PT. PFIZER INDONESIA
Local Product Document

Generic Name: Avibactam, Aztreonam
Trade Name: EMBLAVEO®
EU SPC Effective Date: April 22, 2024
Supersedes: N/A

1. NAME OF THE MEDICINAL PRODUCT

EMBLAVEO® 1.5 g/0.5 g powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1.5 g aztreonam and avibactam sodium equivalent to 0.5 g avibactam.

After reconstitution, 1 mL of solution contains 131.2 mg of aztreonam and 43.7 mg of avibactam (see section 6.6).

Excipient(s) with known effect:

Emblaveo contains approximately 44.6 mg sodium per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

White to slightly yellow lyophilised cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Emblaveo is classified as Reserve antibiotics indicated for the treatment of the following infections in adult patients (see sections 4.4 and 5.1):

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

Consideration should be given to official guidance on the appropriate use of antibacterial agents only with appropriate diagnostic microbiological approach and after consultation with a physician with experience in the management of infectious diseases.

4.2 Posology and method of administration

Posology

Dose in adults with estimated creatinine clearance (CrCL) > 50 mL/min
Table 1 shows the recommended intravenous dose for patients with a creatinine clearance (CrCL) > 50 mL/min. A single loading dose is followed by maintenance doses beginning at the next dosing interval.

Table 1. Recommended intravenous dose by type of infection in adult patients with CrCL[a] > 50 mL/min

Type of infection	Dose of aztreonam-avibactam		Infusion time	Dosing interval	Duration of treatment
	Loading	Maintenance			
cIAI[b]	2 g/0.67 g	1.5 g/0.5 g	3 hours	Every 6 hours	5-10 days
HAP, including VAP	2 g/0.67 g	1.5 g/0.5 g	3 hours	Every 6 hours	7-14 days
cUTI, including pyelonephritis	2 g/0.67 g	1.5 g/0.5 g	3 hours	Every 6 hours	5-10 days

a Calculated using the Cockcroft-Gault formula.
b To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.

Special populations

Elderly
No dosage adjustment is required in elderly patients based on age (see section 5.2).

Renal impairment
No dosage adjustment is required in patients with mild renal impairment (estimated CrCL > 50 to ≤ 80 mL/min).

Table 2 shows the recommended dose adjustments for patients with estimated creatinine clearance ≤ 50 mL/min. A single loading dose is followed by maintenance doses beginning at the next dosing interval.

Table 2. Recommended doses for patients with estimated CrCL ≤ 50 mL/min

Estimated CrCL (mL/min)[a]	Dose of aztreonam-avibactam[b]		Infusion time	Dosing interval
	Loading	Maintenance		
> 30 to ≤ 50	2 g/0.67 g	0.75 g/0.25 g	3 hours	Every 6 hours
> 15 to ≤ 30	1.35 g/0.45 g	0.675 g/0.225 g	3 hours	Every 8 hours
≤ 15 mL/min, on intermittent haemodialysis[c,d]	1 g/0.33 g	0.675 g/0.225 g	3 hours	Every 12 hours

a Calculated using the Cockcroft-Gault formula.
b Dose recommendations are based on PK modelling and simulation.
c Both aztreonam and avibactam are removed by haemodialysis; on haemodialysis days Emblaveo should be administered after the haemodialysis session.
d Aztreonam-avibactam should not be used in patients with CrCl ≤ 15 mL/min unless haemodialysis or another form of renal replacement therapy is initiated.

In patients with renal impairment, close monitoring of estimated creatinine clearance is advised (see sections 4.4 and 5.2).

There are insufficient data to make dosing adjustment recommendations for patients undergoing renal replacement therapy other than haemodialysis (e.g. continuous veno-venous hemofiltration or peritoneal dialysis). Patients receiving continuous renal replacement therapy (CRRT) need a higher dose than patients on haemodialysis. For patients receiving continuous renal replacement therapy, the dose should be adjusted guided by the CRRT clearance (CLCRRT in mL/min).

Hepatic impairment
No dosage adjustment is required in patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Emblaveo in paediatric patients < 18 years of age have not yet been established. No data are available.

Method of administration

Intravenous use.

Emblaveo is administered by intravenous infusion over 3 hours.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins, cephalosporins or carbapenems) (see section 4.4).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Prior to treatment, it should be established if the patient has a history of hypersensitivity reactions to aztreonam or other beta-lactam medicinal products. Emblaveo is contraindicated in patients who have a history of severe hypersensitivity reactions to any beta-lactam agent (see section 4.3). In addition, caution should be exercised when administering aztreonam/avibactam to patients with a history of any other type of hypersensitivity reaction to other beta-lactam medicinal products. In case of severe hypersensitivity reactions, Emblaveo must be discontinued immediately and adequate emergency measures must be initiated.

Renal impairment

In patients with renal impairment, close monitoring is recommended during treatment with Emblaveo. Aztreonam and avibactam are predominantly eliminated via the kidneys, therefore the dose should be reduced according to the degree of renal impairment (see section 4.2). There have been some reports of neurological sequelae with aztreonam (e.g. encephalopathy, confusion, epilepsy, impaired consciousness, movement disorders) in patients with renal impairment and in association with beta-lactam overdose (see section 4.9).

Concomitant treatment with nephrotoxic products (e.g. aminoglycosides) may adversely affect renal function. CrCL should be monitored in patients with changing renal function and the dose of Emblaveo adjusted accordingly (see section 4.2).

Hepatic impairment

Elevated liver enzymes have been observed with Emblaveo (see section 4.8). In patients with hepatic impairment, close monitoring is recommended during treatment with Emblaveo.

Limitations of the clinical data

The use of aztreonam-avibactam to treat patients with cIAI, HAP including VAP and cUTI including pyelonephritis, is based on experience with aztreonam alone, pharmacokinetic-pharmacodynamic analyses of aztreonam-avibactam, and on limited data from the randomised clinical study of 422 adults with cIAI or HAP/VAP.

The use of aztreonam-avibactam to treat infections due to aerobic Gram-negative organism in patients with limited treatment options is based on pharmacokinetic/pharmacodynamic analysis for aztreonam-avibactam and on limited data from the randomised clinical study of 422 adults with cIAI or HAP/VAP (of which 17 patients with carbapenem-resistant [meropenem-resistant] organisms were treated with Emblaveo), and the randomised clinical study of 15 adults (of which 12 patients were treated with Emblaveo) with serious infections due to metallo-β-lactamase (MBL)-producing Gram-negative bacteria (see section 5.1). Clinical discretion may be exercised in scenarios where no alternative treatment options are available

Spectrum of activity of aztreonam-avibactam

Aztreonam has little or no activity against the majority of *Acinetobacter* spp., Gram-positive organisms and anaerobes (see sections 4.2 and 5.1). Additional antibacterial medicinal products should be used when these pathogens are known or suspected to be contributing to the infectious process.

The inhibitory spectrum of avibactam includes many of the enzymes that inactivate aztreonam, including Ambler class A β-lactamases and class C β-lactamases. Avibactam does not inhibit class B enzymes (metallo-β-lactamases) and is not able to inhibit many of the class D enzymes. Aztreonam is generally stable to hydrolysis by class B enzymes (see section 5.1).

Clostridioides difficile-associated diarrhoea

Clostridioides (C.) difficile-associated diarrhoea (CDAD) and pseudomembranous colitis have been reported with aztreonam and may range in severity from mild to life-threatening. This diagnosis should be considered in patients who present with diarrhoea during or subsequent to the administration of Emblaveo (see section 4.8). Discontinuation of therapy with Emblaveo and administration of specific treatment for *C. difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Non-susceptible organisms

The use of Emblaveo may result in overgrowth of non-susceptible organisms, which may require interruption of treatment or other appropriate measures.

