CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216974Orig1s000

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	216974
PDUFA Goal Date	May 29, 2023
OSE RCM #	2022-1987
Reviewer Name(s)	Celeste Karpow, PharmD, MPH*
Team Leader	Naomi Boston, PharmD
Division Director	Laura Zendel, PharmD, BCPS
Review Completion Date	May 22, 2023
Subject	Evaluation of Need for a REMS
Established Name	sulbactam-durlobactam
Trade Name	Xacduro
Name of Applicant	Entasis Therapeutics Inc. (ETI)
Therapeutic Class	Beta-Lactam/Beta-Lactamase Inhibitor
Formulation(s)	A co-packaged kit containing three single-dose vials each containing sterile powder for reconstitution: one clear single-dose vial contains 1 g sulbactam (equivalent to 1.1 g sulbactam sodium) and two amber single-dose vials each contain 0.5 g durlobactam (equivalent to 0.54 g durlobactam sodium) together with sodium hydroxide and hydrochloric acid used for pH adjustment
Dosing Regimen	Administer 1 g sulbactam, 1 g durlobactam every 6 hours by intravenous infusion over 3 hours in patients with creatinine clearance (CLcr) of 45 to 129 mL/min. Dose adjustments are required for patients with CLcr less than 45 mL/min and for patients with CLcr greater than or equal to 130 mL/min.

* At the time of documentation of this review, Dr. Celeste Karpow was on extended leave from the Agency

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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 Xacduro (sulbactam-durlobactam) is necessary to ensure the benefits outweigh its risks. Entasis Therapeutics Inc. (ETI) submitted a New Drug Application (NDA) 216974 for sulbactam-durlobactam with the proposed indication in patients 18 years of age and older for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP), caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex (ABC). The risks associated with sulbactam-durlobactam include hypersensitivity reactions, *Clostridioides difficile*-associated diarrhea (CDAD), and development of drug-resistant bacteria. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Anti-infectives (DAI) determined a REMS is not needed to ensure the benefits of sulbactam-durlobactam outweigh its risks. The efficacy of sulbactam-durlobactam was supported by the phase 3 noninferiority trial, in which the 28-day all-cause mortality rate was 19% (12/63) for sulbactam-durlobactam and 32.3% (20/62) for Colistin; the difference in the mortality rate (95% CI) was -13.2% (-30.0%, 3.5%).[1] The clinical reviewer concluded that the trial provided evidence to support an indication in patients 18 years of age and older for the treatment of HABP and VABP, caused by susceptible isolates of ABC. Hypersensitivity reactions, CDAD, and development of drug-resistant bacteria, will be addressed in the warnings and precautions section of the prescribing information.[2] While the size of the safety population is less than 200 patients, the safety profile of sulbactam-durlobactam is consistent with the pharmacologic class and extensive postmarket experience with sulbactam in combination with ampicillin. The likely prescribers will be internal medicine practitioners, critical care medicine practitioners, and infectious diseases specialists who are expected to be familiar with the management of the risks observed with sulbactam-durlobactam.

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) sulbactam-durlobactam is necessary to ensure the benefits outweigh its risks.[a] Entasis Therapeutics Inc. (ETI) submitted a New Drug Application (NDA) 216974 for sulbactam-durlobactam with the proposed indication of treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP), caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex (ABC). This application is under review in the Division of Anti-Infectives (DAI). The applicant did not submit a proposed REMS or risk management plan with this application.

