Ceftobiprole Medocaril Sodium (ZEVTERA)
National Drug Monograph
October 2025

VA Pharmacy Benefits Management Services and VA National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Ceftibiprole (CFB) is a broad-spectrum 5th generation cephalosporin which is supplied as CFB medocaril, the prodrug that rapidly converts to CFB, which inhibits bacterial cell wall synthesis.
    - CFB has a high-affinity for penicillin binding proteins (PBP) 1-4, including PBP2a in methicillin-resistant *S.*aureus (MRSA) and PBP2x / PBP2b in penicillin-resistance *Streptococcus pneumoniae (S. pneumo)*
- In vitro activity is broad against many gram-positive and gram-negative bacteria, including:
    - **Activity:**
        - Methicillin-susceptible and resistant *Staphylococcus aureus* (MSSA and MRSA), including VAN-resistant *S. aureus* (VRSA) and other staphylococci (*S. epidermidis, S. hominis, S. lugdunesnsis*)
        - *Streptococcus pneumoniae* (including penicillin-resistant strains), *S. pyogenes* (Group A strep) *S. agalactiae* (Group B strep), *S. mitis, S. dysgalactiae, S. anginosus group*
        - *Haemophilus influenzae (H. flu) and H. parainfluenzae*
        - *Moraxella catarrhalis (M. catarrhalis)*
        - Most non-extended-spectrum beta-lactamase or carbapenemases producing *Enterobacterale*, (e.g., *E.coli, Klebsiella pneumoniae, Citrobacter koseri, Enterobacter cloacae, Klebsiella aerogenes, Morganella morganii, Proteus mirabilis)*
        - Some anaerobic bacteria, including *Clostridium spp. and Fusobacterium spp*.
    - **Reduced or no activity:**
        - *Enterococcus faecium (E. faecium)*
        - *Acinetobacter baumannii, Burkholderia cepacia complex, Stenotrophomonas maltophilia*
        - *Proteus vulgaris*
        - Gram-negative anaerobes (e. g. *Bacteroides fragilis* group, *Prevotella* spp., *Veillonella* spp.)
        - ***Enterobacterales* producing acquired extended-spectrum beta-lactamases (ESBLs), highly expressed AmpC cephalosporinases or carbapenemases (e.g., KPC, NDM-1, OXA)**
    - **Breakpoints for CFB are**
        - 2 mg/L for *S. aureus*
        - 0.5 mg/L for *S.pneumonaie, S.pyogenes*
        - 0.25 mg/L for *H. Flu, H. parainfluenzae*, and *Enterobacterales*

Indication(s) Under Review in This Document

CFB was approved by the FDA on 4/3/24 for patients aged 18 years and over for the following indications:

1. *Staphylococcus aureus* bloodstream infection (SAB), including those with right-sided infective endocarditis caused by MSSA and MRSA.
2. Acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of MSSA, MRSA *Streptococcus pyogenes*, and *Klebsiella pneumoniae*.
3. Community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of MSSA, MRSA, *S. pneumoniae, H. flu, H. parainfluenzae, E. coli,* and *K. pneumoniae*

Background History:

- CFB was first submitted to FDA in 2007 by Johnson and Johnson for complicated SSI but received a Complete Response Letter from FDA due to deficiencies in the pivotal Phase 3 trials. The pharmaceutical company that developed the drug withdrew the NDA.
- CFB ownership was transferred to Basilea in 2011 and it was granted Qualified Infectious Diseases Product designation for CABP (2015), ABSSI (2015) and SAB (2017). An NDA for these 3 indications was submitted to FDA in 2023, and FDA approved CFB on 4/3/24.
- Outside of the U.S. CFB was marketed in several countries in 2008, withdrawn from the market in 2010, and re-approved in 2014 for CABP and HABP (excluding ventilator-acquired bacterial pneumonia) and is currently marketed for these indications in 20 countries outside the US (including the European Union and Canada).

Dosage Form(s) Under Review

Indication in Adults	Dose*	Route	Frequency	Infusion Time
SAB	667 mg	IV	Q6h on days 1 to 8 Q8H from day 9	2 hours
ABSSSI	667 mg	IV	Q8H	
CABP	667 mg	IV	Q8H	
* CFB medocaril 667 mg is equivalent to CFB 500 mg. Renal dose adjustments for CrCl <50ml/min and >150 ml/min				

- CFB is provided in a single-dose vial with lyophilized powder that requires reconstitution with sterile water for injection or 5% dextrose injection. After reconstitution shake vigorously until dissolution (which can take up to 10 minutes) then dilute with 250 ml bag of 0.9% sodium chloride (NS) or 5% dextrose in water (D5W).
- Once reconstituted, infusion can be stored at room temperature for 6 hours (D5W) or 4 hours (NS) or refrigerated for 94 hours (D5W) or 24 hours (NS). It must not be mixed or co-administered with calcium-containing solutions.

