CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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	218275
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Reviewer Name(s)	Celeste Will, PharmD, MPH
Team Leader	Naomi Boston, PharmD
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Review Completion Date	April 2, 2024
Subject	Evaluation of Need for a REMS
Established Name	ceftobiprole medocaril sodium
Trade Name	Zevtera
Name of Applicant	Basilea Pharmaceutica International Ltd, Allschwil
Therapeutic Class	Cephalosporin antibiotic
Formulation(s)	Lyophilized powder for reconstitution
Dosing Regimen	*Staphylococcus aureus* bloodstream (SAB) infection in adults: 667 mg IV every 6 hours day 1 to 8 and every 8 hours starting on day 9 for up to 42 days Acute bacterial skin and skin structure (ABSSSI) infection in adults: 667 mg IV every 8 hours for 5 days to 14 days Community-acquired bacterial pneumonia (CABP) in adults: 667 mg IV every 8 hours for 5 days to 14 days Community-acquired bacterial pneumonia (CABP) in pediatrics: • 12 years to 18 years old: 13.3 mg/kg (up to 667 mg/dose) IV every 8 hours for 7 days to 14 days • 3 months to 12 years old: 20 mg/kg (up to 667 mg/dose) IV every 8 hours for 7 days to 14 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 Zevtera (ceftobiprole medocaril) is necessary to ensure the benefits outweigh the risks. Basilea Pharmaceutica International Ltd, Allschwil submitted a New Drug Application (NDA 218275) for ceftobiprole with the proposed indications:

- Treatment of adult patients with *Staphylococcus aureus* bloodstream infection (bacteremia) (SAB)
- Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI)
- Treatment of adult and pediatric patients (aged from 3 months to < 18 years) with community-acquired bacterial pneumonia (CABP)

The risks associated ceftobiprole include increased mortality in ventilator-associated bacterial pneumonia patients, hypersensitivity reactions, seizures and other central nervous system reactions, *Clostridioides difficile*-Associated Diarrhea (CDAD), and development of drug-resistant bacteria. The applicant did not submit a REMS with this application however they did submit a risk management plan which proposes routine pharmacovigilance activities including adverse reactions reporting and signal detection.[1]

DRM and the Division of Anti-infectives (DAI) determined a REMS is not needed to ensure the benefits of ceftobiprole outweigh the risks. The efficacy of ceftobiprole in SAB was supported by the phase 3 noninferiority study in which 69.8% of patients in the ceftobiprole group met the primary endpoint, demonstrating noninferiority to daptomycin.[2] The efficacy of ceftobiprole in ABSSSI was supported by the phase 3 noninferiority study in which 91.3% of patients in the ceftobiprole group had a clinical response compared to 88.1% of patients in the vancomycin plus aztreonam comparator group.[3] The efficacy of ceftobiprole in CABP was supported by the phase 3 noninferiority study in which 86.6% of patients in the ceftobiprole group achieved a clinical cure compared with 87.4% of patients in the ceftriaxone with/without linezolid comparator group.[4] In the CABP pediatric population, the efficacy of ceftobiprole was largely extrapolated from the phase 3 CABP adult study, while the safety of ceftobiprole was supported by a phase 3 study in which pediatric patients were randomized to receive either ceftobiprole or ceftriaxone with/without vancomycin.[4] The clinical reviewer concluded these trials provided evidence to support all proposed indications. The risks of increased mortality in ventilator-associated bacterial pneumonia patients, hypersensitivity reactions, seizures and other central nervous system reactions, CDAD, and development of drug-resistant bacteria will be addressed in the warnings and precautions section of the label.[5] The safety findings are consistent with the cephalosporin class of antibiotic drugs.[4] 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 ceftobiprole.

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) Zevtera (ceftobiprole medocaril) is necessary to ensure the benefits outweigh its risks. Basilea Pharmaceutica International Ltd, Allschwil submitted a New Drug Application (NDA) 218275 for ceftobiprole with the proposed indications:

- Treatment of adult patients with *Staphylococcus aureus* bloodstream infection (bacteremia) (SAB)
- Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI)
- Treatment of adult and pediatric patients (aged from 3 months to < 18 years) with community-acquired bacterial pneumonia (CABP)

This application is under review in the Division of Anti-infectives (DAI). The applicant did not submit a proposed REMS, however they did submit a risk management plan which proposes routine pharmacovigilance activities including adverse reactions reporting and signal detection.[1]

2. Background

2.1. Product Information

Ceftobiprole, a new molecular entity[a], is an advanced-generation broad-spectrum cephalosporin proposed for treatment of adult patients with SAB, adult patients with ABSSSI, and adult and pediatric patients (aged from 3 months to less than 18 years) with CABP.[5] Ceftobiprole medocaril is the prodrug of the active moiety ceftobiprole.[5] Ceftobiprole exhibits bactericidal activity by inhibition of bacterial cell wall synthesis.[5] Bactericidal activity is mediated through binding to essential penicillin-binding proteins (PBPs) and inhibiting their transpeptidase activity, which is essential for the synthesis of the peptidoglycan layer of the bacterial cell wall.[5] Ceftobiprole has a high affinity for *Staphylococcus aureus* PBPs 1 – 4, including PBP2a in methicillin resistant *Staphylococcus aureus* (MRSA), and PBP2x and PBP2b in penicillin resistant *Streptococcus pneumoniae*.[5] Ceftobiprole also has activity against gram-negative organisms such as *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and some non-extended spectrum beta-lactamase (non-ESBL) producing Enterobacterales such as *Klebsiella pneumonia* and *E. coli*.[4]

