Aztreonam/Avibactam (EMBLAVEO)
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. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Aztreonam + avibactam (ATM/AVI) is a combination product consisting of a monobactam and a beta-lactamase inhibitor.

Indication(s) Under Review in This Document

- In combination with metronidazole (MTZ) for adults who have limited or no alternative options for the treatment of complicated intra-abdominal infections (cIAI) caused by susceptible gram-negative bacteria. Approval for this indication is based on limited clinical safety and efficacy data.

Dosage Form(s) Under Review

- Vial for intravenous (IV) injection containing 1.5 g of ATM and 0.5g of AVI (total dose 2g)
- Dose for CrCl > 50 mL/min is 2g IV every 6 hours, infused over 3 hours, after a loading dose of 2.67g
- Dose adjustments are needed for kidney dysfunction

Clinical Evidence Summary

Efficacy Considerations

- Aztreonam's spectrum of activity is limited to aerobic gram-negative (GN) bacteria and, similar to other beta-lactams, it is inhibited by most serine beta-lactamases (e.g., KPC, OXA-48). However, in contrast to other beta-lactams, ATM is not hydrolyzed by most metallo-beta-lactamases (MBLs), including IMP, NDM, and VIM.
- The addition of AVI to ATM expands its coverage to include GN bacteria producing many types of extended-spectrum beta-lactamases, including serine beta-lactamases and MBLs.
- Efficacy data is based on efficacy of ATM for cIAI along with *in vitro* data and animal models for more resistant GN bacteria.
- Supplemental data comes from a Phase 2 study in cIAI (REJUVENATE) and Phase 3 studies (REVISIT and ASSEMBLE) in patients with cIAI, complicated UTI (cUTI), bloodstream infection (BSI), and hospital acquired or ventilator associated pneumonia (HAP-VAP).

- Additional support for the potential role of ATM/AVI comes from a prospective, observational cohort study comparing the combination ceftazidime/avibactam (CZA) + ATM versus other active antibiotics for patients with BSI caused by MBL-producing GN bacteria.

Table 1 Studies supporting efficacy

Study	Design	Demographics	Results
REJUVENATE (Cornely et al. J Antimicrob Chemother. 2020 Mar)	Non-randomized, open-label, Phase 2a dose-ranging trial Adults with cIAC with source control ATM-AVI + MTZ x5-14 days Cohorts 2 and 3 used the FDA approved dose, with the only difference being a smaller loading dose of 500mg ATM/137mg AVI Outcomes included PK and clinical response at various timepoints	Cohorts 2+3 consisted of 18 patients Median age 56 yrs. 78% male 94% white Median CrCl 110 mL/min Included syndromes: gastric/appendiceal/diverticular perforation/abscess, gangrenous cholecystitis, intra-abdominal abscess and secondary peritonitis	PK analysis confirmed the higher dose (used in Cohorts 2+3) would move into Phase 3 For Cohort 2+3, clinical cure at end of treatment (EOT) and test of cure (TOC) was 72 and 56%, respectively
REVISIT (Carmeli et al. Lancet Infect Dis. 2025 Feb)	Randomized (2:1), open-label, central assessor masked Phase 3 trial Hospitalized adults with presumed/confirmed cIAI with source control or confirmed HAP-VAP, with confirmed/suspected GN bacteria Excluded patients w/ GN bacteria not anticipated to respond to either treatment (e.g., *Acinetobacter baumanii*) or GP bacteria only ATM/AVI (+MTZ if cIAI) vs. meropenem (MEM) +/- colistin (CST) x5-14 days for cIAI or x7-14 days if HAP-VAP The primary outcome was clinical cure at TOC in intention to treat (ITT) and clinically evaluable (CE) analysis sets No formal hypothesis testing or power calculation but sample size of 425 patients to assess overall cure rates and by diagnosis	<u>cIAI</u> ATM/AVI + MTZ: n=208 MEM +/- CST: n=104 The most common syndrome was appendiceal perforation/abscess (47-51%). The most frequently isolated pathogen was *E. coli* (73-83%) <u>HAP-VAP</u> ATM/AVI: n=74 MEM +/- CST: n=36 45-50% had VAP and 51-53% were mechanically ventilated. The most frequently isolated pathogen was *K. pneumoniae* (45-63%). Mean age 54 yrs. 66-72% male 46-58% white Mean CrCl 103-104 mL/min 308 aerobic GN isolates tested 23% Non-susceptible ATM (CLSI) 10% Non-susceptible MEM (CLSI) Of 80 isolates tested for carbapenemase, 24% were positive for either serine or MBLs with less than half of those harboring MBLs	Clinical cure at TOC in ITT analysis set: <u>cIAI</u> ATM/AVI + MTZ: 76% MEM +/- CST: 74% <u>HAP-VAP</u> ATM/AVI + MTZ: 46% MEM +/- CST: 42% Similar results in CE analysis set
ASSEMBLE (Daikos et al.	Randomized (2:1), open-label, parallel group Phase 3 trial	ATM/AVI (+MTZ if cIAI): n=12 BAT: n=3	Study terminated early due to insufficient enrollment

