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Ceftobiprole medocaril (Zevtera) – FDA approved antibiotic for three infections including methicillin-resistant *Staphylococcus aureus*

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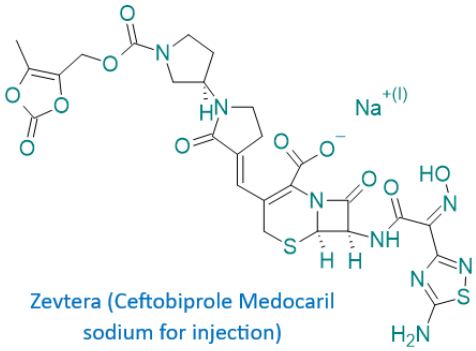
Note



Zevtera (Ceftobiprole Medocaril sodium for injection)

FDA approval for

- Staphylococcus aureus bloodstream infections (bacteremia) (SAB)
- Acute bacterial skin and skin structure infections (ABSSSI);
- Community-acquired bacterial pneumonia (CABP)

ABSTRACT

The U.S. Food and Drug Administration (FDA) has approved Zevtera (ceftobiprole medocaril sodium for injection) for multiple therapeutic indications. Zevtera (a product of Basilea company) is now authorized for use in adults to treat *Staphylococcus aureus* bloodstream infections (bacteremia), including cases of right-sided infective endocarditis. Additionally, it is approved for adults with acute bacterial skin and skin structure infections (ABSSSI). Further, Zevtera is also approved for treating community-acquired bacterial pneumonia (CABP) in pediatric patients aged three months to less than 18 years. This broad-spectrum antibiotic offers a significant advancement in managing severe bacterial infections across different age groups, enhancing treatment options for both healthcare providers and patients.

Keywords: Drug Resistance, Antibiotics, Heterocyclic drug, MRSA, Zevtera, antibacterial drug resistance, Basilea.

INTRODUCTION

Bacterial infections represent a significant burden on global health,[1] contributing to a wide range of diseases that affect various parts of the body. The diverse forms of bacteria are responsible for a number of different infections in human body. Among the diverse array of bacterial pathogens, *Staphylococcus aureus* stands out due to its ability to cause both common and severe infections.[2] The different bacteria are a leading cause of skin infections, bloodstream infections, cough, stomach infections, and respiratory system infections including pneumonia, thus, presenting substantial challenges to public health and clinical management.

Furthermore, the Antibacterial drug resistance is a burgeoning global health crisis, posing a significant threat to public health, modern medicine, and the effective treatment of infectious diseases. It occurs when bacteria evolve mechanisms to withstand the drugs designed to kill them or inhibit their growth. This resistance renders standard treatments ineffective, leading to persistent infections, increased transmission of resistant strains, and heightened morbidity and mortality.[3]

Bacteria can develop resistance through several mechanisms.[4,5] One common method is the alteration of the target site of the antibiotic, rendering the drug ineffective.[4] For example, mutations in bacterial ribosomal proteins can prevent antibiotics from binding properly. Another mechanism is the production of enzymes that inactivate antibiotics, such as beta-lactamases that break down penicillins and cephalosporins. Bacteria can also employ efflux pumps to expel antibiotics from their cells or modify their metabolic pathways to bypass the drug's action. Furthermore, the acquisition of resistance genes through horizontal gene transfer - via plasmids, transposons, or bacteriophages - can rapidly spread resistance among bacterial populations.[3]

Several factors contribute to the rise of antibacterial resistance. Overuse and misuse of antibiotics in human medicine and agriculture are primary drivers. Inappropriate prescribing, such as using antibiotics for viral infections, not completing prescribed courses, and over-the-counter availability of antibiotics in some

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regions, exacerbates the problem. In agriculture, the use of antibiotics to promote growth and prevent disease in livestock leads to the development of resistant bacteria that can transfer to humans through the food chain or direct contact.[3]

The impact of antibacterial resistance on healthcare is profound. Common infections, such as urinary tract infections, pneumonia, and sepsis, become more difficult to treat, leading to longer hospital stays, higher medical costs, and increased mortality. Surgical procedures, cancer chemotherapy, and organ transplants, which rely on effective antibiotics to prevent and treat infections, are jeopardized by the rising resistance. The spread of multi-drug resistant organisms (MDROs) like methicillin-resistant *Staphylococcus aureus* (MRSA)[6] and carbapenem-resistant *Enterobacteriaceae* (CRE) represents a severe challenge to public health systems worldwide.