Ceftobiprole is proposed to be supplied as a 667 mg single-dose vial containing white, yellowish to slightly brownish sterile powder for reconstitution.[5] The proposed dosing regimen in adults with SAB is 667 mg every 6 hours on days 1 to 8 followed by every 8 hours on day 9 for up to 42 days.[b,5] The proposed dosing regimen in adults with ABSSSI or CABP is 667 mg every 8 hours for 5 to 14 days.[b,5] The proposed dosing regimen in pediatric patients 12 years to less than 18 years old with CABP is 13.3 mg/kg (up to 667 mg/dose) every 8 hours for 7 to 14 days.[b,5] The proposed dosing regimen in pediatric patients

[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.*

greater than or equal to 3 months and less than 12 years old is 20 mg/kg (up to 667 mg/dose) every 8 hours for 7 to 14 days.[b,5] Ceftobiprole is eliminated primarily unchanged by renal excretion with a half-life of approximately 3 hours and requires renal dose adjustment in adult and pediatric patients with renal impairment.[5] Ceftobiprole has been granted fast track designation, and is currently marketed in 20 countries, including: Canada, Switzerland, Finland, Norway, the United Kingdom, Argentina, Austria, Germany, Poland, Spain, Denmark, and Sweden.[6-8]

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 218275 relevant to this review:

- 06/03/2004: Fast track designation granted
- 05/18/2007: NDA 22132 for ceftobiprole submitted for complicated skin and skin structure infections, including diabetic foot infections without concomitant osteomyelitis caused by susceptible bacteria including MRSA
- 03/17/2008: the Agency issued an approvable letter that cited data integrity issues identified by the agency at study sites and citing the need for additional site inspections, (b) (4)
- 07/30/2008: Complete Response submitted by the Applicant to address deficiencies from the approvable letter.
- 11/18/2008: Anti-Infective Drugs Advisory Committee to discuss drug development for complicated skin and soft tissue infections (cSSSI). Committee members advised that a 10% non-inferiority margin was reasonable in non-inferiority trials for cSSSI as long as major abscesses are excluded. (b) (4)
- 11/21/2008: Complete response letter (CRL) issued for NDA 22132 due to data integrity issues. The specific issues included:
    - Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60].
    - Failure to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].
    - Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the inspection [21 CFR 312.62 (b)].
    - Failure to provide investigators with the information needed to conduct the study properly, ensure proper monitoring of the study, and ensure the study was conducted in accordance with the protocol and/or investigational plan [21 CFR 312.50].

- Failure to select only investigators qualified by training and experience as appropriate experts to investigate the drug [21 CFR 312.53].

- 06/29/2009: Complete Response submitted by the Applicant to address deficiencies from the CRL.
- 12/28/2009: CRL issued for NDA 22132 due to data integrity issues at some of the clinical sites. Specifically, data from Studies BAP00154 and BAP00414 were deemed unreliable following inspections and audits.
    - The Division of Scientific Investigations cited failure to maintain adequate records of the disposition of the drug (including dates, quantity, and use by subjects), and failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the inspection.
- 01/25/2011: Ceftobiprole rights transferred from Johnson & Johnson back to Basilea.
- 08/03/2023: NDA 218275 submission received for the following indications: SAB, ABSSSI, and CABP

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

3.1.1. *Staphylococcus aureus* bloodstream infection (bacteremia) (SAB)

SAB reflects the potentially life-threatening presence of the *Staphylococcus aureus* bacteria in the bloodstream and can cause sepsis and septic shock. [c,9,10] SAB is associated with morbidity and mortality with MRSA bacteremia associated with higher mortality than methicillin susceptible *Staphylococcus aureus* (MSSA).[c,10] While the reported mortality for SAB varies across studies, the estimated incidence per 100,000 person years in North America is 4.3 to 38.2.[d,11] Another estimate reports that the population incidence of SAB per 100,000 person years in the industrialized world ranges from 10 to 30.[12] In addition, *Staphylococcus aureus* is the most common cause of infective endocarditis (IE) in many settings and is often clinically indistinguishable from *Staphylococcus aureus* bacteremia. *Staphylococcus aureus* IE may be fatal if inadequately treated.[13,14]

[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.*

3.1.2. Acute bacterial skin and skin structure infections (ABSSSI)

ABSSSIs are a subset of skin and soft tissue infections (SSTIs) which are severe bacterial infections of the skin with a lesion size area of at least 75 cm^2.[15] ABSSSI include cellulitis/erysipelas, wound infection, and major cutaneous abscess.[15] Common bacterial pathogens causing ABSSSI are *Streptococcus pyogenes* and *Staphylococcus aureus* including methicillin-resistant *S. aureus*.[15] Less common causes include other *Streptococcus* species, *Enterococcus faecalis*, or Gram negative bacteria.[15]