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

2. Background

2.1. Product Information

Sulbactam-durlobactam is co-packaged product containing sulbactam, a beta-lactam antibacterial and beta lactamase inhibitor, and durlobactam, a beta-lactamase inhibitor, with the proposed indication in patients 18 years of age and older for the treatment of HABP and VABP, caused by susceptible isolates of ABC.[2] Sulbactam, approved by the FDA in 1986, is a beta-lactam antibacterial and beta-lactamase inhibitor derived from penicillin that has intrinsic antibacterial activity against ABC. Sulbactam is bactericidal due to its inhibition of penicillin binding proteins PBP1 and PBP3, which are essential enzymes required for bacterial cell wall synthesis.[2] Durlobactam is a diazabicyclooctane non-beta-lactam, beta-lactamase inhibitor, that protects sulbactam from degradation by certain serine-beta-lactamases. Durlobactam alone does not have any antibacterial activity against ABC isolates.[2]

Sulbactam-durlobactam is proposed to be supplied as a kit containing three single-dose vials of 1 g sulbactam and 1 g durlobactam as two 0.5 g durlobactam vials.[2] The dosing regimen is 1 g sulbactam and 1 g of durlobactam every 6 hours administered by IV infusion over 3 hours in adults with a creatinine clearance of 45 to 129 mL/min.[2] Dose adjustments are recommended for patients with a creatinine clearance less than 45 mL/min.[2] (b) (4) is recommended for patients with a creatinine clearance greater than or equal to 130 mL/min.[2] The recommended duration of treatment is 7 to 14 days and should be guided by the patient's clinical status.[b,2] Sulbactam-durlobactam is not currently approved in any jurisdiction, and has been granted fast track designation.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 216974 relevant to this review:

- 09/01/2017: Fast track designation granted
- 03/25/2022: The need for risk evaluation and mitigation strategies (REMS) was discussed in the context of a complete application at the pre-NDA meeting.
- 09/29/2022: NDA 216974 submission for the treatment of infections due to *Acinetobacter baumannii-calcoaceticus* complex including multidrug-resistant and carbapenem-resistant strains received
- 02/17/2023: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for sulbactam-durlobactam.
- 04/17/2023: Antimicrobial Drugs Advisory Committee Meeting was convened to discuss the overall benefit-risk assessment for the use of sulbactam-durlobactam for the treatment of patients with carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (CRABC) infections. The AC voted 12 in favor and 0 against approval. A REMS proposal was not discussed.

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

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Hospital-acquired bacterial pneumonia is defined as pneumonia onset in the hospital after at least 48 hours of hospitalization.[3] Similarly, VABP is considered pneumonia onset following 48 hours of endotracheal intubation.[3] HABP and VABP are the most common hospital-acquired infections, accounting for 22% of all hospital-acquired infections.[4] HABP and VABP negatively impact patient outcomes. All-cause mortality with VABP is reported between 20% to 50%.[c,4] In addition, VABP results in prolonged ventilation by 7.6 to 11.5 days, and prolonged hospitalization by 11.5 to 13.1 days.[4] Hospital-acquired bacterial pneumonia is considered less severe than VABP but HABP also causes serious complications such as respiratory failure, pleural effusions, septic shock, renal failure, and empyema.[4] Among patients who develop HABP in the intensive care unit, the mortality rate approaches that of patients with VABP.[4] It is estimated that 22,950 cases of carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (CRABC) infections occur annually in the United States and 75,000 globally in developed nations.[d,5] Based on the number of cases and the cost per case, carbapenem resistance costs health-care systems an annual excess of $389 million and 4,590 excess deaths in the United States, and an annual excess of $742 million and 15,000 excess deaths globally.[5]

Acinetobacter spp. are gram-negative, non-lactose fermenting, oxidase negative coccobacilli.[6] *A. baumannii-calcoaceticus complex* (ABC) species includes *A. baumannii* which is the predominant and clinically significant pathogen associated with nosocomial infections.[6] *A. baumannii-calcoaceticus complex species* also includes *A. calcoaceticus*, *A. dijkshoorniae, A. seifertii, A. nosocomialis*, and *A. pittii*.[6] These species are biochemically indistinguishable and often lumped together as *A. baumannii* complex or *A. baumannii-calcoaceticus* or *A. baumannii.*[6] HABP and VABP caused by *Acinetobacter baumannii-calcoaceticus* complex are particularly concerning because *A. baumannii* exhibits several resistance mechanisms including biofilm formation, reduced cell membrane permeability, upregulation of drug efflux, and production of beta lactamases, which may result in rapid emergence of resistance to many classes of antibacterial drugs, including carbapenems.[6]

