CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213972Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	213972
PDUFA Goal Date	October 25, 2024
Nexus TTT #	2024-9230, 2024-9232
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Laura Zendel, Pharm.D.
Review Completion Date	October 24, 2024
Subject	Evaluation of Need for a REMS
Established Name	sulopenem etzadroxil and probenecid
Trade Name	Orlynvah
Name of Applicant	Iterum Therapeutics US Limited
Therapeutic Class	penem antibacterial agent, renal tubular transport inhibitor
Formulation(s)	500 mg sulopenem etzadroxil and 500 mg probenecid combination tablet
Dosing Regimen	Orlynvah (500 mg sulopenem etzadroxil and 500 mg probenecid) 1 tablet orally twice daily for 5 days

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Orlynvah (sulopenem etzadroxil and probenecid) is necessary to ensure the benefits outweigh its risks. Iterum Therapeutics US Limited submitted a New Drug Application (NDA) 213972 for sulopenem etzadroxil and probenecid with the proposed indication in adult women ≥ 18 years of age for the treatment of uncomplicated urinary tract infections (uUTI) caused by designated susceptible microorganisms. The serious risks associated with sulopenem etzadroxil and probenecid include hypersensitivity reactions, *Clostridioides difficile*-associated diarrhea (CDAD), risk of uric acid kidney stone development, exacerbation of gout, and development of drug-resistant bacteria. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and Division of Anti-Infectives (DAI) agree that a REMS is not necessary to ensure the benefits of sulopenem etzadroxil and probenecid outweigh its risks. The efficacy of sulopenem etzadroxil and probenecid was demonstrated in Trial 301 and Trial 310. In Trial 301, sulopenem etzadroxil and probenecid was superior to ciprofloxacin for the primary efficacy endpoint of overall response in the microbiological modified intent-to-treat resistant population. In Trial 310, sulopenem etzadroxil and probenecid was noninferior/superior to amoxicillin/clavulanate in the microbiological modified intent-to-treat susceptible population. The serious risks associated with sulopenem etzadroxil and probenecid of hypersensitivity reactions, CDAD, risk of uric acid kidney stone development, exacerbation of gout, and development of drug-resistant bacteria are consistent with the respective drug classes and will be communicated in the warnings and precautions section of the label.

If approved, sulopenem etzadroxil and probenecid will be the first oral penem antibiotic available in the United States. Use of this product in ambulatory settings where treatment is most commonly empiric raises concern for inappropriate use which may contribute to antimicrobial resistance and was discussed at the Antimicrobial Drugs Advisory Committee Meeting. Based on the Committee's recommendations, the FDA approved indication will be narrowed to the treatment of uUTI caused by the designated microorganisms *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*, in adult women who have limited or no alternative oral antibacterial treatment options. A Limitation of Use is also added to state that sulopenem etzadroxil and probenecid is not indicated for the treatment of complicated urinary tract infections (cUTI) or as step-down treatment after intravenous antibacterial treatment of cUTI and complicated intra-abdominal infections (cIAI) or as step-down treatment after intravenous antibacterial treatment of cIAI. The proposed label instructs to reduce the development of drug-resistant bacteria and maintain the effectiveness of Orlynvah and other antibacterial drugs, Orlynvah should be used only to treat uUTI that are proven or strongly suspected to be caused by susceptible bacteria. Culture and susceptibility information should be utilized in selecting or modifying antibacterial therapy. The FDA will continue to monitor for microbiological resistance to sulopenem in the postmarket setting.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Orlynvah (sulopenem etzadroxil and probenecid) is necessary to ensure the benefits outweigh its risks. Iterum Therapeutics US Limited submitted a New Drug Application (NDA) 213972 for sulopenem etzadroxil and probenecid with the proposed indication in adult women ≥ 18 years of age for the treatment of uncomplicated urinary tract infections (uUTI) caused by designated susceptible microorganisms.[1] This application is under review in the Division of Anti-Infectives (DAI). The applicant did not submit a proposed REMS or risk management plan.