Prolongation of prothrombin time/increased activity of oral anticoagulants

Prolongation of prothrombin time has been reported in patients receiving aztreonam (see section 4.8).

Appropriate monitoring should be undertaken when oral anticoagulants are prescribed concomitantly and adjustments in their dose may be necessary to maintain the desired level of anticoagulation.

Interference with serological testing

A positive direct or indirect Coombs test (direct or indirect antiglobulin test) may develop during treatment with aztreonam (see section 4.8).

Sodium

This medicinal product contains approximately 44.6 mg sodium per vial, equivalent to 2.2% of the WHO recommended maximum daily intake (RDI) of 2 g sodium for an adult.

Emblaveo may be diluted with sodium-containing solutions (see section 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro, aztreonam and avibactam are substrates of organic anion transporters OAT1 and OAT3 which might contribute to the active uptake from the blood compartment and, thereby, renal excretion. Probenecid (a potent OAT inhibitor) inhibits uptake of avibactam by 56% to 70% *in vitro* and, therefore, has the potential to alter the elimination of avibactam when co-administered. Since a clinical interaction study of aztreonam-avibactam and probenecid has not been conducted, co-dosing with probenecid is not recommended.

Aztreonam is not metabolized by cytochrome P450 enzymes. *In vitro*, avibactam showed no significant inhibition of cytochrome P450 enzymes and no cytochrome P450 induction in the clinically relevant exposure range. Avibactam does not inhibit the major renal or hepatic transporters *in vitro* in the clinically relevant exposure range; therefore, the drug-drug interaction potential via these mechanisms is considered low.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of aztreonam or avibactam in pregnant women. Animal studies with aztreonam do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Animal studies with avibactam have shown reproductive toxicity without evidence of teratogenic effects (see section 5.3).

Aztreonam/avibactam should only be used during pregnancy when clearly indicated and only if the benefit for the mother outweighs the risk for the child.

Breast-feeding

Aztreonam is excreted in human milk in concentrations that are less than 1% of those in simultaneously obtained maternal serum. It is unknown whether avibactam is excreted in human milk. A risk to the breastfed child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from aztreonam/avibactam therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effect of aztreonam/avibactam on fertility are available. Animal studies with aztreonam or avibactam do not indicate harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Undesirable effects may occur (e.g. dizziness) which may have a minor influence on the ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse drug reactions (ADRs) in patients treated with aztreonam/avibactam (ATM-AVI) were anaemia (6.9%), diarrhoea (6.2%), alanine aminotransferase (ALT) increased (6.2%), and aspartate aminotransferase (AST) increased (5.2%).

Tabulated list of adverse reactions

The following ADRs have been reported with aztreonam alone and/or identified during Phase 2 and Phase 3 clinical trials with Emblaveo (N = 305).

The ADRs listed in the table below are presented by System Organ Class (SOC) and frequency categories, defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), or frequency not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. Frequency of adverse drug reactions presented by system organ class

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from the available data)
Infections and infestations			Vulvovaginal candidiasis Vaginal infection	Superinfection
Blood and lymphatic system disorders	Anaemia Thrombocytosis Thrombocytopenia	Eosinophil count increased Leukocytosis	Pancytopenia Neutropenia Prothrombin time prolonged Activated partial thromboplastin time prolonged Coombs test positive	

Table 3. Frequency of adverse drug reactions presented by system organ class

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from the available data)
			Coombs direct test positive Coombs indirect test positive	
Immune system disorders		Anaphylactic reaction Drug hypersensitivity		
Psychiatric disorders	Confusional state	Insomnia		
Nervous system disorders	Dizziness	Encephalopathy Headache Hypoaesthesia oral Dysgeusia	Seizure Paraesthesia	
Eye disorders			Diplopia	
Ear and labyrinth disorders			Vertigo Tinnitus	
Cardiac disorders		Extrasystoles		
Vascular disorders		Haemorrhage Hypotension Flushing		
Respiratory, thoracic and mediastinal disorders		Bronchospasm	Dyspnoea Wheezing Sneezing Nasal congestion	
Gastrointestinal disorders	Diarrhoea Nausea Vomiting	*Clostridium difficile* colitis Gastrointestinal haemorrhage	Pseudomembranous colitis Breath odour	

Table 3. Frequency of adverse drug reactions presented by system organ class

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from the available data)
	Abdominal pain	Mouth ulceration		
Hepatobiliary disorders	Aspartate aminotransferase increased Alanine aminotransferase increased Transaminases increased	Gamma-glutamyltransferase increased Blood alkaline phosphatase increased	Hepatitis Jaundice	
Skin and subcutaneous tissue disorders	Rash	Angioedema Toxic epidermal necrolysis Dermatitis exfoliative Erythema multiforme Purpura Urticaria Petechiae Pruritus Hyperhidrosis		
Musculoskeletal and connective tissue disorders			Myalgia	
Renal and urinary disorders		Blood creatinine increased		
Reproductive system and breast disorders			Breast tenderness	
General disorders and administration site conditions	Phlebitis Thrombophlebitis	Chest discomfort Asthenia	Malaise	

Table 3. Frequency of adverse drug reactions presented by system organ class

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from the available data)
	Infusion site extravasation Injection site pain Pyrexia			

Kounis syndrome

Acute coronary syndrome associated with an allergic reaction (Kounis syndrome) has been reported with other beta-lactam antibiotics.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Website: https://e-meso.pom.go.id/ADR

PT Pfizer Indonesia
Email: IDN.AEReporting@pfizer.com
Website: www.pfizersafetyreporting.com

4.9 Overdose

Overdose can cause encephalopathy, confusion, epilepsy, impaired consciousness, and movement disorders particularly in patients with renal impairment (see section 4.4).

If necessary, aztreonam and avibactam may be partially removed by haemodialysis.

During a 4-hour haemodialysis session, 38% of the aztreonam dose and 55% of the avibactam dose is removed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, other beta-lactam antibacterials, monobactams, ATC code: J01DF51

Mechanism of action

Aztreonam inhibits bacterial peptidoglycan cell wall synthesis following binding to penicillin-binding proteins (PBPs), which leads to bacterial cell lysis and death. Aztreonam is generally stable to hydrolysis by class B enzymes (metallo-β-lactamases).

Avibactam is a non β-lactam, β-lactamase inhibitor that acts by forming a covalent adduct with the enzyme that is stable to hydrolysis. Avibactam inhibits both Ambler class A and class C β-lactamases and some class D enzymes, including extended-spectrum β-lactamases (ESBLs), *Klebsiella pneumoniae* carbapenemase (KPC) and OXA-48 carbapenemases, and AmpC enzymes. Avibactam does not inhibit class B enzymes and is not able to inhibit many class D enzymes.

Resistance

Bacterial resistance mechanisms that could potentially affect aztreonam-avibactam include β-lactamase enzymes refractory to inhibition by avibactam and able to hydrolyse aztreonam, mutant or acquired PBPs, decreased outer membrane permeability to either compound, and active efflux of either compound.

Antibacterial activity in combination with other antibacterial agents

No synergy or antagonism was demonstrated in *in vitro* drug combination studies with aztreonam-avibactam and amikacin, ciprofloxacin, colistin, daptomycin, gentamicin, levofloxacin, linezolid, metronidazole, tigecycline, tobramycin, and vancomycin.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretative criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for aztreonam/avibactam.