3.2. Description of Current Treatment Options

The Antibiotic Resistance Threats in the United States report by the CDC in 2019 listed the threat level of carbapenem-resistant *Acinetobacter* as urgent, which indicates the lack of treatment options for

[c] 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.*

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

Acinetobacter infections.[7] *Acinetobacter* was previously listed as serious in the Antibiotic Resistance Threats in the United States report by the CDC in 2013.[7]

Current treatment options for CRABC are limited.[6] Combination therapy is suggested for moderate and severe infections.[6] Ampicillin-sulbactam is suggested to be a part of a combination therapy when susceptibility has been demonstrated.[6] The activity of ampicillin-sulbactam against *Acinetobacter* spp. is mediated by the sulbactam component as *Acinetobacter* spp. are intrinsically resistant to ampicillin.[6] Other treatment options for CRABC infections include cefiderocol, polymyxins, tetracyclines, and aminoglycosides.[6] Limitations of polymyxins and aminoglycosides include toxicity, especially nephrotoxicity.[6] In addition, the efficacy of polymyxins may be limited.[6] Limitations of tetracyclines include lower efficacy of some drugs in the class in the treatment of HABP and VABP.[6,8] Cefiderocol was approved for the treatment of HABP and VABP infections caused by *Acinetobacter* in 2020, but treatment emergent resistance of CRABC to cefiderocol has been reported.[6,9,10]

Products used to treat *Acinetobacter baumannii-calcoaceticus* complex are summarized in Table 1 in the Appendix.

4. Benefit Assessment

The phase 3 noninferiority trial, ATTACK (NCT03894046) supporting this application consisted of a randomized, investigator-unblinded, assessor-blinded, non-inferiority, comparison of sulbactam-durlobactam versus Colistin for treatment of HABP, VABP, ventilator pneumonia (VP) or bacteremia due to ABC.[1] The trial was conducted in two parallel parts, Part A and Part B however only Part A was considered for efficacy due to the single-arm design in Part B.[6] Part A was the pivotal, randomized, assessor-blinded, comparative, noninferiority portion of the study. It compared the efficacy and safety of intravenous (IV) SUL/DUR versus IV Colistin, both in combination with IV imipenem and cilastatin, for the treatment of subjects with ABC HABP, VABP, VP, or bacteremia. Part B was a single-arm portion of the study. It enrolled ABC-infected subjects who did not qualify for Part A because the baseline pathogen was known to be resistant to Colistin as well as subjects with complicated urinary tract infections (cUTIs) and acute pyelonephritis (AP) or surgical or post-traumatic wound infections.

One hundred seventy-seven patients were enrolled in which 91 patients received sulbactam-durlobactam and 86 patients received Colistin. Patients who received sulbactam-durlobactam received 1 g sulbactam and 1 g durlobactam (or renally adjusted dose) intravenously over 3 hours every 6 hours.[6] Patients who received Colistin received 2.5 mg/kg (or renally adjusted dose) intravenously over 30 minutes every 12 hours after an initial loading dose of Colistin 2.5 to 5 mg/kg.[6] Both treatment arms also received 1 g imipenem/1 g cilastatin (or renally adjusted dose) intravenously as background therapy every 6 hours.[6] The treatment period was 7 to 14 days, and the follow-up period was 14 days.[6]

The primary efficacy endpoint was 28-day all-cause mortality, assessed using a 20% noninferiority (NI) margin. Sulbactam-durlobactam met the primary endpoint of noninferiority to Colistin.[6] The 28-day all-cause mortality rate was 19% (12/63) for sulbactam-durlobactam, while the 28-day all-cause mortality rate was 32.3% (20/62) for Colistin; the difference in the mortality rate (95% CI) was -13.2% (-30.0%, 3.5%).[1]