SSTIs are associated with high morbidity and mortality rates leading to prolonged hospital stay, surgery, and antimicrobial therapy.[c,16] In addition, the Infectious Diseases Society of America (IDSA) Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections cite a dramatic increase in the frequency and severity of infections along with antimicrobial resistance to the agents commonly used to treat SSTIs in the past.[17] There was a 29% increase in the total hospital admissions for SSTIs between 2000 and 2004, 6.3 million physician's office visits per year are attributable to SSTIs, and annual emergency department visits for SSTIs increased from 1.2 million to 3.4 million patients between 1993 and 2005.[d,17]

3.1.3. Community-acquired bacterial pneumonia (CABP)

Community-acquired pneumonia (CAP) is defined as a pneumonia infection acquired outside of the hospital.[18] CABP is CAP caused by a bacterial pathogen that typically include *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *S. aureus*, and Enterobacterales. The severity of CAP can vary from mild pneumonia with a fever and productive cough to severe pneumonia characterized by respiratory distress and sepsis.[c,18] The risk factors for CAP include older age (65 years of age and older), chronic comorbidities, concurrent or antecedent respiratory viral infections, impaired airway protection, smoking, alcohol abuse, and other lifestyle factors (such as, crowded living conditions).[18]

CAP is a leading cause of morbidity and mortality both in the United States and worldwide.[18] There are approximately 4.5 million emergency room visits annually for CAP in the United States.[18] In addition, CAP is reported to be the second most common cause of hospitalization and the most common infectious cause of death.[18] Approximately 650 adults per 100,000 are hospitalized with CAP every year.[e,18] In addition, the annual incidence of CAP among pediatric patients in the United States is 15.7–22.5 hospitalizations per 100,000 children and approximately 124,000 pediatric hospitalizations annually for CAP.[e,19]

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

3.2. Description of Current Treatment Options

3.2.1. *Staphylococcus aureus* bloodstream infection (bacteremia) (SAB)

Treatment for SAB consists of prompt source control and antimicrobial therapy.[20] Source control may include management of the infected site by way of incision, drainage, and/or removal of infected devices.[20] Empiric antibiotic therapy generally includes empiric treatment for MRSA although there is limited support for empiric treatment of MSSA.[20] Empiric therapy for MRSA includes vancomycin and daptomycin as an alternative agent.[20] Beta-lactam antibiotics such as nafcillin, oxacillin, or cefazolin, are good choices for de-escalation and MSSA.[20] Follow-up cultures should be conducted once treatment has been initiated. Failure to clear the bacteremia within 48 hours should prompt further evaluation.[20]

Common adverse events for vancomycin include infusion reactions, nephrotoxicity, ototoxicity, *Clostridium Difficile*-associated diarrhea, neutropenia, phlebitis, development of drug-resistant bacteria.[21] Other limitations of vancomycin therapy include the need for therapeutic drug monitoring. Common adverse events for daptomycin include anaphylaxis/hypersensitivity, myopathy/rhabdomyolysis, eosinophilic pneumonia, tubulointerstitial nephritis, peripheral neuropathy, and *Clostridium Difficile*-associated diarrhea.[22] Common adverse events for nafcillin and oxacillin include interstitial nephritis, colitis, and metabolic reactions.[23,24] In addition, elevation of liver transaminases may occur for nafcillin.[23]

Common adverse events for cefazolin include anaphylaxis/hypersensitivity, gastrointestinal symptoms, hematologic abnormalities, elevation of liver transaminases, increased BUN and creatinine levels, as well as renal failure, and injection site reactions.[25] In addition, the following adverse reactions have been reported for cephalosporin-class antibiotics: Allergic reactions, urticaria, serum sickness-like reaction, erythema multiforme, toxic epidermal necrolysis, colitis, renal dysfunction, toxic nephropathy, abdominal pain, reversible hyperactivity, hypertonia, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, superinfection, prolonged prothrombin time, positive direct Coombs' test, false-positive test for urinary glucose, elevated bilirubin, elevated LDH, increased creatinine, pancytopenia, and agranulocytosis.[25] Furthermore, several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced.[25] Ceftobiprole is a cephalosporin antibiotic, like cefazolin, however ceftobiprole has fewer adverse events included in the prescribing information based on the studies and clinical experience to date.[5] The warnings and precautions included in the prescribing information for ceftobiprole include increased mortality in ventilator-associated bacterial pneumonia, hypersensitivity, seizures and other adverse central nervous system reactions, *Clostridioides difficile*-associated diarrhea, and development of drug-resistant bacteria.[5]

For uncomplicated *S. aureus* bacteremia in which infective endocarditis is excluded, no indwelling devices, negative follow-up cultures, patient defervesced within 48 to 72 hours after initiating intravenous antistaphylococcal therapy and removal of the presumed focus of infection, no evidence of metastatic staphylococcal infection on physical examination, the duration of therapy is 14 days from the

first negative blood culture.[20] In patients who do not meet the aforementioned criteria, then a longer duration of treatment might be necessary.[20]

3.2.2. Acute bacterial skin and skin structure infections (ABSSSI)

Similar to SAB, treatment for ABSSSI is composed of source control, if needed, antimicrobial therapy, and de-escalation.[16] In necrotizing infections, debridement can be critical. It is important to note that there is a balance between effective debridement and unnecessary overecision.[16] Empiric antibiotic therapy should be guided by clinical evaluation to establish the cause and severity of the infection.[17] Culture and gram stain are important to guide appropriate treatment and de-escalation.[17]