Clinical Evidence Summary

Efficacy Considerations

Efficacy of CFB was demonstrated in phase 3, randomized, double-blinded, active-controlled, noninferiority trials in adults for each of the indications (SAB, ABSSSI, and CABP) that demonstrated noninferiority to the comparators. The trials are

- **ERADICATE** for complicated SAB (cSAB), including right-sided endocarditis (RIE) vs. daptomycin (DAP) +/- aztreonam (AZT)
- **TARGET** for ABSSI vs. Vancomycin (VAN) +/- AZT
- **Phase 3 for CABP** vs. ceftriaxone +/- linezolid
- Non-inferiority was demonstrated in all 3 trials per the FDA definitions
- An additional study in hospital and ventilator-associated bacterial pneumonia did not meet criteria for non-inferiority but data was submitted for safety.

Table 1: Efficacy results from clinical trials

Study/Design	Methods /Endpoints	Demographics	Results/Comments
ERADICATE (Holland et. al) NCT03138733 **Phase 3:** ***S. aureus* bacteremia** **Randomized, double-blind, double-dummy, non-inferiority trial** **Treatment** • CFB 500 mg IV q6h over 2 hours (days 1-8); day 9 and onwards 500 mg IV q8 (n=189) • DAP 6 mg to 10 mg/kg IV Q24H over 30 minutes +/- AZT 1000 mg IV Q12H (n=198) • Treatment duration initially up to 28 days to assess seizure risk based on animal signal, but extended to up to 42 days based on interim safety analysis	**Inclusion** Positive blood culture within 72 hrs., complicated bacteremia (dialysis, persistent bacteremia, RIE, ABSSI, metastatic infection, epidural/cerebral abscess, osteoarticular infection) **Exclusion** Unremovable prosthetic material, neutropenia, pneumonia, ≥ 48 hours of effective antibiotics w/in 7d, Left-sided IE, CFB MIC >2 or DAP MIC >1 mg/L ITT: all randomized mITT: received drug and SAB **Primary endpoint (mITT)** **Overall treatment success** 70 days after randomization (alive, no new complications, resolution of clinical signs and symptoms and 2 negative blood cultures) **Failure:** death, premature discontinuation, new complications, relapse /reinfection, use of prohibited antibiotics **Secondary endpoints** Death at day 70, microbiologic eradication, success in ITT/mITT/CE, new *S. aureus* bacteremia related complications, time to clearance	387 patients were included in the mITT population (189 CFB and 198 for DAP +/- AZT) **Baseline characteristics:** (CFB vs DAP +/-AZT) Mean age: 57 vs. 58 Male sex: 68% vs. 71% White race: 95 % vs. 97% Immunosuppressed: 4% vs. 1.5% Fever baseline: 55% vs. 53% Abnormal WBC: 37% vs. 42% **Complicated category:** • Persistent SAB: 9% vs. 8% • **ABSSI: 61% both groups** • Osteoarticular: 17% vs. 18% • Abdominal abscess: 14% vs. 15% • Metastatic infection: 36% vs. 33% • Right sided IE: 8% vs. 5% • Dialysis associated: 13% vs. 13% MRSA bacteremia: 24% vs. 25% Median treatment duration: 21 days DAP dose >7 mg/kg: 11%	**Overall treatment success** • **CFB: 69.8%** • **DAP group: 68.7%** • Diff: 1% (95% CI −7.1 to 11.1) ***CFB was noninferior to DAP group with respect to overall treatment success. The superiority of CFB over DAP was not achieved.*** **Overall success by resistance:** **MSSA:** CFB 71% vs. DAP 66% **MRSA:** CFB 69% vs. 78% (n=94) **All-cause mortality:** (CFB vs DAP) • Post-treatment: 9% vs. 9% • Death due to *S. aureus* bacteremia: 3.7% vs. 3.0% **Other findings** (CFB vs DAP) • Micro erad: 82% vs. 77% • Median time to negative blood culture: 4 days for both groups ***Limitations:*** *most patients had ABSSI as complicating factor which is associated with better outcomes. Low numbers of MRSA patients, persistent bacteremia and RIE*
TARGET **Phase 3 Trial:** **ABSSI** **Randomized, double-blind, active-controlled, parallel-group, noninferiority study** **Treatment** • CFB 500 mg IV Q8H over 2 hours (n=335)	**Inclusion** Hospitalized with ABSSSI (wound infection, cellulitis or erysipelas, or major abscess) requiring IV therapy plus at least one regional or systemic sign of infection. Minimum lesion size 75 cm^2 **Exclusion** Antibacterials w/in 14 days, uncomplicated SSTI, diabetic foot infection gangrene, concomitant	**ITT(n) = CFB 335, VAN+/-AZT 344** **CE(n) = CFB 283, VAN 223** **Baseline characteristics** (CFB vs. VAN+/-AZT) Median age: 51 vs. 50 years Male: 59% vs. 58% White race: 95% vs. 96% Fever: 36% vs. 35% Abnormal WBC: 34% vs. 37% **Type of ABSSI** Wound infection: 38% vs. 41%	**Early response** CFB vs. VAN/AZT **ITT: 91% vs. 88%** Diff 3.3% (95% CI -1.2 to 7.8) **CE: 94% vs. 89%** Diff 5.0% (95% CI 0.6 to 9.4) **Investigator-assessed clinical success at the TOC visit** **ITT: 90% vs. 89%**

