjects from this site to determine the robustness of the study results. Of note, in their 22 March 2021 response to an IR, the sponsor had already conducted a reanalysis of the study data as requested by FDA, both with and without the subjects from Site 202.*

RMV reports were also reviewed for Site 218, which was closed to further enrollment on 29 Apr 2019. The site initiation visit occurred in 1 March 2019, and RMV occurred approximately every month in March, April, and May 2019. A for-cause audit was conducted by the sponsor in May 2019. A summary of this audit was provided during the inspection, and no critical findings were identified. (b) (7)(A)

(b) (7)(A). The final close-out visits occurred in July 2020 and were conducted remotely due to the COVID-19 pandemic. Because of this, the monitor was not able to physically review the investigator site files to ensure that all study-related documents were present and in order; rather, the monitor sent a checklist to be completed by the site study coordinator. (b) (7)(A)

***Reviewer's comments:*** (b) (7)(A) *In the 22 March 2021 response to an IR, the sponsor has already conducted a reanalysis of the study data as requested by FDA, without the efficacy data from the subjects at Site 218. As mentioned previously,* (b) (7)(A) *, a post hoc sensitivity analysis should be conducted, excluding all the subjects from this to determine the robustness of the study results.*

{See appended electronic signature page}

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/s/

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# Division of Pediatric and Maternal Health Review

**Date:** 5/4/2021 **Date consulted:** 8/6/2020

**From:** Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

**Through:** Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

**To:** Division of Anti-Infectives (DAI)

**Drug:** Sulopenem etzadroxil/probenecid bilayer tablets

**NDA:** 213972

**Applicant:** Iterum Therapeutics

**Subject:** Pregnancy and Lactation Labeling

**Proposed Indication:** is indicated in adult women ≥ 18 years of age for the treatment of uncomplicated urinary tract infection caused by designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone

**Materials Reviewed:**

- Applicant's submitted background package and proposed labeling for NDA 213972
- DAI consult form for DPMH, DARRTS Reference ID 4759684

**Consult Question:**

DAI is seeking assistance from DPMH in developing Sections 8.1, 8.2 of the product's labeling.

## INTRODUCTION AND BACKGROUND

On November 25, 2020, the applicant (Iterum Therapeutics) submitted a new NDA 213972 for (b) (4) tablets for approval. The Division of Anti-Infectives (DAI) consulted the Division of Pediatric and Maternal Health (DPMH) on March 5, 2021, to assist with the Pregnancy and Lactation subsections of labeling.

### Regulatory History

- Probenecid was initially approved on April 26, 1951 in United States as Benemid oral tablet, which has been withdrawn from sales not for reasons of safety or effectiveness. There are several ANDAs for probenecid, which is indicated for the treatment of the hyperuricemia associated with gout and gouty arthritis and as an adjuvant to therapy with penicillin or with ampicillin, methicillin, oxacillin, cloxacillin, or nafcillin, for elevation and prolongation of plasma levels by whatever route the antibiotic is given.
- On November 25, 2020, Iterum Therapeutics submitted a new NDA for a combination product (b) (4), sulopenem etzadroxil and probenecid tablets, NDA 213972, for the treatment of uncomplicated urinary tract infection caused by designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone.
- This approval is based on 505(b)(1) regulatory pathway of the Federal Food, Drug, and Cosmetic Act for sulopenem etzadroxil; this approval is based on 505(b)(2) regulatory pathway of the Federal Food, Drug, and Cosmetic Act for probenecid, due to the inclusion of a marketed drug probenecid in the formulation. Benemid is the referenced labeled drug (RLD).
- On March 15, 2019, FDA granted sulopenem etzadroxil and probenecid tablets a Fast Track Status.

### Drug Characteristics

Sulopenem etzadroxil Characteristics[1]

| | |
|---|---|
| Drug Class | penem antibacterial |
| Mechanism of action | Sulopenem etzadroxil is rapidly hydrolyzed to the active moiety sulopenem. The bactericidal activity of sulopenem results from the inhibition of cell wall synthesis and is mediated through sulopenem binding to penicillin binding proteins (PBPs). |
| Molecular weight | 477.61 Dalton |
| Half-life | 1 hour |
| Protein Binding | 10% approximately in humans (sulopenem) |
| Bioavailability | 40% fasting and 64% when taken after a high-fat meal |
| Serious Adverse Reactions | • Serious hypersensitivity (anaphylactic) reactions have been reported with β-lactam antibacterial drugs.<br>• Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents. |

[1] Based on Applicant's Proposed Labeling with DAI Review Team Input.

Probenecid Characteristics[2]

| | |
|---|---|
| Drug Class | Renal tubular transport blocking agent |
| Mechanism of action | reduce renal clearance and increase systemic exposure of sulopenem |
| Molecular weight | 285.36 Dalton |
| Half-life | 5-8 hours and is dose dependent[3]<br>4-17 hours for 2 g, the half-life decreased as the dose decreases from 2g to 500mg[4]<br>6-12 hours[5] |
| Protein Binding | 85-90%[6,7] |
| Bioavailability | >90%[8] |
| Serious Adverse Reactions | hepatic necrosis;<br>anaphylaxis;<br>aplastic anemia, leukopenia, hemolytic anemia which in some patients could be related to genetic deficiency of glycose-6-phospahare dehydrogenase in red blood cells. |

Current State of the Labeling for Probenecid, Actavis Pharma, Inc.[9]

- Approved labeling is not in Physician Labeling Rule (PLR) format.
- There is no boxed warning for this drug.
- There are contraindications for use of probenecid:
  - Hypersensitivity to probenecid.
  - Children under 2 years of age.
  - Not recommended in persons with known blood dyscrasias or uric acid kidney stones. Therapy with probenecid should not be started until an acute gouty attack has subsided.

Use in Pregnancy

Probenecid crosses the placental barrier and appears in cord blood. The use of any drug in women of childbearing potential requires that the anticipated benefit be weighed against possible hazards.

- There are no existing pregnancy testing/contraception recommendations.
- There are no drug-drug interactions with hormonal contraceptives.