The antibiotics listed in the *Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America* are classified by disease entity.[17] For impetigo, the recommended antibiotics include dicloxacillin, cephalexin, erythromycin, clindamycin, amoxicillin-clavulanate, retapamulin ointment, mupirocin ointment.[17] For MSSA SSTI, the recommended antibiotics include nafcillin or oxacillin, cefazolin, clindamycin, dicloxacillin, cephalexin, doxycycline or minocycline, and trimethoprim-sulfamethoxazole.[17] For MRSA SSTI, the recommended antibiotics include vancomycin, linezolid, clindamycin, daptomycin, ceftaroline, doxycycline or minocycline, and trimethoprim-sulfamethoxazole.[17] For Streptococcal skin infections, the recommended antibiotics include penicillin, clindamycin, nafcillin, cefazolin, penicillin, and cephalexin.[17]

3.2.3. Community-acquired bacterial pneumonia (CABP)

Treatment of CABP in adults initially involves empirical use of relatively broad-spectrum antibiotic therapy that is effective against probable pathogens and narrowed once cultures are obtained.[26] Although the etiology of CAP is changing, likely bacterial pathogens include *Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Staphylococcus aureus, Legionella species, Chlamydia pneumoniae,* and *Moraxella catarrhalis*.[27]

The antibiotics listed in the *Diagnosis and Treatment of Adults with Community-acquired Pneumonia* differ based on whether the patient is outpatient or inpatient.[27] For healthy outpatient adults without comorbidities or risk factors for antibiotic resistant pathogens, amoxicillin, doxycycline, azithromycin, clarithromycin, amoxicillin/clavulanate, cefpodoxime, cefuroxime, levofloxacin, moxifloxacin, and gemifloxacin are recommended.[27] In inpatient adults with non-severe CAP without risk factors for MRSA or *P. aeruginosa*, combination therapy with a beta lactam such as ampicillin and sulbactam, cefotaxime, ceftriaxone, or ceftaroline and a macrolide such as azithromycin, clarithromycin or doxycycline are recommended.[27] Monotherapy recommendations for inpatient adults with non-severe CAP without risk factors for MRSA or *P. aeruginosa* is a respiratory fluroquinolone such as levofloxacin or moxifloxacin.[27] In inpatient adults with CAP and risk factors for MRSA or *P. aeruginosa,* recommendations for empiric therapy include vancomycin, linezolid to cover MRSA and piperacillin-tazobactam, cefepime, ceftazidime, aztreonam, meropenem, or imipenem to cover *P. aeruginosa.*[27]

Similar to adults, treatment of CABP in pediatric patients involves empiric use of broad-spectrum antibiotics. The likely bacterial pathogens include *Streptococcus pneumoniae*, Group A *Streptococcus*,

MSSA, MRSA, *Haemophilus influenza*, *Mycoplasma pneumoniae*, *Chlamydia trachomatis* or *Chlamydophila pneumoniae*.[28]

The antibiotics listed in *The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America* differ based on whether the patient is outpatient or inpatient.[28] For previously healthy, appropriately immunized infants and preschool children, amoxicillin should be used as first-line therapy followed by macrolide antibiotics.[28] Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with CAP when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive S. pneumoniae.[28] Other antimicrobial agents for empiric therapy include ceftriaxone, cefotaxime, clindamycin, linezolid, vancomycin, second or third generation cephalosporin (cefpodoxime, cefuroxime, cefprozil); oral levofloxacin, or oral cephalexin.[28]

4. Benefit Assessment

4.1. *Staphylococcus aureus* bloodstream infection (bacteremia) (SAB)

The phase 3 noninferiority study, BPR-CS-009 (NCT 03138733) supporting the SAB indication was a randomized, double-blind, active-controlled, parallel-group, multicenter study in which patients were randomized to receive either ceftobiprole or active control, daptomycin.[2] Three hundred ninety patients were enrolled in which 192 patients were in the ceftobiprole arm and 198 patients were in the daptomycin arm.[29] All randomized patients were included in the intent to treat population.[29] Subjects in the test product group received 667 mg of ceftobiprole administered as a 2-hour IV infusion every 6 hours in the first 8 days, and every 8 hours from Day 9 onwards (with dose and/or schedule adjusted in patients with renal impairment).[2,5,30] Patients in the control product group received daptomycin 6 mg/kg (up to 10 mg/kg in accordance with institutional standards) administered as 0.5-hour IV infusion every 24 hours (with schedule adjusted in patients with renal impairment) and aztreonam was optional for qualifying patients randomized to daptomycin, using a standard-dose regimen at the site.[30] The maximum treatment duration was 42 days.[30]

The primary efficacy endpoint was overall success assessed by an independent data review committee (IDRC) in the treatment of SAB using a 15% noninferiority (NI) margin.[2,29] The IDRC was a group of independent clinical experts, blinded to treatment allocation and not associated with the study conduct, who reviewed patient profiles, including signs and symptoms of infection, and relevant microbiological and imaging findings, and assessed the patients' clinical and microbiological outcomes.[2] Overall success assessed by the IDRC was defined as all of the following criteria being met: patient alive at Day 70, no new metastatic foci or complications of the SAB infection, resolution or improvement of SAB-related clinical signs and symptoms and two negative blood cultures for *S. aureus* at prespecified time points.[4] Ceftobiprole met the primary endpoint of demonstrating noninferiority to daptomycin in the modified

intent to treat population (N=387).[29] Specifically, 69.8% of patients (132/189) in the ceftobiprole group were responders, and 68.7% of patients (136/198) in the comparator group were responders.[f,2]

The clinical reviewer concluded the phase 3 study met the agreed primary endpoint for *S. aureus* bacteremia.[4] Although the success rate in the ceftobiprole group was lower for the baseline MRSA subgroup, the overall success favored the ceftobiprole group.