Pharmacokinetic/pharmacodynamic relationship

The antimicrobial activity of aztreonam against specific pathogens has been shown to best correlate with the percent time of free drug concentration above the aztreonam-avibactam minimum inhibitory concentration over the dose interval (%*f*T > MIC of aztreonam-avibactam). For avibactam, the pharmacokinetic/pharmacodynamic (PK-PD) index is the percent time of the free drug concentration above a threshold concentration over the dose interval (%*f*T > C_T).

Antibacterial activity against specific pathogens

In vitro studies suggest that the following pathogens would be susceptible to aztreonam-avibactam in the absence of acquired mechanisms of resistance:

Aerobic Gram-negative organisms

- *Citrobacter freundii* complex

- *Citrobacter koseri*
- *Escherichia coli*
- *Enterobacter cloacae* complex
- *Klebsiella aerogenes*
- *Klebsiella pneumoniae*
- *Klebsiella oxytoca*
- *Morganella morganii*
- *Proteus mirabilis*
- *Proteus vulgaris*
- *Providencia rettgeri*
- *Providencia stuartii*
- *Raoultella ornithinolytica*
- *Serratia* spp.
- *Serratia marcescens*
- *Stenotrophomonas maltophilia*

In vitro studies indicate that the following species are not susceptible to aztreonam-avibactam:

- *Acinetobacter* spp.
- Aerobic Gram-positive organisms
- Anaerobic organisms

Clinical efficacy and safety

Complicated Intra-abdominal Infection (cIAI) or Nosocomial Pneumonia (NP) including Hospital-acquired Pneumonia (HAP) and Ventilator-associated Pneumonia (VAP)

C3601002 was a Phase 3 prospective, randomised, multicentre, open-label, central assessor-blinded, parallel group, comparative study to determine the efficacy, safety, and tolerability of aztreonam-avibactam ± metronidazole (ATM-AVI ± MTZ) versus meropenem ± colistin (MER ± COL) in the treatment of hospitalized adults with cIAI or HAP/VAP. Participants were randomised in a 2:1 ratio to the ATM-AVI ± MTZ treatment arm or the MER ± COL treatment arm. MTZ therapy was administered to participants in the ATM-AVI treatment group with cIAI only. COL was an optional adjunctive therapy administered in the MER treatment arm.

A total of 422 participants were randomised at 81 centres in 20 countries; 282 were randomised to ATM-AVI ± MTZ and 140 were randomised to MER ± COL. Ten participants (7, ATM-AVI ± MTZ; 3, MER ± COL) were randomised but not treated. Overall, the median age was 57 years, and most participants were male (68%) and white (54%), although Asian participants comprised approximately 42% of the study population. The proportion of participants entering the study with cIAI was approximately 74%. Of those entering the study with nosocomial pneumonia (~ 26%), ~ 46% had VAP and ~ 52% had mechanical ventilation at baseline. Approximately 22% of cIAI participants and ~ 88% of HAP/VAP participants had an APACHE II score > 10 at baseline. The proportion of participants with previous treatment failure was ~ 11% in cIAI participants and ~ 64% in HAP/VAP participants.

The primary efficacy endpoint was the clinical response at the Test of Cure (TOC) visit as assessed by the Clinical Adjudication Committee. The cure rate in the Intent-To-Treat (ITT) analysis set was 68.4% (95% CI: 62.8, 73.7) for the ATM-AVI ± MTZ treatment arm and 65.7% (95% CI: 57.6, 73.2) for the MER ± COL treatment arm. The cure rate in the Clinically Evaluable (CE) analysis set was 77.0% (95% CI: 71.0, 82.3) for the ATM-AVI ± MTZ treatment arm and 74.3% (95% CI: 65.3, 81.9) for the MER ± COL treatment arm. The difference in cure rate between the treatment arms is 2.7% for both the ITT and CE analysis sets.

Table 4. Adjudicated Clinical Response at the TOC Visit–- ITT Analysis Set

	Number (%) of Participants, 95% CI		Difference[a] (95% CI[b])
Response	**ATM-AVI ± MTZ (N = 282)**	**MER ± COL (N = 140)**	
Cure	193 (68.4) (62.8, 73.7)	92 (65.7) (57.6, 73.2)	2.7 (-6.6, 12.4)
Failure	67 (23.8)	40 (28.6)	
Indeterminate	22 (7.8)	8 (5.7)	

a. Difference = Difference in clinical cure rates (ATM-AVI ± MTZ treatment arm minus MER ± COL treatment arm).
b. The confidence interval (CI) for the difference is calculated using the unstratified Miettinen and Nurminen method.

Table 5. Adjudicated Clinical Response at the TOC Visit - CE Analysis Set

	Number (%) of Participants, 95% CI		Difference[a] (95% CI[b])
Response	**ATM-AVI ± MTZ (N = 213)**	**MER ± COL (N = 105)**	
Cure	164 (77.0) (71.0, 82.3)	78 (74.3) (65.3, 81.9)	2.7 (-7.0, 13.2)
Failure	49 (23.0)	27 (25.7)	

a. Difference = Difference in clinical cure rates (ATM-AVI ± MTZ treatment group minus MER ± COL treatment group).
b. The confidence interval (CI) for the difference is calculated using the unstratified Miettinen and Nurminen method.

For the subgroup of participants with cIAI infection type, the cure rate in the ITT analysis set was 76.4% for the ATM-AVI ± MTZ treatment arm and 74.0% for the MER ± COL treatment arm. In the CE analysis set, the cure rate was 85.1% for the ATM-AVI ± MTZ treatment arm and 79.5% for the MER ± COL treatment arm.

For the subgroup of participants with HAP/VAP infection type, the cure rate in the ITT analysis set was 45.9% for the ATM-AVI ± MTZ treatment arm and 41.7% for the MER ± COL treatment arm. In the CE analysis set, the cure rate was 46.7% for the ATM-AVI ± MTZ treatment arm and 54.5% for the MER ± COL treatment arm.

Table 6. Adjudicated Clinical Response at the TOC Visit by Type of Infection - ITT Analysis Set

		Number (%) of Participants, 95% CI		Difference (95% CI)
Type of Infectious Disease	**Response**	**ATM-AVI ± MTZ (N = 282)**	**MER ± COL (N = 140)**	
cIAI	n	208	104	
	Cure	159 (76.4) (70.3, 81.8)	77 (74.0) (65.0, 81.7)	2.4 (-7.4, 13.0)
	Failure	34 (16.3)	23 (22.1)	
	Indeterminate	15 (7.2)	4 (3.8)	
HAP/VAP	n	74	36	
	Cure	34 (45.9)	15 (41.7)	4.3 (-15.5, 23.1)

Table 6. Adjudicated Clinical Response at the TOC Visit by Type of Infection - ITT Analysis Set

		Number (%) of Participants, 95% CI		Difference (95% CI)
Type of Infectious Disease	**Response**	**ATM-AVI ± MTZ (N = 282)**	**MER ± COL (N = 140)**	
		(34.9, 57.3)	(26.7, 57.9)	
	Failure	33 (44.6)	17 (47.2)	
	Indeterminate	7 (9.5)	4 (11.1)	

Table 7. Adjudicated Clinical Response at the TOC Visit by Type of Infection – CE Analysis Set

		Number (%) of Participants, 95% CI		Difference (95% CI)
Type of Infectious Disease	**Response**	**ATM-AVI ± MTZ (N = 213)**	**MER ± COL (N = 105)**	
cIAI	n	168	83	
	Cure	143 (85.1) (79.2, 89.9)	66 (79.5) (69.9, 87.1)	5.6 (-4.0, 16.6)
	Failure	25 (14.9)	17 (20.5)	
HAP/VAP	n	45	22	
	Cure	21 (46.7) (32.7, 61.1)	12 (54.5) (34.3, 73.7)	-7.9 (-31.9, 17.3)
	Failure	24 (53.3)	10 (45.5)	

All-cause 28-day mortality rates in cIAI participants were 4/208 (1.9%) and 3/104 (2.9%) for ATM-AVI ± MTZ and MER ± COL treatment arms, respectively; mortality rates in HAP/VAP participants were 8/74 (10.8%) and 7/36 (19.4%) for ATM-AVI ± MTZ and MER ± COL treatment arms, respectively.