2. Background

2.1. Product Information

Orlynvah (sulopenem etzadroxil and probenecid), a 505(b)(2) NDA, is a combination of a penem antibacterial agent and renal tubular transport inhibitor, proposed in adult women ≥ 18 years of age for the treatment of uUTI caused by designated susceptible microorganisms. Sulopenem etzadroxil is a NME. Probenecid was originally approved by the FDA in 1951 and is approved for indications including 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.[1,2,3] Sulopenem etzadroxil is a prodrug that is hydrolyzed to the active drug sulopenem after oral administration. It has *in vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of sulopenem results from the inhibition of cell wall synthesis and is mediated through binding to penicillin binding proteins. Sulopenem has demonstrated activity against Enterobacterales in the presence of certain beta-lactamases and extended spectrum beta-lactamases (ESBLs), e.g., AmpC, CTX-M, TEM, SHV. Probenecid inhibits OAT3-mediated renal clearance of sulopenem, resulting in increased plasma concentrations of sulopenem.

Orlynvah is proposed to be supplied as a 500 mg sulopenem etzadroxil and 500 mg probenecid combination tablet. The proposed dosing regimen is Orlynvah (sulopenem etzadroxil 500 mg and probenecid 500 mg) one tablet orally twice daily for 5 days.[b] Sulopenem etzadroxil is not currently approved in any jurisdiction. Sulopenem etzadroxil and probenecid was designated as a qualified infectious disease product (QIDP) and received fast track designation.

2.2. Regulatory History

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

The following is a summary of the regulatory history for sulopenem etzadroxil and probenecid NDA 213972 relevant to this review:

- 07/29/2016: Qualified infectious disease product designation granted
- 03/15/2019: Fast track designation granted
- 11/25/2020: NDA 2131972 submission for the treatment of uUTI caused by designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone received
- 07/23/2021: Complete Response (CR) letter sent to the Applicant due to Study 301 not providing substantial evidence of effectiveness of sulopenem etzadroxil and probenecid tablets for the proposed indication
- 04/25/2024: NDA 213972 re-submission, with an additional Phase 3 trial, in adult women ≥ 18 years of age for the treatment of uUTI caused by designated susceptible microorganisms received
- 09/9/2024: Antimicrobial Drugs Advisory Committee Meeting was convened to discuss the overall benefits and risks for the use of sulopenem etzadroxil/probenecid for the Applicant's proposed indication and to discuss considerations that would be important for medical providers to know to ensure appropriate use of sulopenem etzadroxil/probenecid

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Uncomplicated urinary tract infections, as defined by the FDA Guidance for Industry in 2019, are a clinical syndrome characterized by pyuria and a documented microbial pathogen on urine culture, accompanied by local signs and symptoms such as lower abdominal discomfort and dysuria and occur in females with normal anatomy of the urinary tract and are not accompanied by systemic signs or symptoms, such as fever greater than 38 degrees Celsius or costovertebral angle pain.[4] Risk factors for uUTI include recent sexual intercourse, use of spermicides, and a history of prior urinary tract infections.[5] Pathogens causing uUTI include *Escherichia coli*, other species of Enterobacteriaceae such as *Proteus mirabilis and Klebsiella pneumoniae*, and *Staphylococcus saprophyticus*.[6] Bacterial resistance is an important issue with urinary tract infections, especially with the emergence of infections caused by ESBL producing bacteria.[7] 50 to 60% of adult women will have at least one urinary tract infection (UTI) during their lifetime.[2] It is estimated that 10% to 12% of adult women in the United States have at least one UTI per year, with 20% to 30% of those having a recurrent infection.[2,8,c] The goal of uUTI treatment

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

is to resolve acute symptoms and reduce the risk of infection progression to the upper urinary tract (e.g., pyelonephritis).[d]

3.2. Description of Current Treatment Options

The decision of which antibacterial drug to use to treat uUTI is often made empirically and if culture results are available they are used to guide treatment choice.[5] Guidelines from the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases for treatment of acute uncomplicated cystitis and pyelonephritis in women list a number of first line antimicrobial agents for uUTI, the selection depending on a patient's allergy and compliance history, local practice patterns, local community resistance prevalence, availability, cost, and patient and provider threshold for failure.[6] First line antimicrobial agents include nitrofurantoin monohydrate/macrocrystals, trimethoprim-sulfamethoxazole, fosfomycin trometamol, and pivmecillinam. Other alternative antimicrobial agents listed in the guidelines include fluoroquinolones and beta-Lactam agents including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil.