[2] From the approved labeling of probenecid by Actavis Pharma, Inc. Revised: December 2016. The approved RLD, Benemid was discontinued, not for the reasons of safety or effectiveness.
[3] Gilman, A.G., T.W. Rall, A.S. Nies and P. Taylor (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, NY. Pergamon Press, 1990., p.746
[4] McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 93. Bethesda, MD: American Society of Hospital Pharmacists, Inc., 1993 (Plus Supplements, 1993)., p.1652
[5] DrugBank URL: https://www.drugbank.ca/drugs/DB01032 Accessed 3/18/2021
[6] Ilett KF, Hackett LP, Ingle B, Bretz PJ: Transfer of probenecid and cephalexin into breast milk. Ann Pharmacother. 2006, 40: 986-989. 10.1345/aph.1G580.
[7] Weber A, de Groot R, Ramsey B, Williams-Warren J, Smith A: Probenecid pharmacokinetics in cystic fibrosis. Dev Pharmacol Ther. 1991, 16: 7-12.
[8] Anderson R, Gambertoglio JG, Schrier RW: Clinical use of drugs in renal failure. 1976, Springfield, Il: Charles C Thomas
[9] The approved labeling for the RLD, Benemid was discontinued, not for the reasons of safety or effectiveness. However, Probenecid labeling is included in Daily Med: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ae126418-5474-4fbe-b83c-bde8b2b4ae6e and was accessed on 4/1/2021

***PREGNANCY***

Condition: Uncomplicated urinary tract infection and pregnancy

An estimated 11% of U.S. women report at least one physician-diagnosed urinary tract infection (UTI) per year, and the lifetime probability that a woman will have a UTI is 60%.[10] Acute cystitis occurs in approximately 1 to 2 percent of pregnant women, and the estimated incidence of acute pyelonephritis during pregnancy is 0.5 to 2 percent which is higher than the general population.[11] Smooth muscle relaxation and subsequent ureteral dilatation that accompany pregnancy are thought to facilitate the ascent of bacteria from the bladder to the kidney, resulting in the greater propensity for bacteriuria to progress to pyelonephritis during pregnancy.[11] The organisms that cause bacteriuria and urinary tract infections (UTI) in pregnant women are of the same species and have similar virulence factors as in nonpregnant women; E. coli is the predominant uropathogen found.[11] Historically UTI is often managed with oral antibiotics including cephalosporins, fluroquinolones, and trimethoprim-sulfamethoxazole, but the use of these agents is being compromised by an increase in extended spectrum-beta-lactamase (ESBL)-producing organisms. Fluoroquinolone-resistant *E. coli* has progressively increased in the United States from 1.2% in 1998 to 25% in 2012-2014.[12] An observational study of 272 patients with uncomplicated pyelonephritis and 181 with complicated pyelonephritis in the US (2013-2014) found that the prevalence of fluoroquinolone resistance across study sites was 6.3% (range by site 0.0%-23.1%) and 19.9% (0.0%-50.0%), respectively; the prevalence of ESBL production was 2.6% (0.0%-8.3%) and 12.2% (0.0%-17.2%), respectively.[13]

Untreated bacteriuria has been associated with an increased risk of preterm birth, low birth weight, and perinatal mortality in most studies.[11] No correlation has been clearly established between acute cystitis of pregnancy that is treated and increased risk of low birth weight, preterm delivery, or pyelonephritis, perhaps because pregnant women with symptomatic lower UTIs usually receive treatment.[11]

Treatment of UTIs is often empiric. See table below for a list of commonly used antibiotics in pregnancy from UpToDate (Table 1).[11] In a committee opinion issued September 2017, American College of Obstetrics and Gynecology cautioned physician usage of nitrofuran and sulfonamide classes of antibiotics during the first trimester of pregnancy as the association between these classes of antibiotics and birth defects are mixed.[14]

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[10] Practice Bulletin Number 91: Treatment of urinary tract infections in nonpregnant women. ACOG Committee on Practice Bulletins. 2016.

[11] Hooton TM, et al. Urinary tract infections and asymptomatic bacteriuria in pregnancy. UpToDate. https://www.uptodate.com/contents/urinary-tract-infections-and-asymptomatic-bacteriuria-in-pregnancy?search=UTI%20in%20pregnancy&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1 Accessed 3/15/21.

[12] Critchley IA, et al. (2019) The burden of antimicrobial resistance among urinary tract isolates of Escherichia coli in the United States in 2017 PLoS ONE 14(12): e0220265. https://doi.org/10.1371/journal.pone.0220265

[13] Talan DA, et al. Fluoroquinolone-Resistant and Extended-Spectrum B-Lactamase-Producing Escherichia coli Infections in Patients with Pyelonephritis, United States. Emerging Infectious Diseases 2016;22 (9): 1594-1603 www.cdc. gov/eid

[14] ACOG Committee Opinion Number 717: Sulfonamides, Nitrofurantoin, and Risk of Birth Defects. September 2017.

Table 1. Commonly Used Antibiotics in Treatment of Urinary Tract Infection in Pregnancy[11]

**Antibiotics for asymptomatic bacteriuria and cystitis in pregnancy**

| Antibiotic | Dose | Duration | Notes |
|---|---|---|---|
| Nitrofurantoin | 100 mg orally every 12 hours | Five to seven days | Does not achieve therapeutic levels in the kidneys so should not be used if pyelonephritis is suspected.<br>Avoid use during the first trimester and at term if other options are available. |
| Amoxicillin | 500 mg orally every 8 hours or<br>875 mg orally every 12 hours | Five to seven days | Resistance may limit its utility among gram-negative pathogens. |
| Amoxicillin-clavulanate | 500 mg orally every 8 hours or<br>875 mg orally every 12 hours | Five to seven days | |
| Cephalexin | 250 to 500 mg orally every 6 hours | Five to seven days | |
| Cefpodoxime | 100 mg orally every 12 hours | Five to seven days | |
| Fosfomycin | 3 g orally as single dose | | Does not achieve therapeutic levels in the kidneys so should not be used if pyelonephritis is suspected. |
| Trimethoprim-sulfamethoxazole | 800/160 mg (one double strength tablet) every 12 hours | Three days | Avoid during the first trimester and at term. |

The durations listed in the table are based on data from studies conducted in both nonpregnant and pregnant women.

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Nonclinical Experience

Sulopenem etzadroxil was orally administered during organogenesis in embryo-fetal studies in mice, rats, and rabbits. In pregnant mice, an increased litter incidence of a fetal malformation, cleft palate, was observed with an oral dose of sulopenem etzadroxil associated with a sulopenem exposure approximately 46 times the clinical sulopenem exposure for the maximum recommended human dose (MRHD) of sulopenem etzadroxil. In pregnant rats and rabbits, orally administered sulopenem etzadroxil was not associated with fetal malformations at any dose, but in rats, maternal toxicity and reduced fetal body weights occurred at a sulopenem etzadroxil dose associated with a sulopenem plasma exposure approximately 11 times the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil. In rabbits, maternal toxicity and reduced fetal body weights occurred at sulopenem etzadroxil doses associated with sulopenem plasma exposures approximately 0.25 and 0.5 times respectively the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil.

The reader is referred to the full Pharmacology Toxicology review by James S. Wild, Ph. D and Terry Miller, Ph. D.