In the micro-ITT analysis set, the clinical cure rates at the TOC visit were 72.9% (95% CI: 66.0, 79.0) in the ATM-AVI ± MTZ treatment group and 72.3% (95% CI: 62.7, 80.6) in the MER ± COL treatment group. The treatment difference is 0.5% (95% CI: -10.2, 12.1).

In the ME analysis set, the clinical cure rates at the TOC visit were 78.5% in the ATM-AVI ± MTZ treatment group and 75.9% in the MER ± COL treatment group. The treatment difference is 2.6% (95% CI: -8.4, 14.7).

Serious Infections due to Multi-Drug Resistant Gram-Negative Bacteria Producing Metallo-β-Lactamase (MBL)

C3601009 was a prospective, randomised, multicentre, open label, parallel group, comparative study to determine the efficacy, safety, and tolerability of ATM-AVI versus best available therapy (BAT) in the treatment of hospitalized adults with complicated intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP), complicated urinary tract infection (cUTI), or bloodstream infections (BSI) due to MBL-producing Gram-negative bacteria. Participants with cIAI assigned to ATM-AVI treatment were to receive Metronidazole (MTZ) co-

therapy. BAT selection for treatment of the participants' primary infection was based upon site practice and local epidemiology.

A total of 15 patients were randomised at 12 centres in 9 countries. Twelve were randomised to ATM-AVI, and 3 were randomised to BAT. One participant (in the BAT arm) was randomised but withdrew from the study before receiving any study treatment. All randomised participants were included in the micro-ITT analysis set. There were 2 participants with cIAI, 4 with HAP/VAP, 4 with cUTI, and 5 with BSI. In total, 10/15 participants had previous treatment failure: 8/12 in the ATM-AVI group and 2/3 in the BAT group.

The primary efficacy endpoint was the clinical response at the TOC visit as assessed by the Clinical Adjudication Committee. In the micro-ITT analysis set, the number of participants with clinical cure at TOC was 5/12 in the ATM-AVI treatment group and 0/3 in the BAT treatment group.

In the ME analysis set, the number of participants with clinical cure at the TOC visit was 5/9 in the ATM-AVI treatment group and 0/1 in the BAT treatment group.

In the ITT analysis set, the all-cause 28-day mortality rate was: 1/12 participants in the ATM-AVI treatment group and 1/3 in the BAT treatment group.

5.2 Pharmacokinetic properties

General introduction

The aztreonam and avibactam geometric mean (CV%) steady-state maximum plasma concentration ($C_{max,ss}$) and area under the concentration-time curve over 24 hours ($AUC_{24,ss}$) in Phase 3 patients with normal renal function (n = 127) after multiple 3-hour infusions of 1.5 g aztreonam/0.5 g avibactam administered every 6 hours were 54.2 mg/L (40.8) and 11.0 mg/L (44.9), respectively, and 833 mg*h/L (45.8) and 161 mg*h/L (47.5), respectively. Pharmacokinetic parameters of aztreonam and avibactam following single- and multiple-dose administration of aztreonam-avibactam in combination were similar to those determined when aztreonam or avibactam were administered alone.

Distribution

The human protein binding of avibactam and aztreonam is concentration independent and low, approximately 8% and 38%, respectively. The steady-state volumes of distribution of aztreonam and avibactam were comparable, about 20 L and 24 L, respectively, in patients with complicated intra-abdominal infections following multiple doses of 1.5 g/0.5 g aztreonam-avibactam every 6 hours infused over 3 hours.

Aztreonam crosses the placenta and is excreted in the breast milk.

Penetration of aztreonam into pulmonary epithelial lining fluid (ELF) has not been studied clinically; a mean ratio of concentration in bronchial secretions to concentration in serum of 21% to 60% has been reported in intubated patients at 2 to 8 hours after a single aztreonam 2 g intravenous dose.

Avibactam penetrates into human bronchial ELF with concentrations around 30% that of plasma, and a similar concentration time profile between ELF and plasma. Avibactam penetrates into the subcutaneous tissue at the site of skin infections, with tissue concentrations approximately equal to free drug concentrations in plasma.

Penetration of aztreonam into the intact blood-brain barrier is limited, resulting in low levels of aztreonam in the cerebrospinal fluid (CSF) in the absence of inflammation; however, concentrations in CSF are increased when the meninges are inflamed.

Biotransformation

Aztreonam is not extensively metabolised. The principal metabolite is inactive and is formed by opening of the beta-lactam ring due to hydrolysis. Recovery data indicate that about 10% of the dose is excreted as this metabolite. No metabolism of avibactam was observed in human liver preparations (microsomes and hepatocytes). Unchanged avibactam was the major drug-related component in human plasma and urine following dosing with [^{14}C]-avibactam.

Elimination

The terminal half-lives ($t_{½}$) of both aztreonam and avibactam are approximately 2 to 3 hours after intravenous administration.

Aztreonam is excreted in the urine by active tubular secretion and glomerular filtration. Approximately 75% to 80% of an intravenous or intramuscular dose was recovered in the urine. The components of urinary radioactivity were unchanged aztreonam (approximately 65% recovered within 8 hours), the inactive β-lactam ring hydrolysis product of aztreonam (approximately 7%) and unknown metabolites (approximately 3%). Approximately 12% of aztreonam is excreted into faeces.

Avibactam is excreted unchanged into the urine with a renal clearance of approximately 158 mL/min, suggesting active tubular secretion in addition to glomerular filtration. The percentage unchanged drug excreted in urine was independent of administered dose and accounted for 83.8% to 100% of the avibactam dose at steady-state. Less than 0.25% of avibactam is excreted into faeces.

Linearity/non-linearity

The pharmacokinetics of both aztreonam and avibactam are approximately linear across the dose range studied (1500 mg to 2000 mg aztreonam; 375 mg to 600 mg avibactam). No appreciable accumulation of aztreonam or avibactam was observed following multiple intravenous infusions of 1500 mg/500 mg of aztreonam-avibactam administered every 6 hours for up to 11 days in healthy adults with normal renal function.

Specific populations

Renal impairment
Elimination of aztreonam and avibactam is decreased in patients with renal impairment. The average increases in avibactam AUC are 2.6-fold, 3.8-fold, 7-fold and 19.5-fold in subjects with mild (here defined as CrCL 50 to 79 mL/min), moderate (here defined as CrCL 30 to 49 mL/min), severe renal impairment (CrCL < 30 mL/min, not requiring dialysis) and end-stage renal disease, respectively, compared to subjects with normal renal function (here defined as CrCL > 80 mL/min). Dose adjustment is needed in patients with estimated CrCL ≤ 50 mL/min, see section 4.2.

Hepatic impairment
The pharmacokinetics of avibactam in patients with any degree of hepatic impairment has not been studied. As aztreonam and avibactam do not appear to undergo significant hepatic metabolism, the systemic clearance of either active substance is not expected to be significantly altered by hepatic impairment.

Elderly patients (≥ 65 years)
Mean elimination half-life of both aztreonam and avibactam is increased, and plasma clearance decreased in the elderly, consistent with age-related reduction in renal clearance of aztreonam and avibactam.