• VAN 1000 mg (or 15 mg/kg) IV Q12H over 2 hours + AZT 1000 mg IV Q12H over 30 mins (n=344) • Treatment duration: 5-10 days (could extend to 14d if required)	infection at other site, ischemic chronic ulcer, necrotizing infection, severe sepsis or septic shock. **Primary endpoint:** early clinical response 48-72 hours (20% size reduction from baseline) and no rescue therapy in ITT (all randomized). CE = ITT who completed TOC **Secondary endpoint:** Investigator-assessed clinical success at the test of cure (TOC) visit ITT and clinically evaluable	Cellulitis/erysipelas: 33% vs. 32% Major abscess: 29% vs. 27% Miscellaneous: – Diabetes: 11% vs. 12% – Illicit drug use: 32% vs. 34% – Drainage: 14% vs 15% – Debridement: 7% vs. 7% Median duration: 6 vs. 7 days Median duration AZT: 3 days Switch to oral therapy was not allowed Patients could receive concomitant metronidazole for suspected anaerobic infection	**CE: 98% vs. 95%** ***CFB was noninferior for the ITT population and superior to VAN group in the CE population for the primary endpoint*** ***CFB was noninferior for the secondary endpoint of clinical success at TOC in ITT and CE populations***
Phase 3 Trial: **CABP** **Double-blinded, randomized, non-inferiority clinical trial** **Treatment** • CFB 500 mg IV q8h over 2 hours (n=231) • Ceftriaxone (CTX) 2 g IV q24h over 30 minutes +/- linezolid (LIN) 600 mg Q12H (if MRSA coverage needed) (n=238) • No adjunctive macrolide allowed • Target duration 7 days (min 5 / max 14 days) Change to oral cefuroxime after day 3 allowed if patient met protocol-defined significant improvement criteria.	**Inclusion** Adults with CABP severe enough to require hospitalization and treatment with IV antibiotics for ≥3 days **Exclusion:** lung cancer, cystic fibrosis, lung abscess, TB, extrapulmonary complications **Primary endpoint:** clinical cure rate at TOC in both the ITT (all randomized patients) and CE (ITT + at least 48 hours study drug and able to be evaluated) **Secondary endpoint**: microbiological eradication rate at TOC in the mITT and ME analysis data sets; clinical cure rate by baseline PSI score in the ITT and CE data sets and 3-day pneumonia-specific mortality in the ITT and CE data sets.	ITT (n) = CFB 314, CTX+/- LIN 324 CE(n) = CFB 231, CTX+/- LIN 238 **Baseline characteristics (ITT)** (CFB vs CTX +/- LIN) Median age: 56 vs. 56 years Male sex: 57% vs. 58% Race: White: 61% vs. 63% Age ≥75 years: 17% vs. 19% PSI score ≥91: 22% vs. 22% SIRS: 53% vs. 55% Bacteremia: 4% vs. 5% + LIN (placebo) 10% vs. 12% The most common pathogen was *S. pneumoniae* (n = 68) followed by *H. influenzae* (n = 26) Duration of therapy: ~ 6 vs 7 days	**Clinical cure rate at TOC (ITT population)** • CFB: 76% • CTX +/- LIN: 79% • Difference -2.9% (95% CI −9.3 to + 3.6) ***Non-inferiority between the CFB and comparator groups for clinical cure rates was observed in both the ITT and CE populations*** **Microbiological eradication rate at TOC (mITT population)** • CFB: 80.5% • CTX +/- LIN: 81.4% • (95% CI −12.4 to + 10.4) ***Non-inferiority between the CFB and comparator groups was observed for the secondary efficacy endpoint of microbiological eradication at the TOC visit both in the microbiological ITT and the ME patients*** **30-day pneumonia mortality (ITT population)** • CFB: (1/314) • Ceftriaxone +/- linezolid: (3/324)