Review of Clinical Trials

There were three patients who became pregnant while enrolled in clinical trials for this drug. Two patients were in the active control arm, and one patient received the drug during the 1st trimester of pregnancy. The patient who received the drug initially had a false negative pregnancy test at the site, and three days after enrollment the pregnancy test was reported to be positive by the central lab. The patient stopped the test medication immediately. She delivered a healthy male infant 8 months later.

Review of Literature

*Applicant's Review of Literature*

The applicant reviewed the published literature and noted that probenecid crosses the placenta.[15] Probenecid was previously listed by the FDA as Pregnancy Category B.

In addition, a review article by Gutman et al.[16] notes there are over 450 instances of probenecid use during pregnancy reported in the literature. "Outcomes were infrequently reported, but the few studies that did include such data did not note an increase in adverse fetal events among those infants exposed to probenecid compared to controls."

*Reviewer comment:*

*This reviewer agrees the available data on probenecid use in pregnancy are limited in both number and quality. The authors' conclusion from this article is that the available data do not suggest any evidence of teratogenic effects. The reader is referred to Table 2 (taken from the review article) below for a list of articles reviewed.*

[15] Probenecid USPI. http://www.drug.com. 5/1/2018.

[16] Gutman, J., Kachur, S.P., Slutsker, L. et al. Combination of probenecid-sulphadoxine-pyrimethamine for intermittent preventive treatment in pregnancy. Malar J 11, 39 (2012). https://doi.org/10.1186/1475-2875-11-39

Table 2. Reported of Probenecid Use During Pregnancy[16]

| Author | Study | N | Treatment | Timing of Treatment | SAEs | Infant Outcome |
|---|---|---|---|---|---|---|
| Cavenee et al. [84] | Treatment of gonorrhoea in pregnancy | 123 | Amoxicillin 3 gm + probenecid 1 gm | 64 patients (25%) treated in 1st trimester of pregnancy | None, one woman reported vomiting several hours after taking the drug | 71 infants were evaluated, 14 treated < 14 week, 1 major malformation (7%), 4 minor malformations (29%); 57 > 14 week, 0 major and 10 minor malformations (18%), overall 1% major and 20% minor malformations, not statistically different from other groups |
| Adelson et al. [85] | Treatment of urinary tract infections in pregnancy | 98 | Ampicillin 3.5 gm + probenecid 1 gm | Not stated | 3 patients developed candidal vulvo-vaginitis, 3 patients developed diarrhoea | Not stated |
| Brown et al. [86] | Renal clearance of oestrogen in pregnancy | 9 | Probenecid 2.5 gm | Last 6 weeks of pregnancy | None reported | No foetal deaths or stillbirths |
| Lee et al. [87] | Gout and pregnancy | 1 | Probenecid 1 gm to 3 gm daily throughout pregnancy | Throughout pregnancy | Anaemia thought related to renal disease | Healthy infant |
| Weingold et al. [88] | Gout and pregnancy | 1 | Colchicine and probenecid | Throughout 1st pregnancy and for the first 14 weeks of 2nd pregnancy | Mild anaemia | 1st pregnancy: infant died on DOL4 due to hyaline membrane disease 2nd pregnancy: healthy infant |
| Goodrich [55] | Gonorrhoea and pregnancy | 163 | Penicillin G 4.8 × $10^6$ U (n = 158) or ampicillin (n = 5) + probenecid 1 gm | Not stated | None reported | Not stated |
| Schackis [89] | Hype-ruricemia and pre-eclampsia | 20* | Probenecid 250 mg twice daily for 7 days | 26-32 weeks gestation | No side-effects to probenecid were recorded | There were 3 intrauterine foetal deaths: 1 from an abruptio placenta (> 1 kg) in the probenecid group and 2 from suspected placental insufficiency (both < 1 kg): 1 each in the probenecid and placebo group. |
| Czaczkes et al. [90] | Pre-eclampsia, eclampsia | 18† | Probenecid 0.5 gm 3 times daily for 5-6 days | Not stated | None reported | Not stated |

*20 women treated and an additional 20 untreated controls

†15 women with pre-eclampsia + 3 pregnant controls without pre-eclampsia

*DPMH's Review of Literature*

DPMH conducted a review of the published literature in Embase, Pubmed, Micromedex,[17] ReproTox,[18] TERIS,[19] and Shepard's.[20] Search terms used were "Sulopenem" or "probenecid" AND "pregnancy," "Sulopenem etzadroxil" or "probenecid" AND "pregnancy" AND "fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage."

- There are no articles on sulopenem use in pregnancy.
- There are a few additional reports and studies on probenecid use in pregnancy.
    - A case series including two case reports of probenecid use during pregnancy without adverse events.[21]
        - A 20-year-old patient utilized amoxicillin (6g/d) and probenecid (1g/d) for 14 days for the treatment of maternal syphilis at 13 weeks of pregnancy. She later delivered a healthy boy at 41 weeks' gestation without congenital birth defects.
        - A 31-year- old patient utilized amoxicillin (3g/d) and probenecid (750mg/d) at 6 weeks' gestation for syphilis for 3 days but had to switch to intravenous ceftriaxone (2g/d) for an additional of 8 days due to hyperemesis. She delivered a healthy girl at 39 weeks. Congenital syphilis was not present.
    - A randomized controlled trial[22] (also included in Table 1 above) of 353 pregnant patients (252 analyzed) with gonorrhea treated at average gestational age of 22 weeks with either ceftriaxone (250mg, intramuscular) (n=114; 84 analyzed), amoxicillin (3g, oral) plus probenecid (1g, oral) ) (n=123; 84 analyzed), or spectinomycin (2 g, intramuscular) (n=116; 84 analyzed). One case of vomiting in the oral amoxicillin plus probenecid group was reported. The authors did not find any significant differences in major or minor malformation rates between the treatment groups.
        - There were 2 cases of major malformations reported, one in the amoxicillin with probenecid group (exposed in the first trimester; symmetric growth retardation with microcephaly) and one in the spectinomycin group.
        - There were 4 cases of minor malformations reported in 14 exposed (29%) to amoxicillin with probenecid in the first trimester; 4 cases out of 20 (20%) exposed to spectinomycin in the first trimester; 2 cases out of 18 cases exposed (11%) to ceftriaxone during the first trimester.[23]

      *Reviewer comment:*
      *The sample population from the randomized controlled trial above[22] has a limited size. The number of major and minor congenital malformations appear to be similar among comparator groups. The background rate of congenital*

[17] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 3/12/21.
[18] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 3/12/21.
[19] Teris database, Truven Health Analytics, Micromedex Solutions. Accessed 3/12/21.
[20] 2020 Shepard's: A Catalog of Teratogenic Agent. Accessed 3/12/21
[21] Katanami Y, et al. Amoxicillin and ceftriaxone as treatment alternatives to penicillin for maternal syphilis. Emerging Infectious Disease. 2017;23(5): 827-830.
[22] Cavenee MR, et al. Treatment of gonrrhea in pregnancy. Obstet Gynecol. 1993 Jan;81(1):33-8.
[23] Comunian-Carrasco G, et al. Cochrane database of systematic reviews: antibiotics for treating gonorrhea in pregnancy (review). 2018(2). Article Number CD011167. DOI: 10.1002/14651858.CD011167.pub2.