Paediatric population
The pharmacokinetics of aztreonam-avibactam have not been evaluated in paediatric patients.

Gender, race and body weight
The pharmacokinetics of aztreonam-avibactam is not significantly affected by gender or race. In a population pharmacokinetic analysis of aztreonam-avibactam, no clinically relevant differences in exposures were observed in adult patients with body mass index (BMI) ≥ 30 kg/m^2 compared to adult patients with BMI < 30 kg/m^2.

5.3 Preclinical safety data

Aztreonam

Aztreonam non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, or toxicity to reproduction. Carcinogenicity studies have not been conducted with aztreonam by the intravenous route.

Avibactam

Avibactam non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity. Carcinogenicity studies have not been conducted with avibactam.

Aztreonam and avibactam combination toxicity

A 28-day combination toxicology study in rats indicated that avibactam did not alter the safety profile of aztreonam when given in combination.

Reproduction toxicity

Animal studies with aztreonam do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or postnatal development.

In pregnant rabbits administered avibactam at 300 and 1 000 mg/kg/day, there was a dose-related lower mean foetal weight and delayed ossification, potentially related to maternal toxicity. Plasma exposure levels at maternal and foetal NOAEL (100 mg/kg/day) indicate moderate to low margins of safety.

In the rat, no adverse effects were observed on embryofoetal development or fertility. Following administration of avibactam throughout pregnancy and lactation in the rat, there was no effect on pup survival, growth or development, however there was an increase in incidence of dilation of the renal pelvis and ureters in less than 10% of the rat pups at maternal exposures greater than or equal to approximately 2.8 times human therapeutic exposures.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arginine

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

After reconstitution

The reconstituted vial should be used within 30 minutes for preparation of the infusion bag or stock solution that delivers the appropriate dose of ATM-AVI for intravenous infusion.

After dilution

Infusion bags
If the intravenous solution is prepared with sodium chloride (0.9%) solution for injection or Lactated Ringer's solution, the chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C – 8 °C followed by up to 12 hours at up to 30 °C.

If the intravenous solution is prepared with glucose (5%) solution for injection, the chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C – 8 °C followed by up to 6 hours up to 30 °C.

From a microbiological point of view, the medicinal product should be used immediately, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and must not exceed those stated above.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Store in the original package in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

30 mL glass vial (Type I) closed with a rubber (chlorobutyl) stopper and aluminium seal with flip-off cap.

The medicinal product is supplied in packs of 10 vials.

6.6 Special precautions for disposal and other handling

The powder must be reconstituted with sterile water for injections and the resulting concentrate must then be immediately diluted prior to use. The reconstituted solution is a clear, colourless to yellow solution and is free of visible particles.

Standard aseptic techniques should be used for solution preparation and administration. Doses must be prepared in an appropriately sized infusion bag.

Parenteral medicinal products should be inspected visually for particulate matter prior to administration.

Each vial is for single use only.

The total time interval between starting reconstitution and completing preparation of the intravenous infusion should not exceed 30 minutes.

Emblaveo (aztreonam/avibactam) is a combination product; each vial contains 1.5 g of aztreonam and 0.5 g of avibactam in a fixed 3:1 ratio.

Instructions for preparing adult doses in an INFUSION BAG:

NOTE: The following procedure describes the steps to prepare an infusion solution with a final concentration of 1.5-40 mg/mL of **aztreonam** and 0.50-13.3 mg/mL of **avibactam**. All calculations should be completed prior to initiating these steps.

1. Prepare the **reconstituted solution** (**131.2 mg/mL** of aztreonam and **43.7 mg/mL** of avibactam):
   a) Insert the needle through the vial closure and inject 10 mL of sterile water for injections.
   b) Withdraw the needle and shake the vial gently to give a clear, colourless to yellow solution free of visible particles.
2. Prepare the **final solution** for infusion (final concentration must be **1.5-40 mg/mL** of aztreonam and **0.50-13.3 mg/mL** of avibactam):
   Infusion bag: Further dilute the reconstituted solution by transferring an appropriately calculated volume of the reconstituted solution to an infusion bag containing any of the following: sodium chloride (0.9%) solution for injection, glucose (5%) solution for injection, or Lactated Ringer's solution.

Refer to Table 8 below.

Table 8. Preparation of Emblaveo for adult doses in an INFUSION BAG

Total dose (aztreonam/avibactam)	**Volume to withdraw from reconstituted vial(s)**	**Final volume after dilution in infusion bag[a,b]**
2000 mg/667 mg	15.2 mL	50 mL to 250 mL
1500 mg/500 mg	11.4 mL	50 mL to 250 mL
1350 mg/450 mg	10.3 mL	50 mL to 250 mL
750 mg/250 mg	5.7 mL	50 mL to 250 mL
675 mg/225 mg	5.1 mL	50 mL to 250 mL
All other doses	Volume (mL) calculated based on dose required: **Dose (mg aztreonam) ÷ 131.2 mg/mL aztreonam** **Or** **Dose (mg avibactam) ÷ 43.7 mg/mL avibactam**	Volume (mL) will vary based on infusion bag size availability and preferred final concentration (Must be 1.5-40 mg/mL of aztreonam and 0.50-13.3 mg/mL of avibactam)

a Dilute to final aztreonam concentration of 1.5-40 mg/mL (final avibactam concentration of 0.50-13.3 mg/mL) for in-use stability up to 24 hours at 2 °C – 8 °C, followed by up to 12 hours up to 30 °C for infusion bags containing sodium chloride (0.9%) solution for injection or Lactated Ringer's solution.

b Dilute to final aztreonam concentration of 1.5-40 mg/mL (final avibactam concentration of 0.50-13.3 mg/mL) for in-use stability up to 24 hours at 2 °C – 8 °C, followed by up to 6 hours up to 30 °C for infusion bags containing glucose (5%) solution for injection.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
Hospira Australia Pty Ltd
1-39 Lexia Place, Mulgrave
Victoria 3170
Australia

Imported by:
PT. Pfizer Indonesia,
Jakarta, Indonesia

8. MARKETING AUTHORISATION NUMBER(S)

EMBLAVEO® 1,5 g/0,5 g powder for concentrate for solution for infusion; Box, 10 vial @ 2,0 g; Reg. No.: DKIxxxx

HARUS DENGAN RESEP DOKTER

9. DATE OF REVISION OF THE TEXT

02/2026

Nama Generik: avibactam, aztreonam
Nama Dagang: EMBLAVEO
Tanggal Berlaku SPC UE: 22 April 2024
Menggantikan: Tidak Ada
Disetujui oleh BPOM:

Informasi Produk untuk Pasien

Emblaveo® 1,5 g/0,5 g serbuk untuk larutan konsentrat untuk infus aztreonam/avibactam

Baca seluruh isi leaflet ini dengan teliti sebelum Anda diberi obat ini karena berisi informasi penting untuk Anda.
- Simpan leaflet ini. Anda mungkin perlu membacanya kembali.
- Jika ada pertanyaan lebih lanjut, tanyakan kepada dokter atau perawat Anda.
- Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter atau perawat Anda. Termasuk setiap kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Lihat bagian 13.

Isi leaflet ini

1. Nama obat
EMBLAVEO®

2. Bentuk sediaan
Serbuk untuk larutan konsentrat untuk infus

3. Deskripsi obat
Emblaveo adalah serbuk putih hingga agak kekuningan untuk larutan konsentrat untuk infus dalam vial kaca dengan sumbat karet dan segel aluminium yang menggunakan tutup flip-off. Obat ini tersedia dalam kemasan berisi 10 vial.

