EMBLAVEO®

IT'S IN THE NAME

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 Gram-negative 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 2050[8]
  - In the EU, infections due to multidrug-resistant (MDR) Gram-negative bacteria cause around 33,000 estimated deaths every year[9]
- 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 perform[6]
- 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 prevalence[10]
- 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 pathogens[10]
  - 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-producers[3]
- 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 regions[9]

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 MBL-producing isolates of Enterobacterales and *S. maltophilia*[1,5,12-15]
- **Clinical data supports the use of EMBLAVEO® to treat serious infections caused by MBL-producing MDR Gram-negative bacteria**[*1,17-20]
- Optimised dosing to achieve joint PTA above 90%[1,16]
- **Favourable risk–benefit profile**[1,11,17-20]

EMBLAVEO® Approved indications[1]

- **Complicated intra-abdominal infection** (cIAI)
- **Hospital-acquired pneumonia** (HAP), including ventilator-associated pneumonia (VAP)
- **Complicated urinary tract infection** (cUTI), including pyelonephritis

EMBLAVEO® is also indicated for the **treatment of infections due to aerobic Gram-negative organisms** in adult patients **with limited treatment options**

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 diseases[1]

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 SBLs[4]
- When combined, avibactam protects aztreonam from SBL hydrolysis restoring its activity against MBL-producing bacteria[4]

Pfizer

EMBLAVEO® aztreonam/avibactam

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Microbiology

EMBLAVEO® is highly active *in vitro* against MBL-producing Enterobacterales and *S. maltophilia*[‡1,5,12-15]

EMBLAVEO®	SUSCEPTIBILITY RATE^
Enterobacterales	
KPC-producing[12]	
NDM-1 producing[13]	
NDM-5 producing[13]	
NDM-7 producing[13]	
VIM-producing[13]	
IMP-producing[12]	
OXA-48-like-producing[12]	
ESBL-producing[14]	
***P. aeruginosa*[15]**	
MBL-producing *P. aeruginosa*[15]	
***S. maltophilia*[5]**	
***A. baumannii*[1]**	

Susceptibility anticipated to be >80% | Susceptibility anticipated to be 30–80% | Intrinsic resistance or susceptibility anticipated to be <30%

***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.

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% *f*T > MIC of 8 mg/L for aztreonam, and 50% *f*T > 2.5 mg/L for avibactam, achieved simultaneously), required for antibacterial efficacy, was considered[16]
  - A loading dose improves probability of achieving both avibactam and aztreonam target exposures in the first dosing interval.[16]
  - A loading dose plus 3-h maintenance infusions of aztreonam-avibactam in a 3:1 fixed ratio q6h optimizes joint PTA[16]

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

§To 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]

- Elderly patients based on age
- Patients with hepatic impairment
- Patients with mild renal impairment (estimated CrCL >50 to ≤80 mL/min)

[§]Recommended dose adjustments of EMBLAVEO® for patients with estimated CrCL ≤ 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*]

- Anaemia (6.9%)
- Alanine aminotransferase (ALT) increased (6.2%)
- Diarrhoea (6.2%)
- Aspartate aminotransferase (AST) increased (5.2%)

Special warnings and precautions for use:[1*]

- Hypersensitivity reactions
- Hepatic impairment
- Renal impairment
- *Clostridioides difficile*-associated diarrhoea

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

Abbreviations: ALT, alanine aminotransferase; **AmpC**, ampicillin class C; **AMR**, antimicrobial resistance; **AST**, aspartate aminotransferase; **BL**, β-lactamase; **CE**, clinically evaluable; **cIAI**, complicated intra-abdominal infection; **COL**, colistin; **CrCL**, creatinine clearance; **CRE**, carbapenem resistant Enterobacterales; **cUTI**, complicated urinary tract infection; **ESBL**, extended-spectrum β-lactamase; **EU**, European Union; **EUCAST**, European Committee on Antimicrobial Susceptibility Testing; ***f*T**, free time; **HAP**, hospital-acquired pneumonia; **IMP**, imipenemase; **ITT**, intent-to-treat; IV, intravenous; **KPC**, *Klebsiella pneumoniae* carbapenemase; ***K. pneumoniae***, *Klebsiella pneumoniae*; **MBL**, metallo-β-lactamase; **MDR**, multidrug-resistant; **MIC**, minimum inhibitory concentration; **MER**, meropenem; **MTZ**, metronidazole; **NDM**, New Delhi metallo-beta-lactamase; **OXA**, oxacillinase; ***P. aeruginosa***, *Pseudomonas aeruginosa*; **PBP**, penicillin-binding protein; **PD**, pharmacodynamics; **PK**, pharmacokinetics; **PTA**, probability of target attainment; **q6h**, every 6 hours; **SBL**, serine-β-lactamase; ***S. maltophilia***, *Stenotrophomonas maltophilia*; **TOC**, test of cure; **VAP**, ventilator-associated pneumonia; **VIM**, Verona integron-encoded metallo-beta-lactamase; **WHO**, World Health Organization.

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