*malformation for pregnant patient with gonorrhea during the first trimester is unknown.*

There are no data found on sulopenem in any of the reference sites. There are data on probenecid use during pregnancy at the reference sites below.

Micromedex[17] and ReproTox[18] both state probenecid crosses the placenta and appears in cord blood.[24] Probenecid has been used with procaine penicillin G in the treatment of gonococcal urethritis occurring in pregnancy with no reported adverse effects including labor complications, prematurity, low birthweight, or neonatal death in the exposed pregnancies.[25,26] There has also been use of probenecid in the treatment of gout during pregnancy without apparent adverse drug effects.[27,28] TERIS[19] noted major congenital anomalies were reported in 17 (5.0%) of 339 infants of women who had received prescriptions for probenecid during the first trimester of pregnancy in a study of Michigan Medicaid recipients,[29] which is similar to the expected rate of 4.1%. There was no pattern of major congenital anomalies observed. In another study, the frequency of malformations did not appear to be increased in the children of about 20 women who were treated with amoxicillin and probenecid for gonorrhea in the first trimester of pregnancy.[30]

*Reviewer comment:*
*There are no published data on use of sulopenem during pregnancy in humans. There is only one case of sulopenem use in pregnancy in the clinical trials with no adverse fetal effect noted. There were no teratogenic effects observed in rats and rabbits treated with sulopenem during organogenesis. Cleft palate was observed in mice treated with sulopenem at exposures 46 times the MRHD.*

*Published studies on probenecid use in pregnancy, including randomized controlled trials and case reports, have not identified a drug related risk of miscarriage, congenital malformations, or adverse maternal or fetal outcomes. The applicant provided an adequate review of published literature regarding probenecid use in pregnancy. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.*

***LACTATION***

Nonclinical Experience

The active metabolite of sulopenem etzadroxil, sulopenem, was present in rat milk after oral dosing of sulopenem etzadroxil to lactating females.

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[24] Product Information: probenecid oral tablets, probenecid oral tablets. Marlex Pharmaceuticals, Inc. (per DailyMed), New Castle, DE, 2012.
[25] Stoll BJ et al: Treated maternal gonorrhea without adverse effect on outcome of pregnancy. South Med J 75:1236-8, 1982.
[26] Cavenee MR, Farris JR, Spalding TR et al: Treatment of gonorrhea in pregnancy. Obstet Gynecol 81: 33-8, 1993.
[27] Lee FI, Loeffler FE: Gout and pregnancy. J Obstet Gynecol Br Commonw 69:299-304, 1962.
[28] Batt RE et al: Gout and salt-wasting renal disease during pregnancy. Diagnosis, management, and follow-up. JAMA 186:835-8, 1963.
[29] Rosa F: Personal Communication, 1993. Cited in: Briggs GG, Freeman RK. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 10th ed. Philadelphia, Pa.: Wolters Kluwer Health, 2015, p 1152.
[30] Cavenee MR, Farris JR, Spalding TR, Barnes DL, Castaneda YS, Wendel GD Jr: Treatment of gonorrhea in pregnancy. Obstet Gynecol 81(1):33-38, 1993.

The reader is referred to the full Pharmacology Toxicology review by James S. Wild, Ph. D and Terry Miller, Ph. D.

Review of Literature

*Applicant's Review of Literature*

The applicant conducted a search of literature and notes very limited information available on the effects of probenecid in breastfed infants in the published labeling.[15] There is only one article found on probenecid use during lactation.

- A case report of a 30-year-old lactating patient who was treated with oral probenecid and cephalexin for a breast infection. Milk was collected over a dose interval at steady-state, and concentrations of probenecid and cephalexin were measured by high-performance liquid chromatography. The average concentrations of probenecid and cephalexin in milk were 964 and 745 ug/L, respectively, corresponding to absolute and relative infant doses of 145 ug/kg/day and 0.7% for probenecid and 113 ug/kg/day and 0.5% for cephalexin. Diarrhea was observed in the breastfed infant. The Naranjo probability scales rating suggested that cephalexin was more likely than probenecid to be the cause of the infant's diarrhea.[31]

The applicant concluded:

> Probenecid excreted in breast milk was quantified in a case report. The probenecid dose delivered to the infant through breast milk, estimated with the observed concentrations in the breast milk, was 145 µg/kg/day.

*DPMH's Review of Literature*

DPMH conducted a review of published literature in PubMed and Embase using the search terms "sulopenem" or "probenecid" AND "lactation" and "sulopenem" or "probenecid" AND "breastfeeding."

- There are no articles on the use of sulopenem during lactation.
- There are no additional articles on the use of probenecid during lactation.

There is no information found on sulopenem in any of the reference sites. There is information found regarding use of probenecid during lactation at the reference sites below.

ReproTox,[18] Hales,[32] Brigg's,[33] and Lactmed[34] all agree that probenecid is excreted in human milk and cite the case report[31] above. Micromedex[17] gives Lactation Rating: "Infant risk cannot be ruled out." Brigg's[33] gives breastfeeding recommendation: "Limited Human Data-Probably Compatible."

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[31] Ilett K.F., Hackett L.P., Ingle B., Bretz P.J. Transfer of probenecid and cephalexin into breast milk. Annals of Pharmacotherapy 2006 40:5 (986-989)

[32] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY.

[33] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 3/13/21.

[34] http;//toxnet.nlm.nih.gov/newtoxnet/lactmed.htm. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The lactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Access 3/13/21.

*Reviewer comment:*
*There are no data on sulopenem use during lactation in humans. Sulopenem is present in animal milk. When a drug is found in animal milk, it is likely to be present in human milk.*

*Probenecid is present in human milk.*

*Overall, the applicant provided an adequate review of published literature regarding probenecid use in lactating women. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.*

***FEMALES AND MALES OF REPRODUCTIVE POTENTIAL***

Nonclinical Experience

Mutagenesis

Sulopenem Etzadroxil

Sulopenem etzadroxil was negative for mutations in an in vitro Ames assay with and without metabolic activation but positive for chromosome aberrations with and without metabolic activation in vitro in peripheral human lymphocytes and Chinese hamster ovary cells. In vivo, sulopenem etzadroxil was negative for genetic toxicity in a bone marrow micronucleus assay in rats.