4. Apa kandungan obat ini?

Zat aktif obat ini adalah aztreonam dan avibactam. Setiap vial berisi 1,5 g aztreonam dan avibactam natrium yang setara dengan 0,5 g avibactam (lihat bagian 9: Emblaveo mengandung natrium).
Bahan lainnya adalah arginin.

5. Kekuatan obat

1,5 g aztreonam/0,5 g avibactam

6. Apa kegunaan obat ini?

Tentang Emblaveo

Emblaveo merupakan obat antibiotik yang mengandung dua bahan aktif yaitu aztreonam dan avibactam.

- Aztreonam termasuk dalam kelompok antibiotik yang disebut “monobactam”. Obat ini dapat membunuh beberapa jenis bakteri tertentu (yang disebut bakteri Gram-negatif).
- Avibactam adalah “penghambat beta-laktamase” yang membantu aztreonam membunuh sebagian bakteri yang tidak dapat dibunuh oleh aztreonam jika diberikan sendirian.

Kegunaan Emblaveo

Emblaveo merupakan antibiotik *reserve* yang diindikasikan untuk mengobati infeksi berikut pada pasien dewasa:

- Infeksi bakteri berat di dalam perut (lambung dan usus) yang sudah menyebar ke rongga perut.
- Infeksi paru-paru (pneumonia) yang terjadi saat di rumah sakit, termasuk pada saat menggunakan ventilator (alat bantu napas).
- Infeksi saluran kemih berat, termasuk infeksi pada ginjal (pielonefritis).

Pemberian antibiotik hanya dapat dilakukan setelah berkonsultasi dengan dokter yang berpengalaman dalam penanganan penyakit menular.

7. Berapa banyak dan seberapa sering Anda seharusnya menggunakan obat ini? Apa yang harus dilakukan jika ada dosis yang terlewat?

Emblaveo akan diberikan kepada Anda oleh dokter atau perawat.

Berapa banyak dosis yang digunakan

Emblaveo diberikan sebagai infus langsung ke pembuluh vena (‘infus intravena’). Dosis normal adalah satu vial (mengandung 1,5 g aztreonam dan 0,5 g avibactam) setiap 6 jam. Dosis pertama diberikan lebih tinggi (2 g aztreonam dan 0,67 g avibactam). Infus akan berlangsung selama 3 jam. Rangkaian pengobatan biasanya membutuhkan 5 hingga 14 hari, bergantung pada jenis infeksi yang Anda derita dan respons Anda terhadap pengobatan.

<u>Pasien dengan masalah ginjal</u>

Jika Anda mengalami masalah ginjal, dokter dapat menurunkan dosis Anda dan meningkatkan interval waktu di antara dosis. Ini karena Emblaveo dikeluarkan dari tubuh Anda oleh ginjal. Jika fungsi ginjal Anda terganggu, kadar Emblaveo dalam darah Anda bisa saja meningkat.

Jika Anda melewatkan satu dosis Emblaveo

Jika Anda melewatkan dosis, segera beri tahu dokter atau perawat Anda.

Jika Anda memiliki pertanyaan lebih lanjut seputar penggunaan obat ini, tanyakan kepada dokter atau perawat Anda.

8. Kapan seharusnya Anda tidak menggunakan obat ini?

Anda tidak boleh diberi Emblaveo jika:

- Anda alergi terhadap aztreonam, avibactam, atau bahan-bahan lain dalam obat ini (tercantum dalam bagian 4).
- Anda pernah mengalami reaksi alergi berat (pembengkakan wajah, tangan, kaki, bibir, lidah, atau tenggorokan; atau kesulitan menelan atau bernapas; atau reaksi kulit berat) terhadap antibiotik yang termasuk dalam golongan penisilin, sefalosporin, atau karbapenem.

9. Apa yang harus dipertimbangkan saat menggunakan obat ini?

Konsultasikan dengan dokter atau perawat Anda sebelum menggunakan Emblaveo jika:

- Anda pernah mengalami reaksi alergi (bahkan jika hanya ruam kulit) terhadap antibiotik lain. Tanda-tanda reaksi alergi antara lain gatal-gatal, ruam kulit, atau kesulitan bernapas.
- Anda memiliki gangguan ginjal atau Anda sedang meminum obat-obatan yang dapat memengaruhi fungsi ginjal, seperti antibiotik yang disebut sebagai aminoglikosida (streptomisin, neomisin, gentamisin). Jika fungsi ginjal Anda terganggu, dokter dapat memberikan dosis Emblaveo yang lebih rendah kepada Anda dan Anda dapat melakukan tes darah secara teratur selama pengobatan untuk mengetahui fungsi ginjal Anda. Selain itu, Anda mungkin berisiko lebih tinggi mengalami efek samping serius yang memengaruhi sistem saraf seperti ensefalopati (gangguan otak yang dapat disebabkan oleh penyakit, cedera, obat-obatan, atau bahan kimia) akibat peningkatan kadar Emblaveo dalam darah kecuali jika dosisnya diturunkan. Gejala ensefalopati antara lain kebingungan, kejang, dan perubahan fungsi mental (lihat bagian 14, 15).
- Anda menderita gangguan hati. Dokter Anda dapat melakukan tes darah secara teratur selama pengobatan untuk memeriksa fungsi hati Anda karena peningkatan enzim hati telah teramati selama penggunaan Emblaveo
- Anda sedang meminum obat yang dikenal sebagai antikoagulan (obat yang mencegah membekunya darah). Emblaveo dapat memengaruhi pembekuan darah. Dokter Anda akan memantau kadar dalam darah Anda untuk memastikan perlunya mengubah dosis antikoagulan selama pengobatan dengan Emblaveo.

Konsultasikan dengan dokter Anda jika setelah memulai pengobatan dengan Emblaveo, Anda mengalami:

- diare yang parah, berkepanjangan, atau berdarah. Ini mungkin merupakan tanda adanya peradangan pada usus besar. Pengobatan dengan Emblaveo mungkin perlu dihentikan untuk memulai pengobatan spesifik untuk diare (lihat bagian 13).
- infeksi lain. Terdapat kemungkinan kecil bahwa Anda dapat terkena infeksi yang berbeda yang disebabkan oleh bakteri lain selama atau setelah pengobatan dengan Emblaveo.

<u>Tes lab</u>

Beri tahu dokter Anda bahwa Anda menggunakan Emblaveo jika Anda akan menjalani suatu tes. Ini karena Anda mungkin mendapatkan hasil yang tidak normal untuk tes yang disebut tes Coombs langsung atau tidak langsung. Tes ini digunakan untuk menemukan antibodi yang melawan sel darah merah Anda.

Pasien anak-anak dan remaja

Emblaveo tidak boleh digunakan pada pasien pediatrik atau remaja berusia di bawah 18 tahun. Ini karena keamanan penggunaan obat ini dalam kelompok usia ini tidak diketahui.

Emblaveo mengandung Natrium

Obat ini mengandung sekitar 44,6 mg natrium (unsur utama garam masak/meja) dalam setiap vial. Ini setara dengan 2,2% dari asupan harian maksimum yang disarankan untuk natrium pada orang dewasa.

10. Apa saja obat lain atau makanan yang harus dihindari selama menggunakan obat ini?

Beri tahu dokter Anda jika Anda sedang menggunakan, baru-baru ini menggunakan, atau mungkin menggunakan obat-obatan lain.