Macrobid (nitrofurantoin monohydrate/macrocrystals), a nitrofuran antimicrobial agent, was approved by the FDA in 1991; it is indicated only for the treatment of acute uUTI (acute cystitis) caused by susceptible strains of *E. coli* or *S. saprophyticus*.[9] The serious risks associated with nitrofurantoin monohydrate/macrocrystals include pulmonary reactions, hepatotoxicity, neuropathy, hemolytic anemia, and *Clostridium difficile*-associated diarrhea (CDAD). Monurol (fosfomycin tromethamine), a phosphonic acid derivative, was approved by the FDA in 1996; it is indicated only for the treatment of uUTI (acute cystitis) in women due to susceptible strains of *E. coli* and *Enterococcus faecalis*.[10] The serious risk associated with fosfomycin tromethamine include CDAD. Bactrim (sulfamethoxazole and trimethoprim), a combination of a sulfonamide antimicrobial agent and a dihydrofolate reductase inhibitor antibacterial agent, was approved by the FDA in 1973; it is approved for indications including the treatment of urinary tract infections due to susceptible strains of the following organisms: *E. coli*, *Klebsiella* species, *Enterobacter* species, *Morganella morganii*, *P. mirabilis*, and *Proteus vulgaris*.[11] The serious risks associated with sulfamethoxazole and trimethoprim include embryo-fetal toxicity, hypersensitivity and other serious or fatal reactions, thrombocytopenia, Streptococcal infections and rheumatic fever, CDAD, risk associated with concurrent use of leucovorin for *Pneumocystis jirovecii* pneumonia, development of drug resistant bacteria, folate deficiency, hemolysis, hypoglycemia, impaired phenylalanine metabolism, porphyria and hypothyroidism, potential risk in the treatment of *P. jirovecii* pneumonia in patients with Acquired Immunodeficiency Syndrome (AIDS), and electrolyte abnormalities.

Recently, Pivya (pivmecillinam), a penicillin class antibacterial agent, was approved by the FDA in 2024 for the treatment of female patients 18 years of age and older with uUTI caused by susceptible isolates of *E. coli*, *P. mirabilis*, and *S. saprophyticus*.[12] The serious risk associated with pivmecillinam include

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

hypersensitivity reactions, severe cutaneous adverse reactions, carnitine depletion, acute porphyria, CDAD, development of drug-resistant bacteria, and interference with newborn screening test. Nitrofurantoin monohydrate/macrocrystals, sulfamethoxazole and trimethoprim, fosfomycin tromethamine, and pivmecillinam do not have a boxed warning in their respective labels and none of these drugs have a REMS. Please refer to DAI integrated review (draft) for sulopenem etzadroxil and probenecid for a detailed clinical review on treatment armamentarium relevant to the proposed indication.

4. Benefit Assessment

The trials supporting this application for sulopenem etzadroxil and probenecid consisted of two Phase 3, multicenter, randomized, double-blind, double-dummy clinical trials for the efficacy and safety in uUTI in adult women, Trial 301 (NCT 03354598) and Trial 310 (NCT 05584657).[1,2] In both studies clinical cure was defined as resolution of patient reported uUTI symptoms and no new uUTI symptoms, and microbiological response was defined as a reduction of all baseline uropathogens to less than 10^3 CFU/mL in the urine. The microbiological modified intent-to-treat (micro-MITT) population included all patients who had at least one uropathogen isolated at baseline (≥10^5 CFU/mL) and received at least one dose of study drug.

In Trial 301, patients (N=1660) were randomized to sulopenem etzadroxil 500 mg and probenecid 500 mg orally twice daily for 5 days and placebo ciprofloxacin orally twice daily for 3 days or ciprofloxacin 250 mg orally twice daily for 3 days and placebo sulopenem etzadroxil/probenecid orally twice daily for 5 days. The primary efficacy endpoint was overall response (combined microbiological response and clinical cure) at the test of cure (TOC) visit (12 days after randomization). Overall response was compared in the micro-MITTS population (micro-MITT population with baseline pathogens susceptible to ciprofloxacin, MIC ≤ 1 μg/mL) and the micro-MITTR population (micro-MITT population with baseline pathogens non-susceptible to ciprofloxacin, MIC ≥ 2 μg/mL). The success rate for the primary efficacy endpoint at the TOC visit in the micro-MITTS population was 60.4% (227/376) in the sulopenem etzadroxil and probenecid group and 71.8% (300/418) in the ciprofloxacin group (treatment difference, -11.4; 95% confidence interval -17.9 to -4.8). The success rate for the primary efficacy endpoint at the TOC visit in the micro-MITTR population was 48.1% (78/162) in the sulopenem etzadroxil and probenecid group and 32.9% (49/149) in the ciprofloxacin group (treatment difference, 15.3; 95% confidence interval 4.3 to 25.8, p=0.006).