Study	Design	Demographics	Results
JAC Antimicrob Resist. 2025 Jul)	Hospitalized adults with confirmed cIAI, cUTI, BSI, HAP-VAP with MBL-positive GN bacteria ATM/AVI (+MTZ if cIAI) vs. best available treatment (BAT) The primary outcome was cure at TOC in ITT analysis set	Median age 57 yrs. 67% male 42% white Median CrCl 74 mL/min The most frequently isolated pathogen was *K. pneumoniae* All isolated GN bacteria had ATM/AVI MIC ≤4 except for one NDM5-positive *E. coli* isolate with ATM/AVI MIC 8	Clinical cure at TOC: 42% in ATM/AVI cohort and 0 in BAT cohort
Falcone et al. Clin Infect Dis. 2021 Jun	Prospective, observational cohort study Adults hospitalized in Italian/Greek hospitals with ≥1 blood culture positive for MBL-producing Enterobacterales who received therapy with an agent with in vitro activity against the isolate for ≥48 hours Antibiotics selected by ID consultants blinded to study results: CZA 2.5g q8H + ATM 2g q8H vs. other active antibiotics (colistin (CST), fosfomycin (FOF), gentamicin, MEM, tigecycline(TGC)) as monotherapy or in combination Primary outcome was 30-day all-cause mortality. Additional outcomes included 14-day clinical failure (death or lack of clinical or microbiological improvement) Univariate, multivariate, and propensity-score matched analyses were reported	CZA+ATM: n=52 Colistin-containing OAA: n=27 Non-colistin-containing OAA: n=23 Median age 70 yrs 69% male More ICU pts in CZA + ATM group (50 vs, 18%), more surgery pts in OAA group (26 vs. 10%), more immunosuppressed pts in OAA group (50 vs 20%) <u>82 NDM-producing isolates</u> 79 *K. pneumoniae* 3 *E. coli* % Susceptible: ATM 7%, CST 90%, TGC 84%, FOF 72%, CZA + ATM synergy 100% <u>20 VIM-producing isolates</u> 14 *K. pneumoniae* 5 *Enterobacter* spp 1 *M. morganii* % Susceptible: ATM 50%, CST 80%, TGC 50%, FOF-80%, CZA + ATM synergy 100%	30-day all-cause mortality: CZAI+ATM: 19% OAA: 44% (p=0.007, HR 0.17, 95% CI 0.07-0.41) 14-day clinical failure: CZA+ATM: 25% OAA: 52% (p=0.005, HR 0.20, 95%CI 0.08-0.48) Adjusted and propensity-score matched analysis yielded similar results Additionally, drug-induced AKI was lower in the CZA group (2 vs. 20%, p=0.003)

Safety Considerations

Safety Results from Clinical Trials:

- Aztreonam has been used for several decades in the United States (US). Avibactam has been approved in combination with ceftazidime since 2015.
- Adverse reactions of ATM/AVI +/- MTZ were compared with MEM +/- CST in the REVISIT trial (details above). The most common adverse reactions (ATM/AVI +/- MTZ vs. MEM +/- CST,

respectively) were hepatic adverse reactions (15% vs. 12%), anemia (8% vs. 5%), diarrhea (6% vs. 4%), hypokalemia (6% vs. 3%), and pyrexia (6% vs. 5%).
    - ALT elevations > 5 x the upper limit of norma occurred in 3.8% vs. 3.1%
    - Discontinuation due to elevated hepatic enzymes in only 4 patients across the development trials
- No unexpected adverse events were noted

Other Therapeutic Options

Other treatment options for carbapenemase-producing Enterobacterales spp are listed in table 2 below.