Beri tahu dokter Anda sebelum menggunakan Emblaveo jika Anda sedang meminum obat-obatan berikut ini:
- obat untuk gout yang disebut probenesid

11. Apakah obat ini aman bagi ibu hamil dan menyusui?

Kehamilan
Jika Anda hamil atau sedang menyusui, menduga bahwa diri Anda sedang hamil, atau berencana untuk hamil, mintalah saran dokter Anda sebelum menggunakan obat ini.

Obat ini dapat membahayakan janin Anda. Obat ini hanya boleh digunakan selama kehamilan jika dokter Anda menilai bahwa penggunaannya diperlukan dan hanya jika manfaatnya bagi sang ibu melebihi risikonya bagi janin.

Menyusui
Obat ini dapat disalurkan melalui ASI. Jika Anda sedang menyusui, keputusan harus diambil apakah Anda harus menghentikan pemberian ASI atau tidak menggunakan terapi dengan obat ini, dengan mempertimbangkan manfaat menyusui bagi anak dan manfaat pengobatan bagi sang ibu.

12. Apakah pasien diperbolehkan mengemudi dan mengoperasikan mesin selama menggunakan obat ini?

Emblaveo dapat menyebabkan efek samping, seperti pusing, yang dapat memengaruhi kemampuan Anda untuk mengemudi dan mengoperasikan mesin. Jangan mengemudi atau mengoperasikan peralatan atau mesin jika Anda mengalami efek samping, seperti pusing (lihat bagian 13).

13. Potensi efek yang tidak diinginkan dari penggunaan obat ini

Seperti obat-obatan lainnya, obat ini dapat menimbulkan efek samping, sekalipun tidak semua orang mengalaminya.

Efek samping serius
Segera beri tahu dokter Anda jika Anda mengamati adanya efek samping serius berikut - Anda mungkin membutuhkan perawatan medis yang urgen:
- Pembengkakan wajah, bibir, mata, telinga, dan/atau tenggorokan, biduran dan kesulitan menelan atau bernapas. Ini mungkin merupakan tanda-tanda reaksi alergi atau angioedema yang mungkin mengancam nyawa.
- Diare yang parah, berkepanjangan, atau berdarah (yang dapat dikaitkan dengan nyeri perut atau demam). Kondisi ini dapat terjadi selama atau setelah pengobatan dengan antibiotik dan dapat menjadi tanda adanya peradangan usus serius. Jika ini terjadi jangan mengonsumsi obat yang menghentikan atau memperlambat gerakan usus.
- Timbulnya ruam parah atau lecet atau terkelupasnya kulit secara mendadak, yang kemungkinan disertai demam tinggi atau nyeri persendian (ini mungkin merupakan tanda-tanda kondisi medis yang lebih serius seperti nekrolisis epidermal beracun, dermatitis eksfoliatif, eritema multiformis).

Efek samping serius ini bersifat tidak umum (dapat dialami hingga 1 di antara 100 orang).

Efek samping lainnya
Beri tahu dokter atau perawat Anda jika teramati adanya efek samping berikut ini:

Umum: (dapat dialami hingga 1 di antara 10 orang)
- Penurunan jumlah sel darah merah – tampak dalam tes darah

- Perubahan jumlah pada jenis sel darah tertentu (disebut “trombosit”) – tampak dalam tes darah
- Kebingungan
- Pusing
- Diare
- Merasa mual atau mengalami muntah-muntah
- Sakit perut
- Peningkatan enzim hati tertentu – tampak dalam tes darah
- Ruam
- Peradangan pembuluh vena
- Peradangan pembuluh vena yang terkait dengan bekuan darah
- Nyeri atau pembengkakan di lokasi injeksi
- Demam

Tidak umum: (dapat dialami hingga 1 di antara 100 orang)
- Peningkatan jumlah beberapa jenis sel darah putih (disebut “eosinofil” dan “leukosit”) – tampak dalam tes darah
- Sulit tidur dan mudah terjaga
- Ensefalopati (suatu kondisi yang memengaruhi otak dan menyebabkan perubahan kondisi mental dan kebingungan)
- Sakit kepala
- Penurunan sensasi terhadap sentuhan, nyeri, dan suhu di mulut
- Gangguan indra perasa
- Detak jantung berlebih
- Perdarahan
- Tekanan darah rendah
- Wajah memerah
- Kontraksi berlebih otot saluran napas yang menyebabkan sulit bernapas
- Perdarahan lambung
- Ulkus di mulut
- Peningkatan kadar beberapa zat dalam darah Anda (Gamma-glutamiltransferase, Alkalin fosfatase darah, Kreatinin)
- Gatal-gatal
- bercak-bercak ungu menyerupai memar, bintik-bintik kecil yang memerah
- Keringat berlebihan
- Nyeri dada
- Rasa lemah

Langka: (dapat dialami hingga 1 di antara 1000 orang)
- Infeksi jamur di vagina
- Kadar sel darah rendah (pansitopenia)
- Penurunan signifikan pada jenis sel darah putih (disebut “neutrofil”) yang digunakan untuk melawan infeksi – tampak dalam tes darah
- Perdarahan luka sayat membutuhkan waktu lama untuk berhenti
- Memar yang muncul secara spontan
- Hasil abnormal untuk tes Coombs langsung atau tidak langsung Tes ini digunakan untuk menemukan antibodi yang melawan sel darah merah Anda.
- Kejang
- Sensasi seperti kebas, kesemutan, sensasi ditusuk-tusuk
- Penglihatan ganda
- Sensasi berputar
- Telinga berdenging atau mendesis

- Kesulitan bernapas
- Suara napas tidak normal (mengi)
- Bersin
- Hidung tersumbat (kongesti hidung)
- Bau mulut
- Peradangan hati
- Kulit dan mata menguning
- Nyeri otot
- Nyeri tekan payudara
- Merasa tidak enak badan

Tidak diketahui: (tidak dapat diestimasi dari data yang tersedia)
- Superinfeksi (infeksi baru yang terjadi setelah Anda diobati karena infeksi yang Anda derita saat ini)

Nyeri dada yang muncul tiba-tiba, yang bisa jadi merupakan tanda reaksi alergi yang berpotensi serius yang disebut sindrom Kounis telah teramati selama pemberian obat lain dengan jenis yang sama. Jika kondisi ini terjadi, segera laporkan kepada dokter atau perawat.

Melaporkan efek samping
Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Termasuk setiap kemungkinan efek samping yang tidak tercantum dalam leaflet ini.
Untuk melaporkan efek samping, kunjungi situs web www.pfizersafetyreporting.com atau kirimkan email ke IDN.AEReporting@pfizer.com.

14. Tanda-tanda dan gejala-gejala overdosis
Efek samping apa pun dapat terjadi, termasuk kebingungan, perubahan fungsi mental, masalah pergerakan, atau kejang.

15. Apa yang harus dilakukan jika Anda menggunakan lebih dari dosis yang dianjurkan?
Emblaveo akan diberikan kepada Anda oleh dokter atau perawat, jadi kecil kemungkinan obat ini diberikan dengan dosis yang terlalu banyak. Namun, jika Anda mengalami efek samping atau beranggapan telah diberi terlalu banyak Emblaveo, segera beri tahu dokter atau perawat Anda. Anda harus memberi tahu dokter Anda jika Anda mengalami kebingungan, perubahan fungsi mental, masalah pergerakan, atau kejang.

16. Bagaimana cara menyimpan obat ini?
Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tertera pada label vial dan kemasan setelah tulisan “EXP”. Tanggal kedaluwarsa mengacu pada tanggal terakhir pada bulan tersebut.

Simpan dalam lemari pendingin (2–8 °C).
Simpan dalam kemasan aslinya untuk melindunginya dari cahaya.