In Trial 310, patients (N=2222) were randomized to sulopenem etzadroxil 500 mg and probenecid 500 mg orally twice daily for 5 days or amoxicillin/clavulanate 875 mg/125 mg orally twice daily for 5 days. The primary efficacy endpoint was overall response (combined microbiological response and clinical cure) at the TOC visit (12 days after randomization). Overall response was compared in the micro-MITTS population (micro-MITT population with baseline pathogens susceptible to amoxicillin/clavulanate, MIC ≤ 8/4 μg/mL) and micro-MITTR population (micro-MITT population with baseline pathogens non-susceptible to amoxicillin/clavulanate, MIC ≥ 16/8 μg/mL). The success rate for the primary efficacy

endpoint at the TOC visit in the micro-MITTS population was 61.7% (296/480) in the sulopenem etzadroxil and probenecid group and 55% (243/442) in the amoxicillin/clavulanate group (treatment difference, 6.7; 95% confidence interval 0.3 to 13). The success rate for the primary efficacy endpoint at the TOC visit in the micro-MITTR population was 52.4% (22/42) in the sulopenem etzadroxil and probenecid group and 68% (17/25) in the amoxicillin/clavulanate group (treatment difference, -15.6; 95% confidence interval -37.5 to 9.1).

The clinical reviewer concluded that substantial evidence of effectiveness for sulopenem etzadroxil/probenecid for the treatment of uUTI in adult women has been provided by statistical superiority in the micro-MITTR population of Trial 301 along with non-inferiority/superiority in the micro-MITTS population of Trial 310.[e]

Two additional trials evaluated intravenous (IV) sulopenem with oral sulopenem etzadroxil and probenecid stepdown treatment for complicated urinary tract infection (cUTI) and complicated intra-abdominal infections (cIAI). The clinical reviewer noted that IV sulopenem with oral sulopenem etzadroxil and probenecid stepdown was inferior to the active comparator, IV ertapenem with stepdown to oral ciprofloxacin or amoxicillin/ clavulanate, based on the primary endpoint of overall response in Trial 302 (NCT 03357614) for the treatment of cUTI. Intravenous sulopenem with oral sulopenem etzadroxil and probenecid stepdown also did not demonstrate noninferiority compared to the active comparator, IV ertapenem with stepdown to oral ciprofloxacin/metronidazole or amoxicillin/clavulanate, based on the primary endpoint of clinical response in Trial 303 (NCT 03358576) for the treatment of cIAI. As clinical benefit has not been established for these indications, a limitation of use statement will be included in labeling.

5. Risk Assessment & Safe-Use Conditions

The safety of sulopenem etzadroxil and probenecid was evaluated in two Phase 3 clinical trials for the treatment of uUTI, Trial 301 and Trial 310.[1,2,f] In the combined safety population from Trial 301 and Trial 310, 1932 patients received sulopenem etzadroxil and probenecid, 822 patients received ciprofloxacin, and 1107 patients received amoxicillin/clavulanate. Discontinuation from treatment due to an adverse reaction occurred in 21/1932 (1%) in the sulopenem etzadroxil and probenecid group, 8/822 (1%) in the ciprofloxacin group, and 4/1107 (0.4%) in the amoxicillin/clavulanate group. Common adverse reactions reported with sulopenem etzadroxil and probenecid included diarrhea, nausea, vulvovaginal mycotic infection, headache, and vomiting.

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[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

The serious risks[g] associated with sulopenem etzadroxil and probenecid which include hypersensitivity reactions, CDAD, risk of uric acid kidney stone development, exacerbation of gout, and development of drug-resistant bacteria are summarized in the sections below.