Safety Considerations

Table 2: Safety results from clinical trials

Study	Results	Comments
ERADICATE	Increased frequency of thrombosis was observed in the CFB arm as compared to DAP arm CFB 5.2% (10/191) vs. DAP 2% (2/198)	• Nonclinical findings of thromboembolic in multiple animal species, a similar finding in humans may be possible, but overall, less likely given confounding factors in the study population (e.g., multiple comorbidities, prolonged hospitalization, prior surgical procedures, and inconsistent DVT prophylaxis) • No significant imbalance in thrombosis events were noted in other clinical trials • Thromboembolic disease has not been reported with CFB in post-marketing reviews (from other countries) • This finding occurred at a rate <2% in clinical trials and will be further monitored by post-market surveillance data
Awad SS, et al 2014	Increased mortality in VABP patients CFB: 26.9% vs. Ceftazidime/linezolid: 19.8%	• The increased deaths in the VABP subgroup may have been due to chance, as there was a small number of subjects in the VABP subgroup relative to the entire trial. Also, the acuity and severity of illness of this subgroup may have led to increased deaths overall, thereby confounding this association. • Based on the information of increased mortality in VABP, CFB is not approved for the treatment of VABP.

- Neurotoxicity including seizures and encephalopathy is included as warning and precaution across the five generations of cephalosporins

- **Boxed warnings:** none
- **Contraindications:** known hypersensitivity to the components of CFB or other members of the cephalosporin class
- **Other warnings / precautions**:
    - Increased mortality with unapproved use in ventilator-associated bacterial pneumonia (VABP)
    - If seizures or other adverse central nervous system (CNS) reactions occur, evaluate patients to determine whether CFB should be discontinued
- **Adverse reactions**
    - **Common**: anemia, nausea, hypokalemia, vomiting, hepatic enzyme and bilirubin increased, diarrhea, blood creatinine increased, hypertension, leukopenia, and pyrexia
    - **Serious Adverse events / Deaths / Discontinuation:** increased mortality in ventilator-associated bacterial pneumonia patients, serious hypersensitivity and skin reactions, seizures and other CNS reactions, *C. difficile* associated diarrhea.

Other Considerations

Pharmacokinetics:

- Cmax (ug/mL): 33.0 mg/L
- AUC_{0-8}: 102
- Binding to plasma proteins: 16%
- Vss: 18L

- Half-life: 3.3 h (Delayed in ESRD)
- Onset of action: 30 mins after the start of infusion
- Elimination: >80 % excreted in urine
- Rapidly (< 1 min) almost completely converted to active CFB

Stability:

Reconstitution solution diluent	Infusion solution diluent	Infusion solutions stored at 25 °C (NOT protected from light)	Infusion solutions stored at 2 °C to 8 °C (protected from light; recommended)
5% Dextrose solution for injection	5% Dextrose solution for injection	6 hours	94 hours
	0.9% Sodium chloride solution for injection	4 hours	24 hours
Sterile water for injection	5% Dextrose solution for injection or 0.9% Sodium chloride solution for injection	6 hours	94 hours

Pregnancy:

CFB medocaril was not associated with adverse developmental effects in rats or rabbits when administered parenterally at doses clinically equivalent to the MHRD. No clinical data is available regarding use in pregnancy.

Lactation:

Although CFB medocaril was detected in rat milk, the concentration in rat milk does not necessarily predict the concentration of drug in human milk. There are no available data on CFB medocaril presence in human milk, on the effects on the breastfed infant or the effects on milk production. There are no concerns for serious adverse reactions in the breastfed infant, risk/benefit discussion.