4.2. Acute bacterial skin and skin structure infections (ABSSSI)

The phase 3 noninferiority study, BPR-CS-008 (NCT 03137173) supporting the ABSSSI indication was a randomized, double-blind, parallel-group, multicenter study in which patients were randomized to receive either ceftobiprole or active control, vancomycin plus aztreonam.[3,29,31] Six hundred seventy nine patients were enrolled in which 335 patients were in the ceftobiprole arm and 344 patients were in the vancomycin plus aztreonam arm. All 679 randomized patients were included in the intent to treat population.[3] Subjects in the test product group received ceftobiprole 500 mg administered as a 2-hour IV infusion every 8 hours, to be adjusted for patients with moderate or severe renal impairment.[3] Patients in the control product group received vancomycin was 1,000 mg or 15 mg/kg administered as a 2-hour IV infusion every 12 hours; however, this could be modified for factors such as renal function or therapeutic drug level monitoring.[3] The dose of aztreonam was 1,000 mg per 0.5-hour IV infusion every 12 hours, to be adjusted for patients with severe renal impairment, and the requirement for aztreonam therapy was to be reassessed at the 72-hour study visit.[3] The duration of treatment was 5-10 days and could be extended up to 14 days if required in the investigator's opinion and approved by the sponsor's medical monitor.[31]

The primary endpoint was early clinical success based on percentage reduction in lesion size at 48 – 72 hours after first treatment in the Intent-to-Treat (ITT) population.[3,29] A clinical response was defined as a percentage reduction in lesion size greater than or equal to 20 percent compared to baseline.[3] Ceftobiprole met the primary endpoint of demonstrating noninferiority to vancomycin plus aztreonam in terms of early clinical response 48 – 72 hours after start of treatment in patients with ABSSSI using a 10% NI margin.[3,29] Specifically, 91.3% of patients (306/335) in the ceftobiprole group were responders and 88.1% of patients (303/344) in the comparator group were responders.[f,3]

The clinical reviewer concluded the phase 3 study met its primary objective of demonstrating non-inferiority of ceftobiprole to vancomycin and aztreonam.[4] Secondary efficacy findings also favor ceftobiprole to vancomycin plus aztreonam.[4] Ceftobiprole provides an additional option for treatment of ABSSSI caused by Staphylococcus aureus (methicillin-susceptible and methicillin-resistant isolates), Streptococcus pyogenes, and Klebsiella pneumoniae.[4]

[f] 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.*

4.3. Community-acquired bacterial pneumonia (CABP)

The phase 3 noninferiority study, CAP-3001 (NCT 00326287) supporting the CABP indication was a randomized, double-blind, active control multicenter study in which patients were randomized to receive either ceftobiprole or active control, ceftriaxone with or without linezolid.[32] Six hundred sixty six patients were randomly assigned to treatment with either ceftobiprole or ceftriaxone with or without linezolid.[33] However, only 632 were assigned to a treatment group.[29] Specifically, 310 patients were in the ceftobiprole arm and 322 patients were in the ceftriaxone arm.[29] Six hundred thirty eight patients were included in the intent to treat population.[32] Subjects in the test product group received ceftobiprole 500 mg administered as a 2-hour IV infusion every 8 hours.[33] Patients in the control product group received ceftriaxone 2 g administered as a 30-minute IV infusion with or without linezolid 600 mg administered as a 1-hour infusion every 12 hours.[33] A switch from IV study drugs to oral cefuroxime axetil (500 mg every 12 hours) was allowed after a minimum of 3 days of IV therapy, but only for patients who met all of the stringent protocol-specified criteria for improvement[g], and were candidates for hospital discharge.[32] The duration of treatment was a minimum of 5 days and a target of 7 days.[33]

The primary endpoint was to demonstrate the non-inferiority of ceftobiprole compared with ceftriaxone with or without linezolid with respect to the clinical cure rate defined as the resolution of signs and symptoms of infection or improvement to such an extent that no further antimicrobial therapy was necessary and improvement/stabilization of chest X-ray findings with a pre-specified noninferiority margin of 15%.[4,32]

For this submission, re-analysis was done to use a different primary efficacy endpoint (clinical success at Day 3).[29] Clinical success is defined as improvement at day 4 in at least two (with no worsening) of the following symptoms of CABP compared with baseline: chest pain, cough, amount of productive sputum, and difficulty breathing.[34] The primary objective of the study was met, demonstrating the non-inferiority of ceftobiprole to ceftriaxone ± linezolid in terms of clinical cure at the test-of-cure (TOC) visit.[32] The overall clinical cure rate was 86.6% for ceftobiprole compared with the overall clinical cure rate of 87.4% for the comparator group.[4] In the ITT population, 76.4% of patients (240/314) in the ceftobiprole group