5.1. Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis and serious skin reactions have been reported with beta-lactam antibacterial drugs. Severe allergic reactions and anaphylaxis have been reported with probenecid. Two patients receiving sulopenem etzadroxil and probenecid during the development program experienced angioedema, with one patient in the sulopenem etzadroxil and probenecid group in Trial 301 experiencing angioedema.[2] Sulopenem etzadroxil and probenecid is contraindicated in patients with a history of hypersensitivity to the components of sulopenem etzadroxil and probenecid or other beta-lactam antibacterial drugs. The proposed label recommends before therapy with sulopenem etzadroxil and probenecid is instituted, healthcare providers carefully inquire about previous hypersensitivity reactions to other carbapenems, cephalosporins, penicillins, or other beta-lactams because cross-hypersensitivity among beta-lactam antibacterial drugs has been reported. It also recommends if an allergic reaction to sulopenem etzadroxil and probenecid occurs, to discontinue the drug and institute appropriate supportive measures. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.2. *Clostridioides difficile*-Associated Diarrhea

Clostridioides difficile-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial drugs. Infections due to hypertoxin-producing strains of *C. difficile* may be serious with an increased morbidity and mortality. No patients in the sulopenem etzadroxil and probenecid group experienced *C. difficile* infection.[2] The proposed label states that CDAD must be considered in all patients who present with diarrhea following antibacterial use and a careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. The proposed label recommends if CDAD is suspected or confirmed that ongoing antibacterial use not directed against *C. difficile* should be discontinued, if possible and appropriate measures such as fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated. If approved, this risk will be communicated in the warnings and precautions section of the label.

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

5.3. Risk of Uric Acid Kidney Stone Development

Sulopenem etzadroxil and probenecid is contraindicated in patients with known uric acid kidney stones. The proposed label states when prescribing sulopenem etzadroxil and probenecid to patients with a history of gout, appropriate measures to reduce the risk of uric acid kidney stone development should be instituted, such as increased fluid intake and alkalization of the urine. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.4. Exacerbation of Gout

Sulopenem etzadroxil and probenecid may cause exacerbation of gout. The proposed label recommends when prescribing sulopenem etzadroxil and probenecid to patients with a known history of gout, ensure appropriate therapy of gout is instituted. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.5. Development of Drug-Resistant Bacteria

As with other antibacterial agents, using sulopenem etzadroxil and probenecid in the absence of a proven or strongly suspected susceptible uUTI may increase the risk of the development of drug-resistant bacteria. See Section 8 for further discussion. If approved, this risk will be communicated in the warnings and precautions section of the label.

6. Expected Postmarket Use

Uncomplicated UTI is typically diagnosed in ambulatory settings such as urgent care, emergency department, telemedicine visits, or physician offices. The likely prescribers will be primary care providers, such as internal medicine practitioners including nurse practitioners and physician assistants, family physicians, obstetrics and gynecology practitioners, and infectious diseases specialists. If approved, sulopenem etzadroxil and probenecid would likely be dispensed from retail pharmacy settings and primarily be self-administered by the patient at home. Based on the indication and Limitations of Use, if approved, sulopenem etzadroxil and probenecid is not expected to be initiated in inpatient settings.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for sulopenem etzadroxil and probenecid beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of sulopenem etzadroxil and probenecid on the basis of the efficacy and safety information currently available.

Uncomplicated urinary tract infections are a clinical syndrome characterized by pyuria and a documented microbial pathogen on urine culture, accompanied by local signs and symptoms such as lower abdominal discomfort and dysuria and occur in females with normal anatomy of the urinary tract and are not accompanied by systemic signs or symptoms. The goal of uUTI treatment is to resolve acute symptoms and reduce the risk of infection progression to the upper urinary tract. Bacterial resistance is an important issue with urinary tract infections, especially with the emergence of infections caused by resistant bacteria. It is estimated that 10% to 12% of adult women in the United States have at least one UTI per year, with 20% to 30% of those having a recurrent infection. The efficacy of sulopenem etzadroxil and probenecid was demonstrated in Trial 301 and Trial 310. In Trial 301, sulopenem etzadroxil and probenecid was superior to ciprofloxacin for the primary efficacy endpoint of overall response in the micro-MITTR population. In Trial 310, sulopenem etzadroxil and probenecid was noninferior/superior to amoxicillin/clavulanate in the micro-MITTS population.

The serious risks associated with sulopenem etzadroxil and probenecid of hypersensitivity reactions, CDAD, risk of uric acid kidney stone development, exacerbation of gout, and development of drug-resistant bacteria will be communicated in the warnings and precautions section of the label. None of the risks associated with sulopenem etzadroxil and probenecid rise to the level of a boxed warning. These risks are consistent with the respective drug classes.