Other Therapeutic Options

Table 3 Treatment Alternatives – MRSA Bacteremia (Monotherapy

Drug	Formulary status	Clinical Guidance	Other Considerations
CFB	TBD	Indications, efficacy	PK, storage, dosing, monitoring, drug-drug interactions
VAN	F	• Approved for MRSA bacteremia and RIE VAN remains the standard initial treatment of MRSA bacteremia at nearly every institution	• Limitations include nephrotoxicity and ototoxicity • Requires need for drug monitoring • Can be used in patients with beta-lactam allergy who cannot receive first-line agents for MSSA (cefazolin, nafcillin, oxacillin)
DAP	PA-F	• Approved for MRSA bacteremia and RIE	• Approved in 2006 for MRSA bacteremia via open-label clinical trial. In this trial there was a, larger noninferiority margin (20% vs. 15%) and smaller sample size than the ERADICATE trial. There were also more microbiologic failures in the DAP arm • Limitations include myalgias, rhabdomyolysis, eosinophilic pneumonia • DAP should not be used for primary pulmonary infections due to inactivation by surfactant.
Ceftaroline	F	• Not FDA-approved for difficult to treat infections such as bacteremia and RIE. Approved for ABSSIE as well as CAB. • Systematic review in 2017 evaluated use for indications outside of its FDA approval that included MRSA bactermia or endocarditis, CNS infection and nosocomial pneumonia. • A retrospective cohort study of adults with MRSA bacteremia described outcomes of 83 patients treated with ceftaroline for at least 72 hours and found similar rates of failure when compared with DAP (32.5% vs. 39%, respectively)	• At clinically relevant concentrations inactivates PBP2a (the molecular determinant of methicillin resistance), thus clinically relevant for MRSA and MSSA bacteremia
Linezolid	PA-F	• Not directly studied for MRSA bacteremia indication in prospective RCT	• Limited by drug-interactions and side effects such as myelosuppression, risk for serotonin syndrome, peripheral neuropathy • Not recommended for initial therapy

Drug	Formulary status	Clinical Guidance	Other Considerations
		• Linezolid has similar rates of clinical cure to VAN in a pooled meta-analysis of bacteremic patients from 5 RCTs of infections due to S. aureus (not limited to SAB although the number of MRSA patients was low 52/3,228) but did not meet prespecified noninferiority criteria when compared with VAN	
Dalbavancin **Oritavancin**	NF	• Indicated for endocarditis, step-down therapy in patients who inject drugs and SSTI	• Until further studies are conducted, caution should be used due to emerging evidence of the possibility of treatment-emergent dalbavancin resistance as well as cross-resistance to DAP and VAN • Awaiting results from the DOTS trial

Other Indications:

For ABSSSI

- A single treatment option that combines MRSA and gram-negative antibacterial coverage may be useful in certain clinical settings.

For CAP:

- There are many antibacterial drugs approved for treatment of CABP. However, with increasing antibacterial resistance, adverse reactions, including hypersensitivity, treatment options may be limited in some patients.
- Important limitation is coverage of ESBL & Acinetobacter and dosing schedule (667mg IV Q8H)
- The use of CFB medocaril monotherapy may simplify initial empirical treatment relative to the use of combination therapies in these patient populations.

MSSA:

- Treatment for SAB and RIE caused by MSSA include cefazolin, nafcillin, oxacillin, and DAP. VAN can be used in patients with beta-lactam allergy or in those who cannot receive other drugs

Projected Place in Therapy

- Ceftobiprole is a later generation cephalosporin, that like ceftaroline contains activity against methicillin-resistant *Staphylococcus aureus* (*S.aureus)* and most Enterobacterales NOT producing ESBLs or Class A, B or D carbapenemases. Activity against gram-negative anaerobes and non-lactose fermenting gram-negative rods is poor.
- Pneumonia (CAP and HAP) and Skin and soft tissue infections (SSTI) are very common in Veterans but have numerous potential treatment options, creating a limited role of CFB for these infections.
- *Staphylococcus aureus* bacteremia (SAB) is common, associated with high morbidity and mortality and can be associated with primary infections in skin/soft tissue, pneumonia, intravenous catheters and others. Treatment options are limited, in particular for patients with MRSA bacteremia.
    - Vancomycin, used most commonly is associated with a need for therapeutic drug monitoring and can cause renal insufficiency.
    - Daptomycin is also commonly used and has an FDA indication for SAB, including with right-sided endocarditis. Increasingly it is being used as primary therapy for difficult to treat infections and for ease after discharge from the hospital.
    - For patients who fail first-line therapy, treatment options are even more limited. Ceftaroline is used commonly, despite a lack of randomized clinical trials or FDA indication. Linezolid also has limited data for complicated bacteremia and long-term can be associated with myelosuppression.
- Ceftobiprole has a long history of safety data from approval in other countries, and numerous additional randomized controlled trials to support use in several infections, including SSTI, CAP and bacteremia.
    - Having randomized controlled trial data supports a better understanding of optimal dosing than with ceftaroline and may be an advantage.
    - Frequency of dosing, especially for SAB, and limited stability may be disadvantages and considerations for use as a second line agent for SAB.
    - Given the complexities of the drug, dosing, and spectrum, use should involve local ID experts and Antimicrobial Stewardship Champions to ensure appropriate use.

References

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