[g]Able to swallow and absorb oral medications; body temperature improved from baseline (rectal temperature ≥35°C and ≤38.8°C, axillary temperature ≥35.5°C and ≤37.3°C, oral temperature ≥36°C and ≤37.8°C, or tympanic temperature ≥36.5°C and ≤38.3°C) for at least 24 consecutive hours in the absence of any antipyretic medications; white blood cell (WBC) count and bands (%) within the normal range for the laboratory; respiratory rate ≤20 breaths per minute; Systolic blood pressure ≥90 mmHg and pulse ≤100 beats per minute for at least 24 consecutive hours; oxygen saturation of ≥92% by pulse oximeter or PO2≥80 mmHg on arterial blood gas while subject is breathing room air OR return to documented pre-infection baseline; significant improvement in clinical symptoms and signs (cough, sputum production, auscultatory findings, chills, and chest pain) compared with enrollment visit (baseline); no clinically significant deterioration observed on the chest X-ray; negative blood cultures at the enrollment visit (baseline) or if blood cultures obtained at the enrollment visit (baseline) are positive for a pathogen, blood cultures should be repeated and must be negative after a minimum of 3 days (72 hours) incubation.

derived clinical cure at the TOC visit and 79.3% of patients (257/324) in the ceftriaxone with/without linezolid group derived clinical cure at the TOC visit.[h,4,32]

A phase 3 randomized, investigator blind, active control, multicenter study, BPR-PIP-002 (NCT 03439124) was conducted to evaluate the safety, tolerability, pharmacokinetics and efficacy of ceftobiprole in 138 pediatric subjects aged 3 months to less than 18 years of age requiring hospitalization and IV antibacterial drugs for the treatment of CABP (vs. ceftriaxone ± vancomycin) and HABP (vs. ceftazidime ± vancomycin) with the primary objective of evaluating safety. Although the trial included patients with both HABP and CABP, only 8 enrolled patients had HABP; the Applicant is not seeking an indication for HABP.[4] A total of 94 patients received ceftobiprole. Efficacy for CABP was largely extrapolated from the successful phase 3 CABP adult study described above.[4]

The clinical reviewer concluded the submitted evidence showed non-inferiority of ceftobiprole to ceftriaxone with or without linezolid.[4] Efficacy in the pediatric population was extrapolated from the adult trial.[4] Ceftobiprole provides an additional option for treatment of CABP caused by *Staphylococcus aureus* (methicillin-susceptible), *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Escherichia coli*, and *Klebsiella pneumoniae*.[4]

5. Risk Assessment & Safe-Use Conditions

<u>*Staphylococcus aureus* bloodstream infection (bacteremia) (SAB)</u>

The safety of ceftobiprole was evaluated in 191 patients who received the proposed dose of ceftobiprole.[4] Eleven patients received ceftobiprole for 29 days or more, 151 patients received ceftobiprole for 15 days to 29 days, and 29 patients received ceftobiprole for less than 15 days.[4]

Treatment-emergent adverse events (TEAEs) leading to death were similar in both treatment arms and occurred in 8.9% [17/191] in the ceftobiprole arm and 9.1% [18/198] in the daptomycin arm.[4] The majority of deaths in both treatment groups appeared to be related to underlying medical conditions or concurrent illness in a critically ill population.[4] The number of patients who had TEAEs leading to treatment discontinuation was comparable in each arm (9.4% [18/191] in the ceftobiprole group and 9.1% [18/198] in the daptomycin arm).[4]

The incidence of SAEs was lower in the ceftobiprole arm compared to the daptomycin arm (18.8% [36/191] vs 22.7% [45/198]).[i,4] The most common adverse reactions leading to treatment discontinuation were gastrointestinal disorders, rash, and urticaria.[4] The following adverse reactions occurred in at least 4% of ceftobiprole-treated patients: anemia, nausea, hypokalemia, vomiting, hepatic enzyme and bilirubin increased, diarrhea, blood creatinine increased, and leukopenia.[4] Seizure and

[h] 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*.

[i] 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.*

hypersensitivity reactions were reported and are listed as warnings in the proposed labeling.[4] Postmarketing data reported cases of myoclonus, agranulocytosis, Stevens-Johnson syndrome, toxic skin eruption, and drug reaction with eosinophilia and systemic symptoms.[4]

Acute bacterial skin and skin structure infections (ABSSSI)

The safety database included 334 patients.[4] TEAEs leading to death occurred at a similar frequency in both treatment arms (44.3% in the ceftobiprole arm and 38.3% in the vancomycin and aztreonam arm); the single death in the ceftobiprole arm was unrelated to ceftobiprole.[h,4] SAEs occurred in 1.8% (6/334) in the ceftobiprole arm compared to 3.5% (12/342) in the vancomycin and aztreonam arm.[4] The incidence of TEAEs that led to treatment discontinuation was lower in the ceftobiprole (6/334; 1.8%) arm compared to the vancomycin and aztreonam arm (10/342; 2.9%).[4] The adverse reactions that led to treatment discontinuation in the ceftobiprole arm included rash, pruritus, and dysguesia.[4] The following adverse reactions occurred in at least 4% of ceftobiprole-treated patients: nausea, diarrhea, and headache.[4]

Community-acquired bacterial pneumonia (CABP)