Sulopenem

Sulopenem did not induce mutations in a reverse mutation assay in bacterial cells with and without metabolic activation or in a CHO HGPRT mammalian cell mutation assay with and without metabolic activation. Sulopenem was positive for chromosome aberrations in vitro in V79 Chinese hamster lung cells, but negative for genetic toxicity in vivo in bone marrow micronucleus assays in mice and rats.

Probenecid

Probenecid was shown to be negative for mutagenicity in an in vitro Ames assay with and without metabolic activation and negative for chromosome aberrations in an in vitro chromosome aberration assay in Chinese hamster ovary cells with and without metabolic activation.

Impairment of Fertility

Sulopenem etzadroxil

Male and female fertility and early embryonic development were examined in rats (20/sex/group) administered sulopenem etzadroxil in oral doses of 100, 400, or 2000 mg/kg before and during mating. Male rats were administered sulopenen etzadroxil for 28 days before mating and during the 14-day mating period, and females were administered sulopenem etzadroxil for 14 days before mating and during the mating period. There were no treatment-related effects on estrous cycle length, mating and fertility rates, implantation, conceptus viability, sperm concentration and motility, or accessory male sex gland weights with any dose of sulopenem etzadroxil up to the high dose of 2000 mg/kg/day (approximately equal to 19-times the recommended human dose based on body surface area comparison)

Probenecid

Fertility studies have not been conducted with probenecid.

The reader is referred to the full Pharmacology Toxicology review by James S. Wild, Ph. D and Terry Miller, Ph. D.

Review of Literature

*Applicant's Review of Literature*

The applicant did not find any relevant articles on probenecid use and fertility.

*DPMH's review of literature*

DPMH conducted a review of published literature review using Embase, Pubmed, Micromedex,[35] ReproTox,[36] and TERIS.[37] Search terms used were "sulopenem" or "probenecid" AND "reproduction," "sulopenem" or "probenecid" AND "infertility," and "sulopenem" or "probenecid" AND "contraception." The following articles were located.

- In a prospective cohort study of 20 male patients with spinal cord injury, the patients were administered probenecid for 4 weeks (250mg twice a day for 1 week, followed by 500mg twice a day for 3 weeks). Semen quality was assessed pre-treatment, post-treatment, and 4-week post-treatment. The mean sperm motility improved from 19% to 26% and continued into 4 weeks post-treatment. Total sperm count also improved. Sperm concentration did not significantly change.[38]

ReproTox[36] did not have any information on possible adverse effects of probenecid on female or male reproductive function.

*Reviewer comment:*
*There is no published literature regarding the effect of sulopenem on human fertility. Animal study did not show any adverse effects on fertility.*

*There are no studies that show that probenecid adversely affects fertility in humans.*

*There is no anticipated interaction between hormonal contraception and sulopenem plus probenecid. This was confirmed in discussion with DAI Clinical Pharmacology Team.*

*Overall, the applicant provided an adequate review of published literature regarding probenecid use in males and females of reproductive potential. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.*

**DISCUSSION AND CONCLUSIONS**

Pregnancy

There was one pregnant patient exposed to sulopenem during the first trimester of pregnancy in the clinical trials which resulted in a term delivery of a normal infant. Overall, animal

[35] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 3/13/21.
[36] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 3/13/21.
[37] Teris database, Truven Health Analytics, Micromedex Solutions, Accessed 3/13/21.
[38] Ibrahim E, et al. (2018) Oral probenecid improves sperm motility in men with spinal cord injury, The Journal of Spinal Cord Medicine, 41:5, 567-570, DOI: 10.1080/10790268.2017.1320875

reproduction studies did not demonstrate concerns for embryofetal toxicity with use of sulopenem in pregnant animals. There were no teratogenic effects observed in rats and rabbits treated with sulopenem during organogenesis. Although cleft palate was observed in mice treated with sulopenem, this occurred at high exposures that were 46x the MRHD.

Probenecid has been approved for use in the US since 1951. Available published studies over several decades of probenecid use in pregnancy, including two randomized controlled trials and case reports, have not identified a drug-related risk of miscarriage, congenital malformations, or adverse maternal or fetal outcomes.

Although there is anticipated use of sulopenem etzadroxil/probenecid in pregnant patients and in females of reproductive potential for the treatment of quinolone resistant uncomplicated urinary infection, there are a variety of drugs that are currently used for the treatment of quinolone resistant UTIs in pregnancy. Additionally, although sulopenem is a penem and not a carbapenem, the two classes of drugs are very similar in their physical properties and structure. The penems and carbapenems both contain 5-membered ring attached to the beta-lactam ring, with the key difference being that carbapenems have a carbon-containing 5-membered ring attached to the beta-lactam ring, whereas the penems have a sulfur atom incorporated into the 5-membered ring. Sulopenem has the additional distinction of having 2 other sulfur atoms included in the side chain attached to the core 5-membered ring. Both classes of drugs have short half-lives and at least 50% of an administered dose is excreted unchanged in urine. This was confirmed in discussion with the DAI Clinical Pharmacology Team and DAI Clinical Team. Since carbapenems have been on the market for decades, and teratogenic risks and adverse maternal and fetal outcomes have not been identified with carbapenem use during pregnancy, DPMH does not recommend a postmarking study for sulopenem etzadroxil/probenecid at this time.

Lactation

It is not known if sulopenem is present in human milk. Sulopenem is present in animal milk. When a drug is present in animal milk, it is likely to be present in human milk. There are no available data with use of sulopenem in lactating women, the effect on breastfed infant, or on milk production.

Probenecid is present in human milk. One case report of oral probenecid and cephalexin use during lactation resulted in diarrhea in the breastfed infant, however, the authors noted that cephalexin was the likely cause of the diarrhea.

Although there is anticipated use of sulopenem etzadroxil/probenecid during lactation for the treatment of uncomplicated urinary infection, sulopenem is similar to the carbapenems. Decades of experience with carbapenems indicates that several carbapenems are found in small amounts in milk, and the low levels of the drug are not expected to cause harmful effects in the breastfed infants. Therefore, sulopenem is not expected to cause harmful effects in the breastfed infants. DPMH does not recommend a postmarking lactation study for sulopenem etzadroxil/probenecid at this time.

Females and Males of Reproductive Potential

There is no evidence in the literature to suggest that sulopenem or probenecid adversely affects male or female fertility. There is no anticipated drug-to-drug interaction between sulopenem or probenecid with hormonal contraceptives. DPMH recommends omitting subsection 8.3.