The clinical reviewer concluded that Part A of the phase 3 noninferiority trial demonstrated that sulbactam-durlobactam was non-inferior to Colistin for 28-day all-cause mortality in the CRABC microbiologically modified intent-to-treat (m-MITT) primary analysis population in the treatment of HABP or VABP.[e,1] Approximately 96% of subjects had HABP or VABP and only 2% (3 subjects) had bacteremia in the CRABC m-MITT population.[1] In addition, sulbactam-durlobactam did not meet superiority over Colistin because the 95% CI included 0%.[6]

5. Risk Assessment & Safe-Use Conditions

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant safety information to date for sulbactam-durlobactam. The safety of sulbactam-durlobactam was evaluated in 158 subjects who received sulbactam-durlobactam at the proposed dose and duration including a phase 2 study (CS2514-2017-0003, NCT 03445195) a double-blind, randomized, placebo-controlled study comparing sulbactam-durlobactam to placebo in subjects with cUTI including pyelonephritis and the phase 3 study, ATTACK, in subjects with HABB/VABP caused by *Acinetobacter baumannii-calcoaceticus* complex.[6] The data from the phase 2 and 3 trials were not pooled for the Agency's safety assessments given differences in randomization, comparators and treatment duration.[6] Of note, the study drugs were not masked for logistical reasons and the treating physician and other health care providers were not blinded in the trial except for the outcome assessor.[6]

There were no unexpected safety signals identified in the sulbactam-durlobactam development program.[6] In addition, sulbactam has been approved in combination with ampicillin since 1986. The prescribing information for ampicillin-sulbactam includes warnings for hypersensitivity reactions, hepatotoxicity including hepatitis and cholestatic jaundice, severe cutaneous adverse reactions, and *Clostridioides difficile*-associated diarrhea.[f,6,11]

The most common adverse events occurring in more than 5% of subjects receiving sulbactam-durlobactam include abnormal liver function test, diarrhea, anemia, hypokalemia, pyrexia, septic shock, arrhythmias, acute kidney injury, thrombocytopenia, and constipation.[6] The Treatment-Emergent Adverse Events (TEAEs) occurring with a higher frequency in the sulbactam-durlobactam arm than in the Colistin arm were diarrhea 15/91 vs. 9/86 (16.5% vs. 10.5%), hypokalemia 11/91 vs. 9/86 (12.1% vs. 10.5%), and thrombocytopenia 5/91 vs. 3/86 (5.5% vs. 3.5%).[6] However, acute kidney injury was higher in the Colistin arm 31/86 (36%) than the sulbactam-durlobactam arm 5/91 (5.5%).[6] Discontinuation from treatment due to an adverse event occurred in 10/91 (11%) in the sulbactam-durlobactam arm and 14/86 (16.3%) in the Colistin arm of Part A, the randomized portion of the phase 3 trial.[6] Deaths occurred in 24/91 (26.4%) in the sulbactam-durlobactam arm and 30/86 (34.9%) in the Colistin arm of Part A, the randomized portion of the phase 3 trial.[6] The most commonly reported causes of death were

[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.*

septic shock and sepsis in the sulbactam-durlobactam group, and septic shock, sepsis, pneumonia, and *Acinetobacter* sepsis in the polymyxin E group.[6] Overall, the mortality outcomes appear to be related to the underlying comorbidities, complications in a critically ill subject or progression of the presenting pneumonia.[6] There was no apparent biologic plausibility or causal assignment to sulbactam-durlobactam treatment identified.[6]

The clinical reviewer's conclusion is that the safety database was limited, however, the safety profile of sulbactam-durlobactam is consistent with the pharmacologic class.[1] The adverse events of special interest include hypersensitivity reactions, *Clostridioides difficile*-associated diarrhea (CDAD), and development of drug-resistant bacteria.[2] These adverse events will be described in the warnings and precautions section of the prescribing information and are summarized below.[2]