In the adult CABP study, there were 9 deaths in each treatment arm (2.8%) which appear to be related to underlying comorbidities not related to treatment.[4] Approximately 11.3% (35/310) of patients treated with ceftobiprole developed an SAE compared to 11.5% (37/322) of patients in the comparator group who received ceftriaxone with or without linezolid.[j,4] Nearly 6% (18/310) of patients treated with ceftobiprole discontinued treatment due to an AE compared to 3.7% (12/322) of patients in the comparator group.[4] The most common TEAEs in patients treated with ceftobiprole included nausea, vomiting, liver enzyme increased, and diarrhea.[4]

No safety concerns were identified in the pediatric study, and there were no deaths.[4] Although a numerically greater number of participants had SAEs in the ceftobiprole vs. comparator groups (7.9% vs 4.9% respectively) and discontinued drug due to AEs (4.5% vs. 0 respectively), only hypersensitivity and urticaria in two participants appeared related to ceftobiprole.[4] Occurrence of TEAEs was balanced between treatment groups.[4] In the ceftobiprole arm, 31.5% (28/89) of patients experienced a TEAE compared to 29.3% (12/41) of patients in the ceftriaxone with or without vancomycin arm.[i,4] The most common TEAEs in the ceftobiprole group were vomiting (8% of patients), and headache, viral infection and pneumonia (all in less than 5% of patients).[i,4]

The clinical reviewer's conclusion is that ceftobiprole is well-tolerated overall and the safety profile is similar to other cephalosporins.[4] The safety database for ceftobiprole was adequate for the proposed dosing regimen for the intended patient population and respective indications.[4] Additionally, the benefits and risks of ceftobiprole have been communicated in labeling.[4] Monitoring for TEAEs of special interest will continue in the postmarketing phase.[4]

[j] 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.*

5.1. Increased Mortality with Unapproved Use in Ventilator-Associated Bacterial Pneumonia Patients

Increased mortality with ceftobiprole was observed in an active-controlled, randomized, double-blind, multicenter, phase 3 study. The mortality of patients with hospital-associated bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP) who were treated with ceftobiprole was (34/103 [33%] versus 24/102 [24%] in patients treated with the comparator.[5] The clinical team evaluated the narratives and concluded that most of the deaths do not appear to be related to the study treatment itself and may be due to chance as the subgroup of patients with VABP was small relative to the entire trial and the severity of illness in this subgroup may have led to increased deaths overall. Therefore, the labeling for ceftobiprole asserts that the safety and effectiveness of ceftobiprole for the treatment of HABP/VABP has not been established and the use of ceftobiprole for HABP/VABP is not approved by the FDA.[5]

5.2. Hypersensitivity Reactions

Hypersensitivity reactions were observed in patients treated with ceftobiprole in the clinical trials.[5] In Study BPR-CS-009, there were 3 patients (3/191; 1.6%) patients in the ceftobiprole arm with the AE of hypersensitivity compared to 1 patient (1/198; 0.5%) in the daptomycin arm with the AE of hypersensitivity.[k,4] The MO considered all three AEs could have been related to ceftobiprole.[4] In Study BPR-CS-008, no patients in the ceftobiprole arm experienced an AE of hypersensitivity.[4] In Study CAP-3001, one patient (1/310; 0.3%) in the ceftobiprole arm developed hypersensitivity compared with no patients in the ceftriaxone arm.[s,4] The patient fully recovered after resuscitation.[4] In study BPR-PIP-002, one patient (1/89; 1.1%) in the ceftobiprole arm experienced the SAE of hypersensitivity compared with no patients in the ceftriaxone ± vancomycin arm.[s,4]

Recommendations in labeling for management of hypersensitivity reactions are to inquire about previous hypersensitivity reactions to other cephalosporins, penicillins, or other beta-lactam antibacterial drugs, maintain clinical supervision if this product is to be given to a penicillin- or other β lactam allergic patient because cross sensitivity among β lactam antibacterial agents has been established and discontinue ceftobiprole if a hypersensitivity reaction occurs, and institute appropriate treatment.[5]

5.3. Seizures and Other Central Nervous System Reactions

Seizures and other adverse central nervous system (CNS) reactions have been reported during treatment with ceftobiprole and other cephalosporins.[5] In Study BPR-CS-009, there were 3 patients (3/191; 1.6%) patients in the ceftobiprole arm with the AE of seizure compared to 2 patients (2/198; 1%)

[k] 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.*

in the daptomycin arm with the AE of seizure.[s,4] Two of the patients who experienced seizures may have been associated with ceftobiprole however the seizure that occurred in one patient was attributed to hypoglycemia.[4] In Study BPR-CS-008, no patients in the ceftobiprole arm experienced an AE of seizure.[4] In Study CAP-3001, one patient (1/310; 0.3%) in both the ceftobiprole arm ceftriaxone arm developed as seizure.[j,4] In study BPR-PIP-002, no patients in the ceftobiprole arm experienced an AE of seizure.[4]

Recommendations in labeling for management of seizures and other CNS reactions include continuation of anticonvulsant therapy in patients with known seizure disorders and if CNS adverse reactions, including seizures, occur, patients should undergo a neurological evaluation to determine whether ceftobiprole should be discontinued.[5]

5.4. *Clostridioides difficile*-Associated Diarrhea

The use of antibacterial agents is a risk factor for *Clostridioides difficile*-Associated Diarrhea (CDAD). This infection may be serious and result in increased morbidity and mortality. *C. difficile* colitis was not reported among patients receiving ceftobiprole in Study BPR-CS-009, Study BPR-CS-008, or Study CAP-3001.[4] Recommendations in labeling for management of CDAD are to discontinue antibacterial use not directed against *C. difficile* if possible and to manage fluid and electrolyte levels as appropriate, supplement protein intake, monitor antibacterial treatment of C*. difficile*, and institute surgical evaluation as clinically indicated.[5]

5.5. Development of Drug-Resistant Bacteria

As with other antibacterial agents, using ceftobiprole 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.[5]

6. Expected Postmarket Use

Due to the IV route of administration of this drug, we expect this product will be administered in inpatient settings and outpatient settings such as infusion centers or under a specialized outpatient IV medication protocol. 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 ceftobiprole.