**LABELING RECOMMENDATIONS**

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

**DPMH Proposed Pregnancy and Lactation Labeling**

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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# M E M O R A N D U M

**From:** Shamir Tuchman, MD, MPH, Medical Officer
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

**Through:** Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John J. Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

**To:** Division of Anti-Infectives (DAI)

**Subject:** Review of label referencing Probenecid contraindication in patients younger than 2 years of age

**Applicant:** Iterum Therapeutics, U.S. Ltd.[1]

**Application number:** NDA 213972

**Drug:** Sulopenem etzadroxil/Probenecid [2]

[1] This review will refer to "Iterum Therapeutics, U.S. Ltd." as the "Applicant"

[2] This review will refer to the drug product as "Sulopenem/Probenecid"

**Drug Class:** Penem antibacterial/Uricosuric agent

**Proposed Indication:** Treatment of uncomplicated urinary tract infection in adult women

**Proposed Dosage Form(s):** Tablet: 500 mg sulopenem etzadroxil and 500 mg probenecid

**Proposed Route of administration:** Oral

**Proposed Dosing Regimen:** 1 tablet twice daily for 5 days

**Consult Request:**
DAI requests DPMH to review and provide recommendations on subsection 8.4 of the proposed labeling and to opine on the inclusion from approved probenecid containing drug products of a contraindication for use in patients younger than 2 years of age.

**Materials Reviewed:**

- The following documents included for Sulopenem etzadroxil/Probenecid entered into DARRTS under NDA 213972, November 25, 2020:
  - Annotated Draft Labeling, Module 1.14.1.2 (eCTD #0)
  - Annotated Comparison with Listed Drug, Module 1.14.3.1 (eCTD #0)
  - Approved Labeling Text for Listed Drug, Module 1.14.3.2 (eCTD#0)
  - Probenecid Literature Review, Module 5.4 (eCTD#0)

- The following documents included for Sulopenem etzadroxil/Probenecid entered into DARRTS under NDA 213972, December 4, 2020:
  - Agreed Initial Pediatric Study Plan, Module 1.9.6 (eCTD #1)

- The following documents included for Sulopenem etzadroxil/Probenecid entered into DARRTS under IND 129849
  - Meeting Minutes for PeRC discussion of Agreed iPSP, March 19, 2018
  - Initial Agreement letter – Agreed Initial Pediatric Study Plan, February 26, 2018
  - Sponsor Response to FDA comments in iPSP, Module 1.12.4 (eCTD #39), January 31, 2018
  - Meeting Minutes for PeRC discussion of iPSP, November 22, 2017
  - Pediatric Study Plan Written Response, November 21, 2017
  - Initial Pediatric Study Plan, Module 5.3.5.4, (eCTD#30), September 19, 2017

# I. NDA 213972

## A. Drug Product:

Sulopenem etzadroxil/probenecid is a fixed dose combination (FDC) oral drug product of the pro-drug sulopenem etzadroxil and probenecid. The Applicant submitted this NDA for the treatment of uncomplicated urinary tract infection (uUTI) in adult women caused by designated susceptible microorganisms proven or strongly suspected to be non-susceptible to a quinolone antimicrobial drug. Sulopenem etzadroxil is cleaved in the intestinal wall, releasing the active parent drug sulopenem into the bloodstream. Probenecid is included in the drug product to reduce renal clearance and increase systemic exposure to sulopenem. Sulopenem is a broad-spectrum penem β-lactam antimicrobial that possesses potent activity against species of the *Enterobacteriaceae* that encode extended spectrum β-lactamases (ESBL) or AmpC-type β-lactamases that confer resistance to third generation cephalosporins. Sulopenem also demonstrates in vitro microbiological activity against a range of bacterial pathogens including penicillin-resistant *Streptococcus pneumoniae* and β-lactamase-producing clinical isolates of *Haemophilus influenzae* and *Moraxella catarrhalis* and anaerobes.

## B. Regulatory Background:

Sulopenem etzadroxil/probenecid is subject to study requirements under the Pediatric Research Equity Act (PREA) because the new FDC is considered a new active ingredient under PREA. The initial Pediatric Study Plan (iPSP) submitted by the Applicant proposed (b) (4) (b) (4). The Pediatric Review Committee (PeRC) discussed the iPSP on November 8, 2017.[3] Both DAI and the PeRC agreed that the Applicant's plan (b) (4) (b) (4) was inappropriate (b) (4) (b) (4). Both DAI and PeRC agreed that a plan to request a partial waiver in patients less than 2 years of age may be appropriate based on the rationale that studies would be impossible or highly impracticable because most UTIs in patients less than 2 years of age are considered complicated. Additional DAI comments to the Applicant in the iPSP included a recommendation to provide or conduct additional safety assessments for probenecid in patients younger than 2 years of age. The PeRC recommended that DAI identify the rationale for a contraindication against probenecid use in patients less than 2 years of age.

[3] Pediatric Review Committee Meeting Minutes in DAARTS under IND 129849, dated November 22, 2017.

In its 90-day Response Letter to the iPSP, the Applicant noted that the current contraindication to probenecid use in patients less than 2 years of age would not support evaluation of the combination oral dosing regimen in this age range.

The Applicant submitted an Agreed iPSP to the Agency on February 21, 2018 containing a plan (b) (4) (b) (4) (b) (4) For uUTI, the Applicant proposes an open-label, comparator-controlled phase 3 trial of oral sulopenem etzadroxil/probenecid in patients 2 to less than 18 years of age. Following the PeRC's concurrence, DAI provided Initial Agreement to the Agreed iPSP on February 26, 2018.[4]

## C. Probenecid

Probenecid, originally FDA approved in 1951 under the trade name BENEMID, is a uricosuric and renal tubular blocking agent.[5] Probenecid is currently approved for the treatment of hyperuricemia associated with gout and gouty arthritis as well as an adjuvant to therapy with penicillins for elevation and prolongation of plasma levels by whatever route the antibiotic is given. Probenecid is also currently approved in a FDC product with colchicine for the treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout.[6] The originally approved drug products BENEMID (probenecid) and COLBENEMID (colchicine/probenecid) are no longer marketed in the U.S.[7] These products were withdrawn from the U.S. market for business reasons and not due to safety or efficacy concerns. Both are marketed as generic drug products approved

[4] Pediatric Study Plan – Initial Agreement Letter in DAARTS under IND 129849, dated November 26, 2017.