Addressing antibacterial resistance requires a multifaceted approach.[7] Surveillance and monitoring of resistance patterns are essential for informed antibiotic prescribing and infection control measures. Stewardship programs aimed at optimizing antibiotic use can reduce unnecessary exposure to antibiotics and slow the development of resistance. Research and development of new antibiotics,[8,9] along with alternative therapies such as bacteriophages,[10] immunotherapies, and vaccines, are crucial for staying ahead of resistant bacteria.[3]

The specific bacteria cause particular type of infections in human and thus have specific physiological characteristics and specific mode of infection.

Staphylococcus aureus is a gram-positive bacterium commonly found on the skin and in the nasal passages of healthy individuals. While often harmless, it can cause a variety of infections when it breaches the body's barriers. One of the most severe conditions caused by *S. aureus* is bloodstream infection, or bacteremia.[11] This occurs when the bacteria enter the bloodstream, potentially leading to life-threatening complications such as sepsis and infective endocarditis, particularly right-sided endocarditis, which affects the heart's right valves. The high morbidity and mortality rates associated with S. aureus bacteremia underscore the need for effective antimicrobial therapies and prompt medical intervention.[12]

Acute bacterial skin and skin structure infections (ABSSSI) are another common manifestation of *S. aureus*.[13] These infections range from minor conditions like impetigo and cellulitis to more severe infections such as abscesses and necrotizing fasciitis. ABSSSI can result from minor cuts, abrasions, or insect bites that become contaminated with the bacteria. Symptoms typically include redness, swelling, warmth, and pain at the infection site, often accompanied by fever. Timely diagnosis and treatment are crucial to prevent the spread of infection and more serious complications.

In addition to skin infections and bacteremia, community-acquired bacterial pneumonia (CABP) is a significant illness caused by various bacteria, including *Streptococcus pneumoniae*. CABP refers to lung infections contracted outside of hospital settings, presenting with symptoms such as cough, fever, chest pain, and difficulty breathing. In children, pneumonia can lead to severe respiratory distress and is a leading cause of pediatric hospitalizations. The treatment of CABP often involves antibiotics, with the choice of agent depending on the suspected or confirmed pathogen and the patient's clinical condition.

The antibacterial drug resistance is a complex and escalating threat that requires urgent and coordinated action across multiple sectors. There continuous demand for the development of new antibiotic drugs to combat the emerging antibiotic resistance to existing drugs.

The approval of new antibiotics like Zevtera (ceftobiprole medocaril sodium) represents a critical advancement in the fight against these bacterial infections. Zevtera, a β-lactam compound,[14] is particularly noteworthy for its broad-spectrum activity and effectiveness against multi-drug resistant strains of *S. aureus*. It is approved by the U.S. Food and Drug Administration for treating adults with *S. aureus* bacteremia, including those with right-sided infective endocarditis, as well as adults with ABSSSI. Furthermore, Zevtera is indicated for pediatric patients aged three months to less than 18 years with CABP, addressing a significant unmet need in pediatric infectious disease management.

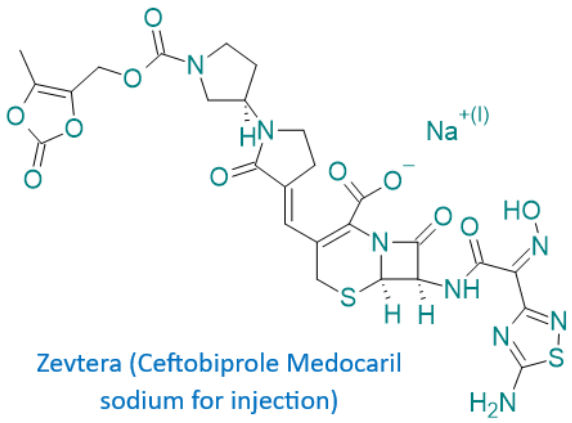

Figure 1. Chemical structure of Zevtera (ceftobiprole medocaril sodium)

CLINICAL TRIALS:

Zevtera (ceftobiprole medocaril sodium) is a broad-spectrum cephalosporin antibiotic recently approved by the U.S. Food and Drug Administration (FDA) for multiple indications, including *Staphylococcus aureus* bloodstream infections (bacteremia), acute bacterial skin and skin structure infections (ABSSSI), and community-acquired bacterial pneumonia (CABP) in pediatric patients. The efficacy and safety of Zevtera have been evaluated in several clinical trials, providing robust data to support its use in these indications.[15]

Staphylococcus aureus Bloodstream Infections (Bacteremia)

In a pivotal clinical trial assessing the efficacy of Zevtera in treating *Staphylococcus aureus* bloodstream infections[16,17] including right-sided infective endocarditis, the study demonstrated significant therapeutic benefits. The trial was a randomized, double-blind, multicenter study comparing

ceftobiprole to standard therapy, typically involving vancomycin with or without an aminoglycoside. The primary endpoint was clinical cure rates at the test-of-cure (TOC) visit.[17]
Key Findings:

- Clinical Cure Rate: Patients treated with Zevtera showed a comparable or superior clinical cure rate to those receiving standard therapy.
- Safety Profile: The safety profile of Zevtera was consistent with other cephalosporins, with common adverse events including gastrointestinal disturbances, headache, and infusion site reactions.

Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

Zevtera's efficacy in ABSSSI was evaluated in two major Phase III trials, CANVAS 1 and CANVAS 2,[13] which were randomized, double-blind studies comparing ceftobiprole to vancomycin plus ceftazidime.[13] The primary endpoint for these studies was the clinical response rate at the early follow-up visit.[17]
Key Findings:

- Clinical Response: Zevtera demonstrated non-inferiority to the comparator regimen, with clinical response rates of over 90% in both studies.[18]
- Pathogen Eradication: The drug was particularly effective against methicillin-resistant *Staphylococcus aureus* (MRSA),[12] a common pathogen in ABSSSI.
- Safety and Tolerability: Zevtera was well tolerated, with a safety profile similar to the comparator regimen, and no new safety signals were identified.

Community-Acquired Bacterial Pneumonia (CABP) in Pediatric Patients

The approval of Zevtera for pediatric patients aged three months to less than 18 years with CABP was supported by a randomized, active-controlled trial.[19,20] This study compared the efficacy and safety of ceftobiprole to standard-of-care antibiotics, such as ceftriaxone or cefotaxime, combined with vancomycin or linezolid for suspected MRSA cases.[21]
Key Findings:

- Efficacy: Zevtera was shown to be effective in treating CABP in pediatric patients,[22] with clinical cure rates similar to those observed in adults.[23]
- Safety: The safety profile in pediatric patients was consistent with that observed in adults, with common adverse events including diarrhea, nausea, and rash.[19]

Overall Analysis

The clinical trial data for Zevtera (ceftobiprole medocaril sodium) highlight its efficacy and safety across multiple serious bacterial infections.[24] The trials demonstrated that Zevtera is at least as effective as existing standard therapies, with a comparable safety profile. Its broad-spectrum activity, including efficacy against MRSA and other resistant pathogens, positions it as a valuable addition to the antibiotic arsenal.[6]

Strengths:

- Broad-Spectrum Efficacy: Effective against a wide range of gram-positive and gram-negative pathogens.
- MRSA Activity: Demonstrated efficacy in infections caused by MRSA, a significant clinical challenge.[25]
- Safety Profile: Comparable to other cephalosporins, with no major safety concerns.[26]

Limitations:

- Resistance Development: As with all antibiotics, there is a potential for resistance development, necessitating careful use and monitoring.
- Pediatric Data: While data in pediatric patients are promising, long-term safety and efficacy need further observation.[27]

Zevtera's clinical trial results provide strong evidence supporting its use for the approved indications, offering a potent option for managing difficult-to-treat bacterial infections.[28] Its inclusion in treatment protocols can enhance outcomes for patients with serious infections, particularly those caused by resistant bacteria.

Conclusions

In conclusion, bacterial infections caused by pathogens like *Staphylococcus aureus* pose significant health risks across all age groups. The development and approval of effective antimicrobial agents such as Zevtera are vital for improving patient outcomes. Continuous research, surveillance, and innovation in antibiotic therapy are essential to combat these infections and mitigate their impact on global health.

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Conflict of Interest Statement

This study report has not received any financial support from any agency or institute. Authors do not have any conflict of interest for publication of this brief note.

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