5.1. Hypersensitivity Reactions

Hypersensitivity reactions were more frequent in the sulbactam-durlobactam group compared with the Colistin group (16.5% versus 11.5%), which is expected with penicillin derivatives and β-lactamase inhibitors.[6] The most common reaction related to study drug was rash in both groups (3.4% in sulbactam durlobactam and 2.3% in the Colistin arm).[6] Rash and contact dermatitis were mild to moderate in nature and resolved with treatment discontinuation.[6] Recommendations in labeling for management of hypersensitivity reactions are to inquire about pervious hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta lactams, and other allergens and to discontinue treatment if an allergic reaction occurs.[2]

5.2. *Clostridioides difficile*-Associated Diarrhea (CDAD)

The use of antibacterial agents is a risk factor for CDAD. This infection may be serious and result in increased morbidity and mortality. *C. difficile* colitis and antibiotic-associated colitis each were reported in 1 subject (0.8%) in the sulbactam-durlobactam group compared with 3 subjects (3.5%) and 2 subjects (2.3%), in the Colistin group, which is expected with antibacterials.[6] Recommendations in labeling for management of CDAD are to assess the risk or benefit of continuing treatment with sulbactam-durlobactam and to ensure appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation are instituted as clinically indicated.[2]

5.3. Development of Drug-Resistant Bacteria

As with other antibacterial agents, using sulbactam-durlobactam in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication increases the risk of the development of drug-resistant bacteria.[2]

6. Expected Postmarket Use

If approved, sulbactam-durlobactam will primarily be used in inpatient settings. The likely prescribers will be internal medicine practitioners, critical care medicine practitioners, and infectious diseases

specialists who are expected to be familiar with the management of the risks observed with sulbactam-durlobactam.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for sulbactam-durlobactam beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of sulbactam-durlobactam based on the efficacy and safety information currently available.

Sulbactam-durlobactam is a co-packaged product containing sulbactam, beta-lactam antibacterial and beta lactamase inhibitor, combined with durlobactam, a beta-lactamase inhibitor indicated in patients 18 years of age and older for the treatment of HABP and VABP, caused by susceptible isolates of ABC.[2] Both HABP and VABP caused by CRABC are serious infections that negatively impact patient outcomes, especially critically ill patients, resulting in prolonged ventilation, hospitalization, and increased cost to the health-care system.[4,5] HABP and VABP caused by ABC are concerning due to the multiple resistance mechanisms exhibited by *A. baumannii species*.[6]

The efficacy of sulbactam-durlobactam was supported by the phase 3 noninferiority trial, ATTACK in which the primary efficacy endpoint was 28-day all-cause mortality assessed using a 20% NI margin.[2] While sulbactam-durlobactam did not meet superiority over Colistin, sulbactam-durlobactam offers less acute kidney injury and a well-known safety profile of the sulbactam component since sulbactam has been marketed since 1986 in combination with ampicillin.[6,11]

While the size of the safety population is less than 200 patients, the safety profile of sulbactam-durlobactam is consistent with the pharmacologic class and extensive postmarket experience with sulbactam in combination with ampicillin. The risks associated with sulbactam-durlobactam include hypersensitivity reactions, CDAD, and development of drug-resistant bacteria.[2] These risks will be addressed in the warnings and precautions section of the label.[2] There are currently no boxed warnings for any risk in the prescribing information for sulbactam-durlobactam.[2] The likely prescribers will be internal medicine practitioners, critical care medicine practitioners, and infectious diseases specialists who are expected to be familiar with the management of the risks observed with sulbactam-durlobactam.

An Antimicrobial Drugs Advisory Committee (AC) Meeting was held on April 17, 2023 to discuss the overall benefit-risk assessment for the use of sulbactam-durlobactam for the treatment of patients with HABP and VABP caused by susceptible strains of ABC organisms.[12] If an AC member finds the overall benefit-risk assessment favorable, then they were asked to provided their rationale and if the AC member does not find the benefit-risk assessment favorable, then they were asked to describe what additional studies/trials are needed.[12] The AC voted 12 in favor and 0 against approval of sulbactam-durlobactam. Committee members overall stated that sulbactam-durlobactam's favorable safety profile

compared to other medications used in the treatment of HABP and VABP will provide another option of treatments in patients suffering from these diseases. A REMS proposal was not discussed.