[5] Found under BENEMID at Drugs@FDA.gov

[6] Found under Probenecid and colchicine tablet at dailymed.nlm.nih.gov

[7] Found under BENEMID and COLBENEMID at Drugs@FDA.gov

as ANDA applications.[8] The antibiotic combination drug products containing ampicillin and probenecid are no longer marketed in the U.S.[9]

Probenecid inhibits the organic anion transporters (OATs) OAT1, OAT2, OAT3, and OAT4 at current approved doses. The OATs, especially OAT1 and OAT3 located in the proximal tubule of the kidney, are important in the tubular transport and therefore renal clearance of a relatively wide variety of toxins, metabolites, nutrients, and drug products.[10,11] Through the inhibition of OATs 1 and 3, probenecid inhibits tubular secretion of penicillin and thereby increases penicillin plasma levels between 2- and 4-fold.[12] Probenecid also has binding affinity for the UDP-Glycotransferase (UGT) superfamily of enzymes responsible for glucuronidation of several drug products which facilitate their elimination.[13] The OAT's localized to the kidney mature at different rates compared to other measures of renal function such as glomerular filtration rate.[14] OAT function, as measured by the maximum tubular secretory capacity for para-aminohippurate ($Tm_{PAH}$), at birth is approximately 2.4% of adult activity and 25% of adult activity by 2 years of age.[15]

Dosing of probenecid as an adjuvant to therapy with penicillins is provided in the current probenecid labeling for patients 2 to 14 years of age as an initial dose of 25 mg/kg followed by maintenance dosing of 10 mg/kg four times per day. Patients greater than 50 kg are dosed as per adult dosing. Probenecid labeling contains a current contraindication against its use in patients under 2 years of age. This contraindication was added to the labeling in 1970.[16] The addition of this contraindication was referenced in an Addendum to Summary of Supplement Letter dated January 16, 1970. The letter states that the contraindication should be added based on information found in the drug therapy section of Nelson's 1969 "Textbook of Pediatrics" which was based on Shirkey's 1969 "Pediatric Therapy." The

[8] Found under probenecid at Drugs@FDA.gov

[9] Found under POLYCILLIN-PRB, PRINCIPEN w/PROBENECID, and PROBAMPICIN at Drugs@FDA.gov

[10] Wu W, Bush KT and Nigam SK. Key role for the organic transporters, OAT1 and OAT3, in the in vivo handling of uremic toxins and solutes. *Scientific Reports* 2017; 7(1)1-9.

[11] Bush KT, Wu W, Lun C and Nigam SK. The drug transporter OAT3 (SLC22A8) and endogenous metabolite communication via the gut–liver–kidney axis. *J Biol Chem.* 2017; 292(38):15789-15803.

[12] Found in the Clinical Pharmacology section of the label for Probenecid at dailymed.nlm.nih.gov

[13] Uchaipichat V, Mackenzie PI, Guo XH, et al. Human udp-glucuronosyltransferases: isoform selectivity and kinetics of 4-methylumbelliferone and 1-naphthol glucuronidation, effects of organic solvents, and inhibition by diclofenac and probenecid. *Drug Metab Dispos.* 2004; 32(4):413-23.

[14] Momper JD, Yang J, Gockenbach M, Vaida F, Nigam SK. Dynamics of Organic Anion Transporter-Mediated Tubular Secretion during Postnatal Human Kidney Development and Maturation. *Clin J Am Soc Nephrol.* 2019; 14(4):540-548.

[15] Ibid

[16] Filed under NDA 7-898/S-001. Email communication

letter provides no further scientific justification or explanation for the addition of the contraindication. Review of Shirkey's "Pediatric Therapy" finds probenecid listed among compounds that can precipitate hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency but makes no mention of the reason for a contraindication in patients less than 2 years of age.

### D. Safety of Probenecid in Patients less than 2 Years of Age

Published literature on probenecid use and safety in neonates and infants in the first two years of life is scant. A randomized clinical trial examining probenecid use in patients less than 2 years of age was published in 1979.[17] This trial examined the use of 10 days of IV amoxicillin compared to 10 days of IV amoxicillin and oral probenecid (10 mg/kg orally every 6 hours for 4 doses) for the treatment of susceptible bacterial meningitis in 43 patients. The trial collected efficacy data in the form of cerebral spinal fluid indices and cultures, complete blood counts, and clinical status endpoints. Safety data were collected in the form of reported adverse reactions and laboratory measures. Pharmacokinetic parameters were also measured as amoxicillin concentrations in serum and cerebrospinal fluid in the two treatment groups. The mean age of patients treated with amoxicillin and probenecid was 15.6 months. There were no differences in the sex, race, nor the organisms causing meningitis between treatment groups. There were no reported differences in adverse reactions between the two treatment groups and there were no adverse reactions attributed to probenecid in the trial.

## II. Conclusions:

There does not appear to be a readily apparent scientific justification for the labeling contraindication of probenecid use in patients younger than 2 years of age. FDA appears to have added this contraindication after initial U.S. marketing approval of probenecid and subsequently carried this contraindication forward in NDA and ANDA labeling for FDC products containing probenecid.

The safety profile for probenecid use in patients less than 2 years of age has not been established. Given the current contraindication for probenecid use in the approved labeling, relatively few studies have evaluated probenecid in this age range of patients. Furthermore, given what is understood about OAT maturation in patients less than 2 years of age, what effect dosing with probenecid would have on these immature transport systems is unclear.

[17] Craft JC, Feldman WE, Nelson JD. Clinicopharmacological evaluation of amoxicillin and probenecid against bacterial meningitis. *Antimicrob Agents Chemother.* 1979; 16(3):346-52.

The combined impact of renal and OAT immaturity in this age group may result in the need for a lower probenecid dose, and possibly no probenecid dosing, to maintain systemic exposure of sulopenem in a therapeutic range. There is the potential that the exposure to active ingredients dependent on OATs for clearance may be increased in FDC products containing probenecid or if given concomitantly with probenecid containing drug product in this patient population. The implications for the safe use in patients less than 2 years of age in these circumstances is unknown.