The Antimicrobial Drugs Advisory Committee was convened on September 9, 2024 to discuss the overall benefits and risks for the use of sulopenem etzadroxil and probenecid for the Applicant's proposed indication and to discuss considerations that would be important for medical providers to know to ensure appropriate use of sulopenem etzadroxil and probenecid. Sulopenem etzadroxil and probenecid, if approved, would be the first oral penem antibacterial drug available in the United States. The use of the drug in an ambulatory setting where treatment is most commonly empiric raised concern for inappropriate use which may contribute to antimicrobial resistance and there was concern for potential off-label use as stepdown treatment for cUTI and cIAI despite Trials 302 and 303 failing to meet their primary endpoint. The clinical reviewer stated although there were no voting questions the Advisory Committee members discussed concerns for potential downstream risks to both individual patients and to society from antimicrobial cross-resistance to other carbapenems arising from unrestricted empiric use of oral sulopenem for uUTI in an ambulatory setting and the lack of mechanisms for effective antimicrobial stewardship in an ambulatory setting in general. The Advisory Committee members recommended restricting the indication and providing limitations of use. The FDA approved indication will be for treatment of uUTI caused by the designated microorganisms *E. coli*, *K. pneumoniae*, or *P. mirabilis*, in adult women who have limited or no alternative oral antibacterial treatment options. A Limitation of Use states that sulopenem etzadroxil and probenecid is not indicated for treatment of cUTI or as step-down treatment after intravenous antibacterial treatment of cUTI and cIAI or as step-down treatment after intravenous antibacterial treatment of cIAI. The proposed label instructs to reduce the

development of drug-resistant bacteria and maintain the effectiveness of Orlynvah and other antibacterial drugs, Orlynvah should be used only to treat uUTI that are proven or strongly suspected to be caused by susceptible bacteria. Culture and susceptibility information should be utilized in selecting or modifying antibacterial therapy.

If approved, based on the efficacy and risks associated with sulopenem etzadroxil and probenecid for the treatment of uUTI caused by the designated microorganisms *E. coli*, *K. pneumoniae*, or *P. mirabilis*, in adult women who have limited or no alternative oral antibacterial treatment options, the DRM and DAI agree that a REMS is not necessary to ensure that the benefits outweigh the risks as the risk can be adequately communicated in labeling. DAI is recommending a post-marketing requirement (PMR) to monitor for antibacterial resistance related to sulopenem etzadroxil/probenecid. The clinical reviewer stated microbiological surveillance as a PMR will evaluate the possible emergence of resistance to oral sulopenem and cross-resistance to FDA-approved IV carbapenems with the use of sulopenem etzadroxil/probenecid and the Agency will conduct enhanced post-marketing pharmacovigilance to monitor for potential inappropriate use of the product.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable for the limited indication, therefore, a REMS is not necessary for sulopenem etzadroxil and probenecid to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

[1] Proposed prescribing information for sulopenem etzadroxil and probenecid as currently edited by FDA, last accessed October 18, 2024.

[2] Sulopenem etzadroxil/probenecid NDA 213972 integrated review. Last accessed October 18, 2024.

[3] Probenecid package insert. Parsippany, NJ: Teva Pharmaceuticals; 2024 April.

[4] Refer to Guidance for Industry Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment for more information (https://www.fda.gov/media/129531/download)

[5] Sulopenem etzadroxil/probenecid multi-disciplinary review and evaluation NDA 213972, July 22, 2021.

[6] Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52(5):e103-120.

[7] Steiger SN, Comito RR, Nicolau DP. Clinical and economic implications of urinary tract infections. *Expert Rev Pharmacoecon Outcomes Res*. 2017;17(4):377-383.

[8] Kaye KS, Gupta V, Mulgirigama A, et al. Antimicrobial Resistance Trends in Urine Escherichia coli Isolates From Adult and Adolescent Females in the United States From 2011 to 2019: Rising ESBL Strains and Impact on Patient Management. *Clin Infect Dis*. 2021;73(11):1992-1999.

[9] Macrobid (nitrofurantoin monohydrate/macrocrystals) package insert. Morristown, NJ: Almatica Pharma LLC; 2020 December.