Based on the efficacy and risks associated with sulbactam-durlobactam for the treatment of HABP and VABP, caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex, this reviewer's recommendation is that a REMS is not necessary to ensure the benefits outweigh the risks; all risks can be adequately communicated with prescribing information.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile of sulbactam-durlobactam is favorable for the treatment of patients 18 years of age and older for the treatment of HABP and VABP, caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex. Therefore, a REMS is not necessary for sulbactam-durlobactam 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. Table 1: Products used to treat *Acinetobacter baumannii-calcoaceticus* complex

Product Trade Name (Generic) Year of Approval	Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
FDA Approved Treatments				
Unasyn[11] (ampicillin-sulbactam) 12/31/1986	for the treatment of infections due to susceptible strains of the designated microorganisms in the following conditions: Skin and Skin Structure Infections, intra-abdominal infections, gynecological infections.	9 g IV q8h over 4 hours or 27 g IV q24h as a continuous infusion For mild infections caused by CRAB isolates susceptible to ampicillin-sulbactam, it is reasonable to administer 3 g IV q4h—particularly if intolerance or toxicities precludes the use of higher dosages.[13]	Hypersensitivity; Hepatotoxicity; Severe Cutaneous Adverse Reactions; Clostridium Difficile-Associated Diarrhea	Warnings and Precautions
Minocin[14] (minocycline) 10/26/1972	treatment of infections due to susceptible isolates	200 mg IV/PO q12h[13]	Tooth development; skeletal development; dermatologic reaction; anti-anabolic action; photosensitivity; central nervous system effects; clostridium difficile associated diarrhea; intracranial hypertension	Warnings and Precautions

Tygacil[8] (tigecycline) 06/15/2005	treatment of Complicated Skin and Skin Structure Infections, Complicated Intra-abdominal Infections, & Community-Acquired Bacterial Pneumonia	200 mg IV × 1 dose, then 100 mg IV q12h[13]	All-Cause Mortality; Mortality Imbalance and Lower Cure Rates in Hospital-Acquired Pneumonia; Anaphylactic Reactions; Hepatic Adverse Effects; Pancreatitis; Monitoring of Blood Coagulation Parameters; Tooth Discoloration and Enamel Hypoplasia; Inhibition of Bone Growth; Clostridioides difficile-Associated Diarrhea; Sepsis/Septic Shock in Patients With Intestinal Perforation; Tetracycline-Class Adverse Effects; Development of Drug-Resistant Bacteria	Warnings and Precautions
Polymyxin B[15]	Acute Infections Caused by Susceptible Strains of Pseudomonas aeruginosa; H influenzae, specifically meningeal infections; Escherichia coli, specifically urinary tract infections; Aerobacter aerogenes, specifically bacteremia; Klebsiella pneumoniae, specifically bacteremia	Loading dose: 2.0–2.5 mg/kg for polymyxin B, based on total body weight. Maintenance dose: 1.25–1.5 mg/kg (equivalent to 12,500–15,000 IU/kg TBW) every 12 hours is infused over 1 hour.[13]	Clostridium difficile associated diarrhea	Boxed Warning, Warnings and Precautions