## III. Recommendations:

- As there is no clear scientific basis for the prior inclusion of the labeling contraindication found in the labeling of probenecid and FDC products containing probenecid, DPMH recommends not including a contraindication for use in patients less than 2 years of age in the proposed sulopenem etzadroxil/probenecid labeling.
- Because multiple approved generic FDC products containing probenecid are currently being marketed that contain the labeling contraindication, inform the Office of Generic Drugs (OGD) about the approach being taken for this NDA product to promote consistency across NDA and ANDA labeling. DPMH has initiated communications with OGD regarding this issue.
- DAI could consider consulting the Office of Surveillance and Epidemiology (OSE) for a focused post-marketing safety review of adverse events reported for probenecid, as either monotherapy or as a FDC drug product, in pediatric patients less than 2 years of age to help determine if there are any safety signals with the off-label use of these products in this age group.
- PREA study requirements should not be waived on the basis of safety in patients less than 2 years of age for probenecid-containing drug products unless there is new safety data to support such requests.
- Probenecid containing drug products (b) (4) subject to PREA should be studied down to birth if the proposed indication is relevant and the drug product could provide benefit to patients in the first two years of life.
- Pediatric studies designed to fulfill PREA post-marketing requirements (PMRs) in patients less than 2 years of age for this drug product or any probenecid-containing drug products should incorporate safety measures within the study protocol to closely monitor patients in this age group for adverse events of interest. Based on the immaturity of OATs in patients less than 2 years of age, the use of probenecid to further block these transporters may cause the potential build-up of toxins, endogenous metabolites, and medications cleared through these transporters.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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|---|---|
| Date of This Review: | March 22, 2021 |
| Requesting Office or Division: | Division of Anti-Infectives (DAI) |
| Application Type and Number: | NDA 213972 |
| Product Name and Strength: | sulopenem etzadroxil and probenecid Tablets, 500 mg/500 mg |
| Product Type: | Multi-Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | Iterum Therapeutics, Inc. (Iterum) |
| FDA Received Date: | November 25, 2020 |
| OSE RCM #: | 2020-2499 |
| DMEPA Safety Evaluator: | Deborah Myers, RPh, MBA |
| DMEPA Team Leader (Acting): | Valerie S. Vaughan, PharmD |

## 1 REASON FOR REVIEW

As part of the approval process for sulopenem etzadroxil and probenecid Tablets, the Division of Anti-Infectives (DAI) requested that we review the proposed sulopenem etzadroxil and probenecid prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

| Table 1. Materials Considered for this Label and Labeling Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B – N/A |
| ISMP Newsletters* | C – N/A |
| FDA Adverse Event Reporting System (FAERS)* | D – N/A |
| Other | E – N/A |
| Labels and Labeling | F |

N/A=not applicable for this review

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

## 3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

| Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| Full Prescribing Information – Section 16 How Supplied/Storage and Handling | | | |
| 1. | As currently presented, the storage statement is, "… (b) (4) at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to | The lower temperatures in the ranges may be overlooked. | To provide clarity and consistency with the storage statement as presented on the proposed container labels and carton labeling, add the Centigrade symbol (C) |

| Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | 86°F)." The units of measurement following the first numbers in the temperature ranges are missing. | | following 20° and 15°, and Fahrenheit symbol (F) following 68° and 59°within the storage statement.<br><br>For example, "… (b) (4) at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)."<br><br>Additionally, we note that the proposed container labels and carton labeling do not include "excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room temperature]*." as part of the storage statement. We defer to the Office of Pharmaceutical Quality (OPQ) to determine if this excursion information should be included in the storage statement on the container labels and carton labeling. |

| Table 3. Identified Issues and Recommendations for Iterum Therapeutics, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| Container Labels and Carton Labeling | | | |
| 1. | As currently presented, the terminology within the recommended dosage statement (b) (4) (b) (4) (b) (4) is inconsistent with the | The recommended dosage statement terminology should be consistent across the labeling to mitigate risk of confusion. | To ensure consistency with the Prescribing Information, we recommend revising the recommended dosage statement, (b) (4) (b) (4) |

| Table 3. Identified Issues and Recommendations for Iterum Therapeutics, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | terminology in the Prescribing Information." | | (b) (4) to read "Recommended Dosage: See prescribing information." |
| Container Labels | | | |
| 1. | As currently presented, the linear barcode is missing on the 10-count and 30-count bottle labels. | The drug linear barcode is often used as an additional verification before drug administration or dispensing; therefore, it is an important safety feature that should be part of the label and is required per 21 CFR 201.25(c)(2). | Ensure that a linear barcode is included on the 10- and 30-count bottle labels in accordance with 21 CFR 201.25(c)(2). Additionally, we recommend that the container label linear barcode be oriented in a vertical position, as a barcode placed in a horizontal position may be difficult to scan due to the curvature of the bottle. Furthermore, when determining placement of the linear barcode, consider that the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i). |
| | | | (b) (4) |

| Table 3. Identified Issues and Recommendations for Iterum Therapeutics, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | | (b) (4) | |
| Carton Labeling | | | |
| 1. | (b) (4) | | |
| 2. | As currently presented, the intended location of the human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) is not provided. | The Drug Supply Chain Security Act (DSCSA) requires manufacturers and re-packagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. | Ensure that the human-readable and machine-readable product identifier is included on each carton labeling. We recommend you include the intended location of the machine-readable (2D data matrix barcode) product identifier, near the human-readable portion of the product identifier information.<br><br>For more information, see draft guidance, Product Identifiers Under the Drug Supply Chain Security Act - |

| Table 3. Identified Issues and Recommendations for Iterum Therapeutics, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | | | Questions and Answers (September 2018).[a]<br><br>Additionally, we recommend you ensure there is sufficient white space between the linear barcode and 2-D matrix barcode to allow barcode scanners the ability to correctly read each barcode. |

## 4 CONCLUSION

Our evaluation of the proposed sulopenem etzadroxil and probenecid prescribing information (PI), container labels, and carton labeling, identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Iterum Therapeutics, Inc. so that recommendations are implemented prior to approval of this NDA.

[a] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for sulopenem etzadroxil and probenecid (NDA 213972) that Iterum Therapeutics, Inc. submitted on November 25, 2020.

| Table 2. Relevant Product Information for sulopenem etzadroxil and probenecid | |
|---|---|
| Initial Approval Date | N/A |
| Active Ingredients | sulopenem etzadroxil and probenecid |
| Indication | In adult women ≥ 18 years of age for the treatment of uncomplicated urinary tract infections caused by designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone: *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis.* |
| Route of Administration | oral |
| Dosage Form | tablets |
| Strength | 500 mg/500 mg |
| Dose and Frequency | One tablet orally twice daily for 5 days, taken with food (b) (4). |
| How Supplied | Bottles of 30 tablets with child-resistant caps, bottles of 10 tablets with child-resistant caps, and a blister (b) (4). |
| Storage | Store 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*]. |

## APPENDIX F. LABELS AND LABELING

### F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following sulopenem etzadroxil and probenecid labels and labeling submitted by Iterum Therapeutics, Inc.

- Container labels received on November 25, 2020
- Carton labeling received on November 25, 2020
- Unit-Dose Blister labels received on November 25, 2020
- Unit-Dose Carton Labeling received on November 25, 2020
- Prescribing Information (PI) received on November 25, 2020
    - Draft labeling available at the following link: \\CDSESUB1\evsprod\nda213972\0000\m1\us\11413-draft-labeling-text.docx.
    - Annotated draft labeling available at the following link: \\CDSESUB1\evsprod\nda213972\0000\m1\us\11412-annotated-draft-labeling-text.docx.
    - Annotated comparison with listed drug: \\CDSESUB1\evsprod\nda213972\0000\m1\us\11431-annotated-comparison-listed-drug.pdf.

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

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

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