Table 2 Treatment options for Carbapenemase-Producing Enterobacterales

Drug	Formulary status	FDA Indication Available Clinical Guidance	Other Considerations
Aztreonam-Avibactam (ATM/AVI)	TBD	FDA approved for cIAI in patients with limited treatment options EMA approved for HAP, cIAI, and cUTI in patients with limited treatment options No IDSA recommendation yet but ATM/AVI data used to support recommendation for CZA+ATM (below) Has activity against carbapenemases, including MBLs Can be used in patients with severe IgE-mediated cephalosporin allergy (other than ceftazidime)	Less than 20% of Carbapenem-Resistant Enterobacterales (CRE) in the US produce MBL In a study of 511 CRE isolates, ≥98% were susceptible to ATM/AVI by EUCAST breakpoints (MIC ≤4), including 50 isolates producing MBLs EUCAST breakpoints available Must be administered over 3 hours every 6 hours Complicated preparation and possible drug wastage

Drug	Formulary status	FDA Indication Available Clinical Guidance	Other Considerations
Ceftazidime-Avibactam plus Aztreonam (CZA + ATM)	PA-F, F	IDSA preferred option for infections outside of the urinary tract caused by MBL-producing Enterobacterales spp Can be used in patients with severe IgE-mediated cephalosporin allergy	CZA + ATM susceptibility testing available through broth disk elution method CZA administered and aztreonam administered simultaneously via Y-site administration over 3 hours every 8 hours
Ceftazidime-Avibactam (CZA)	PA-F	FDA approved for HAP-VAP, cIAI, cUTI IDSA preferred option for infections outside of the urinary tract caused by KPC and OXA-48 producing Enterobacterales spp	Has the most clinical data for treating KPC and OXA-48 producing Enterobacterales spp compared to other beta-lactam/beta-lactamase inhibitor combination agents ≥95% of KPC and OXA-48 producing Enterobacterales susceptible to CZA No activity against MBL producing organisms
Imipenem + cilastatin + relebactam (I-R)	PA-F	FDA approved for HAP-VAP, cIAI, cUTI IDSA preferred option for infections outside of the urinary tract caused by KPC-producing Enterobacterales spp	Carbapenem backbone very stable against ESBL and AmpC enzymes ≥95% of KPC producing Enterobacterales susceptible to I-R No activity against MBLs or OXA-48 Limited stability in solution Concern for seizure risk with high doses of imipenem
Meropenem + vaborbactam (MBV)	PA-F	FDA approved for cUTI IDSA preferred option for infections outside of the urinary tract caused by KPC-producing Enterobacterales spp	Carbapenem backbone very stable against ESBL and AmpC enzymes ≥95% of KPC producing Enterobacterales susceptible to MBV No activity against MBLs or OXA-48 Limited stability in solution
Cefiderocol	PA-F	FDA approved for HAP-VAP, cUTI IDSA alternate option for infections outside of the urinary tract caused by KPC and OXA-48 producing Enterobacterales spp	Reserve for MBL-producing Enterobacterales

Drug	Formulary status	FDA Indication Available Clinical Guidance	Other Considerations
Colistin (CST), polymyxin B (PMB)	NF, F	FDA-approved for susceptible GN infections IDSA: No longer recommended against infections outside of the urinary tract caused by CRE	In vitro activity against many multi-drug resistance bacteria, including those with MBLs Observational studies have shown increased neurotoxicity, nephrotoxicity, and mortality compared to other agents
Eravacycline (ERV), Tigecycline (TGC)	PA-F, F	ERV FDA approved for cIAI; TGC: FDA approved for cSSTI, cIAI, CAP IDSA: Suggested as an alternate option for CRE if beta-lactam containing options not available	Activity independent of presence of carbapenemases Use of lower TGC doses for pneumonia associated with increased mortality Neither agent suggested for the treatment of bloodstream or urinary infections due to rapid distribution and limited concentrations in those spaces

Projected Place in Therapy

- Several available beta-lactam / beta-lactamase inhibitor combination agents have good in vitro activity and clinical data supporting their use for the treatment of infections caused by Enterobacterales producing the more common carbapenemases (KPC and OXA-48).

- Infections due to Enterobacterales producing MBLs are much less common in the US and usually seen in patients with extensive prior antibiotic exposure or international travel to countries where these organisms are more prevalent.

- Aztreonam is not hydrolyzed by most MBLs but cannot be used alone against MBL-producing Enterobacterales because these bacteria frequently harbor other beta-lactamases, which can inhibit ATM. The addition of AVI to ATM can allow treatment of Enterobacterales that produce both MBLs and other beta-lactamases.

- While administration of CAZ + ATM will accomplish similar coverage, it does add the patient's beta-lactam exposure, which can increase adverse effects. Additionally, patients with severe IgE-mediated cephalosporin allergy may not be able to tolerate CAZ + ATM.

- It is likely that the use of ATM/AVI will be limited to select patients with infections caused by difficult to treat GN bacteria.

- The use of ATM/AVI should generally be managed by experts in Infectious Diseases and Antimicrobial Stewardship to ensure appropriate use.

References

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