Jangan buang obat melalui saluran pembuangan air atau bersama sampah rumah tangga. Tanyakan kepada apoteker mengenai cara membuang obat yang sudah tidak digunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

17. Berapa lama umur simpan obat setelah kemasannya pertama kali dibuka?Setelah rekonstitusi

Vial yang telah direkonstitusi harus digunakan dalam waktu 30 menit untuk penyiapan kantong infus atau larutan stok yang mengandung dosis ATM-AVI yang sesuai untuk infus intravena.

Setelah pengenceran

Kantong infus
Jika larutan infus disiapkan dari larutan natrium klorida (0,9%) untuk injeksi atau larutan Ringer Laktat, stabilitas kimia dan fisika selama penggunaannya terbukti mencapai 24 jam pada suhu 2–8 °C diikuti dengan maksimal 12 jam pada suhu hingga 30 °C.

Jika larutan intravena disiapkan dengan larutan glukosa (5%) untuk injeksi, stabilitas kimia dan fisika selama penggunaannya telah terbukti mencapai 24 jam pada suhu 2–8 °C diikuti dengan maksimal 6 jam pada suhu hingga 30 °C.

Dari sudut pandang mikrobiologi, produk obat harus digunakan dengan segera, kecuali rekonstitusi dan pengenceran telah dilakukan dalam kondisi aseptik terkontrol dan tervalidasi. Jika tidak segera digunakan, waktu penyimpanan selama penggunaan dan kondisi sebelum penggunaan menjadi tanggung jawab pengguna dan tidak boleh melebihi yang tersebut di atas.

18. Petunjuk penggunaan/penanganan
Informasi berikut ini ditujukan untuk petugas kesehatan saja:

Penting: Harap melihat Ringkasan Karakteristik Produk sebelum meresepkan.

Produk obat ini tidak boleh dicampur dengan produk obat lain kecuali larutan natrium klorida (0,9%) untuk injeksi, larutan glukosa (5%) untuk injeksi, atau larutan Ringer Laktat sebagaimana disebutkan di bawah ini.

Serbuk harus direkonstitusi dengan air steril untuk injeksi dan konsentrat yang dihasilkan selanjutnya harus diencerkan sebelum digunakan. Larutan yang direkonstitusi adalah larutan bening tidak berwarna hingga kekuningan dan bebas dari partikel tampak.

Emblaveo (aztreonam/avibactam) adalah produk kombinasi; setiap vial berisi 1,5 g aztreonam dan 0,5 g avibactam dalam rasio tetap 3:1.

Teknik aseptik standar harus digunakan dalam penyiapan dan pemberian larutan. Dosis harus disiapkan dalam kantong infus dengan ukuran yang tepat.

Produk obat parenteral harus diperiksa secara visual untuk melihat adanya partikulat sebelum diberikan.

Setiap vial hanya untuk sekali pakai.

Interval waktu total antara dimulainya rekonstitusi hingga selesainya penyiapan infus intravena tidak boleh melebihi 30 menit.

Petunjuk untuk menyiapkan dosis dewasa dalam KANTONG INFUS:

CATATAN: Prosedur berikut ini menjelaskan langkah-langkah untuk menyiapkan larutan infus dengan konsentrasi akhir 1,5–40 mg/ml **aztreonam** dan 0,50–13,3 mg/ml **avibactam**. Semua perhitungan harus diselesaikan sebelum memulai langkah-langkah ini.

1. Siapkan **larutan yang direkonstitusi** (**131,2 mg/ml** aztreonam dan **43,7 mg/ml** avibactam):
   a) Tusukkan jarum hingga menembus penutup vial dan suntikkan 10 ml air steril untuk injeksi.
   b) Cabut jarum dan kocok vial secara perlahan untuk menghasilkan larutan bening tidak berwarna hingga kekuningan yang bebas dari partikel tampak.
2. Siapkan **larutan akhir** untuk infus (konsentrasi akhir **1,5–40 mg/ml** aztreonam dan **0,50–13,3 mg/ml** avibactam):
   Kantong infus: Encerkan lebih lanjut larutan rekonstitusi dengan memindahkan volume larutan rekonstitusi yang telah dihitung dengan tepat ke kantong infus yang berisi larutan mana pun berikut ini: larutan natrium klorida (0,9%) untuk injeksi, larutan glukosa (5%) untuk injeksi, atau larutan Ringer Laktat.

Lihat Tabel 1 di bawah ini.

Tabel 1: Penyiapan Emblaveo untuk dosis dewasa dalam KANTONG INFUS

Total dosis (aztreonam/avibactam)	**Volume yang diambil dari vial rekonstitusi**	**Volume akhir setelah pengenceran dalam kantong infus[1,2]**
2000 mg/667 mg	15,2 ml	50 ml hingga 250 ml
1500 mg/500 mg	11,4 ml	50 ml hingga 250 ml
1350 mg/450 mg	10,3 ml	50 ml hingga 250 ml
750 mg/250 mg	5,7 ml	50 ml hingga 250 ml
675 mg/225 mg	5,1 ml	50 ml hingga 250 ml
Semua dosis lainnya	Volume (ml) dihitung berdasarkan dosis yang dibutuhkan: **Dosis (mg aztreonam) ÷ 131,2 mg/ml aztreonam** **Atau** **Dosis (mg avibactam) ÷ 43,7 mg/ml avibactam**	Volume (ml) akan bervariasi bergantung pada ketersediaan ukuran kantong infus dan konsentrasi akhir yang diinginkan (Konsentrasinya harus 1,5–40 mg/ml aztreonam dan 0,50–13,3 mg/ml avibactam)

[1]Encerkan hingga konsentrasi akhir aztreonam 1,5–40 mg/ml (konsentrasi akhir avibactam 0,50–13,3 mg/ml) untuk stabilitas selama penggunaan hingga 24 jam pada suhu 2–8 °C, diikuti dengan maksimal 12 jam pada suhu hingga 30 °C untuk kantong infus yang berisi larutan natrium klorida (0,9%) untuk injeksi atau larutan Ringer Laktat.
[2]Encerkan hingga konsentrasi akhir aztreonam 1,5–40 mg/ml (konsentrasi akhir avibactam 0,50–13,3 mg/ml) untuk stabilitas selama penggunaan hingga 24 jam pada suhu 2–8 °C, diikuti dengan maksimal 6 jam pada suhu hingga 30 °C untuk kantong infus yang berisi larutan glukosa (5%) untuk injeksi.

Dari sudut pandang mikrobiologi, produk obat harus digunakan dengan segera, kecuali rekonstitusi dan pengenceran telah dilakukan dalam kondisi aseptik terkontrol dan tervalidasi. Jika tidak segera digunakan, waktu penyimpanan selama penggunaan dan kondisi sebelum penggunaan menjadi tanggung jawab pengguna dan tidak boleh melebihi yang tersebut di atas.

Produk obat yang tidak terpakai atau limbah harus dibuang sesuai dengan persyaratan setempat.

19. Daftar Zat Tambahan

Arginine.

20. Nomor izin edar

EMBLAVEO® 1,5 g/0,5 g serbuk untuk larutan konsentrat untuk infus; Dus, 10 vial @ 2,0 g;
Reg. No.: DKIxxxx

21. Nama dan alamat pemohon dan/atau pemilik obat sesuai dengan ketentuan yang berlaku

Diproduksi oleh:
Hospira Australia Pty Ltd
1-39 Lexia Place, Mulgrave
Victoria 3170
Australia

Diimpor oleh:
PT. Pfizer Indonesia,
Jakarta, Indonesia

22. Tanggal revisi

02/2026

23. Peringatan khusus

HARUS DENGAN RESEP DOKTER