Foreign postmarketing experience with ceftobiprole incudes a retrospective case series conducted in Italy in which 29 patients received ceftobiprole.[4,35] Of the 29 patients, 2 patients developed myoclonus and 1 patient developed a rash that were attributed to ceftobiprole.[4,35] No deaths were reported in this case series in patients while receiving ceftobiprole.[4,35] A case report identified agranulocytosis in a patient receiving ceftobiprole after drug rash with eosinophilia and systemic symptoms (DRESS) associated with vancomycin and rifampin.[4,36] After discontinuation of ceftobiprole, the patient's neutrophils recovered without further issues.[4,36]

7. Risk Management Activities Proposed by the Applicant

While the Applicant submitted a Risk Management Plan with their submission, they did not propose any risk management activities for ceftobiprole beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of ceftobiprole on the basis of the efficacy and safety information currently available.

The 3 proposed indications, SAB, ABSSSI, and CABP for ceftobiprole are serious and often life threatening infections with significant morbidity and mortality.[4] Approved treatments for SAB, including right sided endocarditis, due to MRSA are limited.[4] Although there are multiple antibacterial drugs currently approved to treat ABSSSI and CABP, the continued evolution of antibacterial resistance mechanisms, drug-drug interactions, and adverse effects of available antibacterial drugs can limit the available treatment options.[4] In addition, there is an urgent need to develop antibacterial drugs which cover both gram-negative and gram-positive organisms, especially MRSA, which is a major cause of hospital and community acquired infections worldwide.[4,37] Current treatments for MRSA infections have limitations.[4] Specifically, vancomycin is associated with nephrotoxicity and need for drug monitoring, linezolid has drug-drug interactions and toxicities, daptomycin does not penetrate the lung parenchyma, and ceftaroline is not FDA-approved for difficult to treat infections such as bacteremia and right-sided infective endocarditis.[4]

Ceftobiprole is an advanced generation cephalosporin antibiotic drug that provides effective treatment for SAB, ABSSSI, and CABP with a favorable safety profile.[4] The efficacy of ceftobiprole was supported by three noninferiority trials, trial BPR-CS-009 for SAB, trial BPR-CS-008 for ABSSSI, and CAP-3001 for CABP. Trial BPR-CS-009 demonstrated that ceftobiprole is noninferior to daptomycin in the treatment of patients with SAB, including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin resistant isolates based on the primary endpoint of overall success based on IDRC assessment at the PTE visit in the mITT population which met the prespecified 15% NI margin.[4] Trial BPR-CS-008 demonstrated that ceftobiprole is noninferior to vancomycin plus aztreonam in treatment of patients with ABSSSI based on the primary endpoint of early clinical response in the ITT population which met the prespecified 10% NI margin.[4] Trial CAP-3001 demonstrated that ceftobiprole is noninferior to ceftriaxone plus linezolid in treatment of adult patients with CABP.[4] In the ITT population, the clinical cure rate in the ceftobiprole group was 76.4% compared with the comparator group at 79.3% which met the prespecified 10% NI margin.[4] Efficacy for CABP in the pediatric population was extrapolated from the adult CABP trial.[4] Of note the labeling will include a warning and precaution of increased mortality in ventilator-associated bacterial pneumonia patients since safety and effectiveness of ceftobiprole for the treatment of HABP/VABP has not been established.[5]

The safety data for ceftobiprole demonstrated that ceftobiprole was similar to the active comparator in each trial.[4] In addition, the risks observed for ceftobiprole are consistent with the risks associated with other fourth and fifth generation cephalosporin drugs.[38-40] The risks associated with ceftobiprole include

increased mortality in VABP, hypersensitivity reactions, seizures and other CNS reactions, CDAD, and development of drug-resistant bacteria.[5] At the time of this review labeling negotiations were ongoing, however, there are currently no boxed warnings for any risk in the prescribing information for ceftobiprole.[5] 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 ceftobiprole. Overall, ceftobiprole has a favorable safety profile, and risks will be adequately addressed in the warnings and precautions section of the labeling and by routine pharmacovigilance.[4,5]

Based on the efficacy and risks associated with ceftobiprole for the treatment of SAB, ABSSSI, and CABP, 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 is favorable for 1) Treatment of adult patients with SAB, including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin resistant isolates, 2) Treatment of adult patients with ABSSSI caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pyogenes*, and *Klebsiella pneumoniae, and* 3) Treatment of adult and pediatric patients (greater than or equal to 3 months to less than 18 years of age) with CABP caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible), *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Escherichia coli*, and *Klebsiella pneumoniae*.[4] Therefore, a REMS is not necessary for ceftobiprole 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

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