Coly-mycin M[16] (colistin) 06/04/1970	for the treatment of acute or chronic infections due to sensitive strains of certain gram-negative bacilli. It is particularly indicated when the infection is caused by sensitive strains of Pseudomonas aeruginosa. This antibiotic is not indicated for infections due to Proteus or Neisseria. Coly-Mycin M Parenteral has proven clinically effective in treatment of infections due to the following gram-negative organisms: Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae and Pseudomonas aeruginosa.	Loading dose: 300 mg CBA (~9 million IU) infused over 0.5–1 hour followed by the first maintenance dose 12–24 hours later. Maintenance dose: 300–360 mg CBA (~9–10.9 million IU), divided into two and infused over 0.5–1 hour at 12-hour intervals.[13]	Transient neurological disturbances may occur. These include circumoral paresthesia or numbness, tingling or formication of the extremities, generalized pruritus, vertigo, dizziness, and slurring of speech. Nephrotoxicity can occur and is probably a dose-dependent effect of colistimethate sodium. Clostridium difficile associated diarrhea has been reported with use of nearly all antibacterial agents, including Coly-Mycin M Parenteral, and may range in severity from mild diarrhea to fatal colitis.	Warnings and Precautions
Fetroja[9] (cefiderocol) 11/14/2019	Complicated Urinary Tract Infections (cUTIs), Including Pyelonephritis & Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)	2 g IV q8h, infused over 3 hours[13]	Increase in All-Cause Mortality in Patients with Carbapenem-Resistant Gram-Negative Bacterial Infections; Hypersensitivity Reactions; Clostridioides difficile-associated Diarrhea; Seizures and Other Central Nervous System (CNS) Adverse Reactions;	Warnings and Precautions

			Development of Drug-Resistant Bacteria	
Extended-infusion Merrem IV[17] (meropenem) 06/21/1996	Complicated Skin and Skin Structure Infections (Adult Patients and Pediatric Patients 3 Months of Age and Older Only); Complicated Intra-abdominal Infections (Adult and Pediatric Patients); Bacterial Meningitis (Pediatric Patients 3 Months of Age and Older Only)	500 mg given every 8 hours for skin and skin structure infections and 1 gram given every 8 hours for intra-abdominal infections given extended infusion over 3-4 hours. When treating complicated skin and skin structure infections caused by P. aeruginosa, a dose of 1 gram every 8 hours is recommended given extended infusion over 3-4 hours.[13]	Hypersensitivity Reactions; Severe Cutaneous Adverse Reactions; Seizure Potential; Risk of Breakthrough Seizures Due to Drug Interaction with Valproic Acid; Clostridium difficile–associated Diarrhea; Development of Drug-Resistant Bacteria; Overgrowth of Nonsusceptible Organisms; Thrombocytopenia; Potential for Neuromotor Impairment	Warnings and Precautions
Xerava[18] (eravacycline) 08/27/2018	Complicated Intra-abdominal Infections caused by susceptible microorganisms: Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii, Enterobacter cloacae, Klebsiella oxytoca, Enterococcus	1 mg/kg/dose IV q12h[13]	Hypersensitivity Reactions; Tooth Discoloration and Enamel Hypoplasia; Inhibition of Bone Growth; Clostridium difficile-Associated Diarrhea; otential for Microbial Overgrowth; Tetracycline Class Adverse Reactions;	Warnings and Precautions

	faecalis, Enterococcus faecium, Staphylococcus aureus, Streptococcus anginosus group, Clostridium perfringens, Bacteroides species, and Parabacteroides distasonis in patients 18 years or older		Development of Drug-Resistant Bacteria	
Primaxin[19] (imipenem-cilastatin) 11/26/1985	lower respiratory tract infections caused by susceptible strains of Staphylococcus aureus (penicillinase-producing isolates), Acinetobacter species, Enterobacter species, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella species, Serratia marcescens; urinary tract infections (complicated and uncomplicated) caused by susceptible strains of Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing isolates),	500 mg IV q6h, infused over 3 hours[13]	Hypersensitivity Reactions; Seizure Potential; Increased Seizure Potential Due to Interaction with Valproic Acid; Clostridioides difficile-Associated Diarrhea; Development of Drug-Resistant Bacteria	Warnings and Precautions