[10] Monurol (fosfomycin tromethamine) package insert. Madison, NJ: Allergan USA, Inc.; 2018 May.

[11] Bactrim (sulfamethoxazole and trimethoprim) package insert. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2024 June.

[12] Pivya (pivmecillinam) package insert. Florham Park, NJ: UTILITY therapeutics Ltd; 2024 April.

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/s/

BRAD T MORIYAMA
10/24/2024 02:42:45 PM

NAOMI S BOSTON
10/24/2024 02:47:38 PM

LAURA A ZENDEL
10/24/2024 02:51:29 PM

Division of Risk Management (DRM)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Application Type	NDA
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Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Deputy Director	Doris Auth, Pharm.D.
Review Completion Date	June 8, 2021
Subject	Defer comment on DRM evaluation of the need for a REMS for sulopenem etzadroxil/probenecid
Established Name	sulopenem etzadroxil/probenecid
Trade Name	Orlynvah
Name of Applicant	Iterum Therapeutics, Inc.
Therapeutic Class	Antibacterial agent
Formulation(s)	Tablets: 500 mg of sulopenem etzadroxil and 500 mg of probenecid
Dosing Regimen	One tablet orally twice daily with food for 5 days.

This memo is to defer the Division of Risk Management (DRM) review of the need for a risk evaluation and mitigation strategy (REMS) for sulopenem etzadroxil/probenecid, NDA 213972.

On September 29, 2020, the Applicant submitted NDA 213972, sulopenem etzadroxil/probenecid with the proposed indication for the treatment of uncomplicated urinary tract infections (uUTI) caused by designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone. The submission included draft labeling but did not include a REMS.

The Division of Anti-Infectives (DAI) clinical reviewer recommends Complete Response (CR) for regulatory action based on the submission[1]:

> *In uncomplicated urinary tract infections (uUTI) Study 301, sulopenem was found to be superior to ciprofloxacin with respect to overall response (clinical response and microbiologic response) in the prespecified subgroup of subjects with a ciprofloxacin-nonsusceptible pathogen. Overall response was attained by 77/160 (48%) of sulopenem subjects and 49/149 (33%) ciprofloxacin subjects with a difference of 15% (95% CI, 4.4% to 26.1%; p-value 0.0065). However among subjects with a ciprofloxacin-susceptible pathogen, sulopenem was found to be inferior to ciprofloxacin. The overall response was 218/365 (60%) for sulopenem and 296/410 (72%) for ciprofloxacin with a difference of -12.5% (95% CI, -19.1% to -5.9%). Of note, clinicians usually do not obtain urine cultures when treating uUTI. As a result, the role of sulopenem in treating uUTI is unclear and also raises concerns about how to distinguish an appropriate patient population. In addition, in the related indications of cUTI and complicated intra-abdominal infections (*cIAI*), sulopenem was not noninferior to the active comparator based on the primary efficacy endpoints in each trial. Overall, there is no confirmatory evidence to support the findings of benefit for sulopenem in patients with a uUTI caused by a ciprofloxacin-nonsusceptible pathogen. DAI recommends that the NDA receive a Complete Response given lack of substantial evidence of effectiveness and that the Applicant consider the following:*
>
> 1. *Re-evaluate the proposed dose/dosing regimen given the issues associated with PK-PD/target attainment.*
> 2. *Conduct a second Phase 3 uUTI study to provide additional evidence of effectiveness.*
> 3. *Use a more relevant comparator given current standard of care, such as nitrofurantoin.[1,2]*

Therefore, an evaluation of the need for REMS for sulopenem etzadroxil/probenecid will be undertaken by DRM after the Applicant addresses the deficiencies in the CR letter. Please send DRM a new consult request at such time. This memo serves to close the existing consult request to DRM for sulopenem etzadroxil/probenecid under NDA 213972.

References

[1] DAI. Multi-disciplinary Review and Evaluation (draft) for NDA 213972 for sulopenem etzadroxil/probenecid, dated May 28, 2021.

[2] Sulopenem etzadroxil/probenecid Late-Cycle Meeting Background Package. COR-MEET-07, dated May 21, 2021. [Reference ID: 4799079]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed May 26, 2021.

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/s/

TILL OLICKAL
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NAOMI S BOSTON
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DORIS A AUTH
06/08/2021 03:44:49 PM