EMBLAVEO®

The first^{*} β-lactam/β-lactamase inhibitor combination designed with metallo-β-lactamases (MBLs) in mind^{1-5†}

Why EMBLAVEO®

- Antimicrobial resistance (AMR) is one of the biggest threats to global health particularly in Gramnegative bacteria that have significant clinical importance in hospitals^{6,7}
- An estimated 1.27 million deaths globally were caused by bacterial AMR in 2019 alone, and a continued rise in AMR could lead to 10 million deaths annually across the globe by 2050⁸
 - In the EU, infections due to multidrug-resistant (MDR) Gram-negative bacteria cause around 33,000 estimated deaths every year⁹
- Without solutions, a continued rise of AMR could diminish the efficacy of common antibiotics against widespread bacterial infections and make medical procedures too risky to perform⁶
- The WHO's latest annual review of the pre-clinical and clinical antibacterial pipelines highlights the paucity of antimicrobials to adequately address the WHO bacterial priority pathogens and target MBLs, which continue to grow in prevalence¹⁰
- Novel combinations of existing agents are in clinical development and can help managing patients with serious bacterial infections due to Gram-negative bacteria, including MBL-producing MDR pathogens¹⁰
 - MBL-producing Enterobacterales represent a major threat globally. The emergence of carbapenem resistance among Enterobacterales, mostly due to the acquisition of carbapenemases, and the frequent association of carbapenem resistance with cross-resistance with other antibiotic classes limit the treatment options^{3,10}
 - The distribution of MBL-carbapenem resistant Enterobacterales (CRE) exhibits a significant increasing trend over time worldwide, with high incidence of NDM-producers³
- In addition, implementing infection prevention and control measures along with antimicrobial stewardship programmes, including rapid diagnostic tests, can prevent potentially around 27,000 deaths per year in European regions⁹

EMBLAVEO® has the potential to address an important unmet medical need in management of MDR aerobic Gram-negative bacterial infections^{1,11}



High *in vitro* activity against MBLproducing isolates of Enterobacterales and *S. maltophilia*^{1,5,12-15}

Optimised dosing to achieve joint PTA above 90%^{1,16}



MDR Gram-negative bacteria^{*1,17-20} Favourable risk–benefit

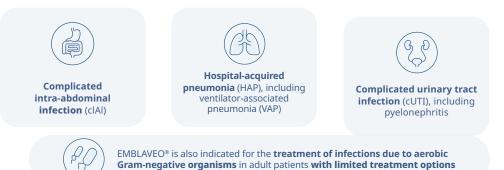
profile1,11,17-20

infections caused by MBL-producing

Clinical data supports the use

of EMBLAVEO® to treat serious

EMBLAVEO® Approved indications¹



Consideration should be given to official guidance on the appropriate use of antibacterial agents.

It is recommended that EMBLAVEO® should be used to treat infections due to aerobic Gram-negative organisms in adult patients with limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases¹

EMBLAVEO® Mode of action

EMBLAVEO[®] is the first* β -lactam/ β -lactamase inhibitor combination specifically designed to act against MBL-producing bacteria that may also co-produce SBLs (serine BL) – including ESBLs, AmpC and the carbapenemase enzymes, KPC, and OXA-48-like^{2,4}

AZTREONAM

Monobactam with bactericidal activity due to high affinity for PBP3, hydrolysed by most SBLs but not hydrolysed by MBLs^{21,22}

AVIBACTAM

Non-β-lactam β-lactamase inhibitor, which inhibits Ambler classes A, C, and some D β-lactamases (e.g., ESBLs, KPC, AmpC and OXA-48-like)⁴

- Aztreonam alone is not effective against MDR Gram-negative bacteria that co-produce MBLs and SBLs⁴
- When combined, avibactam protects aztreonam from SBL hydrolysis restoring its activity against MBL-producing bacteria⁴

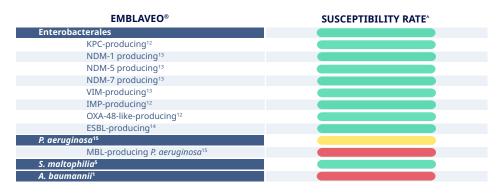


EMBLAVEO[®]

The first^{*} β-lactam/β-lactamase inhibitor combination designed with metallo-β-lactamases (MBLs) in mind^{1-5†}

Microbiology

EMBLAVEO® is highly active in vitro against MBL-producing Enterobacterales and S. maltophilia^{‡1,5,12-15}