	Enterobacter species, Escherichia coli, Klebsiella species, Morganella morganii, Proteus vulgaris, Providencia rettgeri, Pseudomonas aeruginosa; intra-abdominal infections caused by susceptible strains of Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing isolates), Staphylococcus epidermidis, Citrobacter species, Enterobacter species, Escherichia coli, Klebsiella species, Morganella morganii, Proteus species, Pseudomonas aeruginosa, Bifidobacterium species, Clostridium species, Eubacterium species, Peptococcus species, Peptostreptococcus species, Propionibacterium species, Bacteroides species including B. fragilis, Fusobacterium species; gynecologic infections caused by susceptible strains			

	of Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing isolates), Staphylococcus epidermidis, Streptococcus agalactiae (Group B streptococci), Enterobacter species, Escherichia coli, Gardnerella vaginalis, Klebsiella species, Proteus species, Bifidobacterium species, Peptococcus species, Peptostreptococcus species, Propionibacterium species, Bacteroides species including B. fragilis; bacterial septicemia caused by susceptible strains of Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing isolates), Enterobacter species, Escherichia coli, Klebsiella species, Pseudomonas aeruginosa, Serratia species, Bacteroides species including B. fragilis; bone and joint infections			

	caused by susceptible strains of Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing isolates), Staphylococcus epidermidis, Enterobacter species, Pseudomonas aeruginosa; skin and skin structure infections caused by susceptible strains of Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing isolates), Staphylococcus epidermidis, Acinetobacter species, Citrobacter species, Enterobacter species, Escherichia coli, Klebsiella species, Morganella morganii, Proteus vulgaris, Providencia rettgeri, Pseudomonas aeruginosa, Serratia species, Peptococcus species, Peptostreptococcus species, Bacteroides species including B. fragilis, Fusobacterium species;			

	endocarditis caused by susceptible strains of Staphylococcus aureus (penicillinase-producing isolates).			

10.2. References

1. Draft FDA Presentations for Sulbactam-durlobactam April 2023.
2. Draft prescribing information for sulbactam-durlobactam May 2023.
3. Zasowski EJ, Blackford M. Lower Respiratory Tract Infections. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey LM, eds. *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*. McGraw Hill; 2023.
4. Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. Sep 1 2016;63(5):e61-e111. doi:10.1093/cid/ciw353
5. Spellberg B, Rex JH. The value of single-pathogen antibacterial agents. *Nat Rev Drug Discov*. Dec 2013;12(12):963. doi:10.1038/nrd3957-c1
6. FDA Briefing Document for Sulbactam-durlobactam. April 17, 2023:
7. Prevention CfDC. *Antibiotic resistance threats in the United States, 2019*. 2019. Accessed March 30, 2023. https://www.cdc.gov/drugresistance/biggest-threats.html
8. Tygacil [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Updated June 2020. Accessed March 30, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021821s049lbl.pdf
9. Fetroja [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Updated November 2021. Accessed March 30, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209445s004lbl.pdf
10. Falcone M, Tiseo G, Leonildi A, et al. Cefiderocol- Compared to Colistin-Based Regimens for the Treatment of Severe Infections Caused by Carbapenem-Resistant Acinetobacter baumannii. *Antimicrob Agents Chemother*. May 17 2022;66(5):e0214221. doi:10.1128/aac.02142-21
11. Unasyn [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Updated October 2020. Accessed March 30, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/050608s047lbl.pdf
12. Meeting of the Antimicrobial Drugs Advisory Committee- Draft Questions. April 17, 2023:
13. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of AmpC beta-Lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. *Clin Infect Dis*. Jul 6 2022;74(12):2089-2114. doi:10.1093/cid/ciab1013
14. Minocin [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Updated April 2015. Accessed March 30, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050444s049lbl.pdf
15. Polymyxin B [Prescribing Information]. National Library of Medicine DailyMed. Updated December 2022. Accessed April 11, 2023. https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a14373aa-c5fa-4f90-8e8f-fc9e2219039c
16. Coly-mycin M [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Updated April 2017. Accessed March 30, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050108s033lbl.pdf
17. Merrem IV [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Updated April 2019. Accessed March 30, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/050706s041lbl.pdf
18. Xerava [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Updated August 2018. Accessed March 30, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211109lbl.pdf

19. Primaxin [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Updated January 2022. Accessed March 30, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/050587Orig1s083lbl.pdf

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