Susceptibility anticipated to be >80% Susceptibility anticipated to be 30–80%

Intrinsic resistance or susceptibility anticipated to be <30%</p>

In vitro susceptibility testing breakpoint for Enterobacterales^{1,23}

MIC breakpoint established by the EUCAST for EMBLAVEO®#

ORGANISMS	SUSCEPTIBLE	RESISTANT
Enterobacterales	≤4 mg/L	>4 mg/L

Colour coding adapted from Tamma PD, et al. J Pediatric Infect Dis Soc. 2019;8(3):251-60.24

"The breakpoint defines whether a species of bacteria is susceptive or resistant to the antibiotic. If the MIC is less than or equal to the susceptibility breakpoint, the bacteria are considered susceptible.^{25,26}

The clinical significance of *in vitro* activity is unknown unless the safety and effectiveness of EMBLAVEO® in treating clinical infections due to these pathogens have been established in adequate and well-controlled clinical trials.

Abbreviations: ALT, alanine aminotransferase; AmpC, ampicillin dass C; AMR, antimicrobial resistance; AST, aparate aminotransferase; BL, B-lactamase; CE, clinically evaluable; cAL, complicated intraadominal infection; COL, constituine clearance; CBE, cardapenent resistant Enterobacterales; cUTL, complicated intraultion; EUCAST, European Committee on Antimicrobial Susceptibility Testing; *ff*, free time; HAP, hospital-acquired pneumonia; IMP, imipenemase; ITT, intent-to-treat; IV, intravenous; KPC, Klebsiela pneumoniae cardapenemase; *K. pneumonine*, Klebsiela pneumoniae; MBL, metallo-B-tactamase; MDR, multiful-greessant; MIC, minimum inhibitory concentration; MBL, meropenem; MIZ, metronidazole; NOM, Nevo Delim metallo-beta-lactamase; CAK, availinae; *P. exemplisae*; Senotrophomonas analophilia; TOC, test of cure; VAP, ventilator-associated pneumonia; VIM, Verona integron-encoded metallo-beta-tamase; WA, Void Health Organization.

PP-A1E-NLD-0014

EMBLAVEO® Dosage & Administration

- The dosing regimen of EMBLAVEO[®] optimises the simultaneous achievement of both aztreonam and avibactam PK/PD targets [joint probability of target attainment (PTA)] in more than 90% of patients.¹⁶
 - For the aztreonam and avibactam combination, a joint PK/PD target (defined as attainment of 60% fT > MIC of 8 mg/L for aztreonam, and 50% fT > 2.5 mg/L for avibactam, achieved simultaneously), required for antibacterial efficacy, was considered¹⁶
 - A loading dose improves probability of achieving both avibactam and aztreonam target exposures in the first dosing interval. $^{\rm 16}$
 - A loading dose plus 3-h maintenance infusions of aztreonam-avibactam in a 3:1 fixed ratio q6h optimizes joint PTA¹⁶

Recommended IV dose by type of infection in adult patients with CrCL >50 mL/min \ast_1

Dose of Emblaveo® (aztreonam/avibactam)		Infusion time	Dosing interval	
	Loading	Maintenance		
	2 g/0.67 g	1.5 g/0.5 g	3 hours	Every 6 hours

Note, a single loading dose is followed by maintenance doses beginning at the next dosing interval. *Calculated using the Cockcroft-Gault formula.

Type of infection	Duration of treatment (days)	
cIAI [§]	5-10	
HAP, including VAP	7-14	
cUTI, including pyelonephritis	5-10	
Infections due to aerobic Gram-negative organisms in patients with limited treatment options	Duration in accordance with the site of infection and may continue for up to 14 days	

⁵To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.

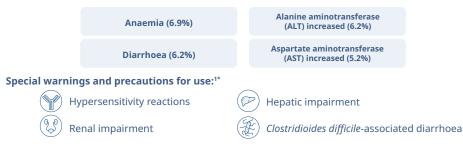
No dosage adjustment is required for:15



 $^{\rm S} Recommended dose adjustments of EMBLAVEO^{\oplus}$ for patients with estimated CrCL \pm 50 mL/min can be found in the current approved PI. In patients with renal impairment, close monitoring of estimated creatinine clearance is advised.

EMBLAVEO® Safety & Tolerability

Phase 2 and Phase 3 studies demonstrated EMBLAVEO® has a favourable risk-benefit profile.^{1,17-20} The overall safety profile is in line with that of aztreonam alone.^{1,17-20,27} The most common adverse drug reactions (ADRs) in patients treated with EMBLAVEO® were:^{1*}



*SMPC: https://ec.europa.eu/health/documents/community-register/2024/20240422162367/anx_162367_en.pdf.