1. NAME OF THE MEDICINAL PRODUCT

Emblaveo (Aztreonam 1.5 g/ Avibactam 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 List of excipients.

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 indicated for the treatment of the following infections in adult patients (see sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties):

- 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 (see sections 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, and 5.1 Pharmacodynamic properties).

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

4.2 Posology and method of administration

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.

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
Infections due to aerobic Gram-negative organisms in patients with limited treatment options	2 g/0.67 g	1.5 g/0.5 g	3 hours	Every 6 hours	Duration in accordance with the site of infection and may continue for up to 14 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 Pharmacokinetic properties).

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 hemodialysis[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 hemodialysis; on hemodialysis days Emblaveo should be administered after the hemodialysis session.
d Aztreonam-avibactam should not be used in patients with CrCl ≤ 15 mL/min unless hemodialysis 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 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

There are insufficient data to make dosing adjustment recommendations for patients undergoing renal replacement therapy other than hemodialysis (e.g. continuous veno-venous hemofiltration or peritoneal dialysis). Patients receiving continuous renal replacement therapy (CRRT) need a higher dose than

patients on hemodialysis. 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 Pharmacokinetic properties).

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 Special precautions for disposal and other handling.

4.3 Contraindications

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

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

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 Contraindications). 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 Posology and method of administration). 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 Overdose).

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 Posology and method of administration).

Hepatic impairment

Elevated liver enzymes have been observed with Emblaveo (see section 4.8 Undesirable effects). 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 randomized 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 randomized 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 randomized 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 Pharmacodynamic properties). 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 Posology and method of administration and 5.1 Pharmacodynamic properties). 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 Pharmacodynamic properties).

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 Undesirable effects). 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 Undesirable effects). 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 Undesirable effects).

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 Special precautions for disposal and other handling) 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 Preclinical safety data). Animal studies with avibactam have shown reproductive toxicity without evidence of teratogenic effects (see section 5.3 Preclinical safety data).

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 Preclinical safety data).

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 Undesirable effects).

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	Anemia Thrombocytosis Thrombocytopenia	Eosinophil count increased Leukocytosis	Pancytopenia Neutropenia Prothrombin time prolonged Activated partial thromboplastin time prolonged Coombs test positive Coombs direct test positive Coombs indirect test positive	
Immune system disorders		Anaphylactic reaction Drug hypersensitivity		
Psychiatric disorders	Confusional state	Insomnia		

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)**
Nervous system disorders	Dizziness	Encephalopathy Headache Hypoesthesia oral Dysgeusia	Seizure Paresthesia	
Eye disorders			Diplopia	
Ear and labyrinth disorders			Vertigo Tinnitus	
Cardiac disorders		Extrasystoles		
Vascular disorders		Hemorrhage Hypotension Flushing		
Respiratory, thoracic and mediastinal disorders		Bronchospasm	Dyspnea Wheezing Sneezing Nasal congestion	
Gastrointestinal disorders	Diarrhoea Nausea Vomiting Abdominal pain	*Clostridium difficile* colitis Gastrointestinal hemorrhage Mouth ulceration	Pseudomembranous colitis Breath odor	
Hepatobiliary disorders	Aspartate aminotransferase increased Alanine aminotransferase increased Transaminases increased	Gamma-glutamyl transferase increased Blood alkaline phosphatase increased	Hepatitis Jaundice	
Skin and subcutaneous tissue disorders	Rash	Angioedema Toxic epidermal necrolysis		

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)**
		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 Infusion site extravasation Injection site pain Pyrexia	Chest discomfort Asthenia	Malaise	

Kounis syndrome

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

4.9 Overdose

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

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

During a 4-hour hemodialysis 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 and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx.

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 (%fT > 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 (%$fT > C_T$).

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

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 metabolized. 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 feces.

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 feces.

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 Posology and method of administration.

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.

Pediatric population
The pharmacokinetics of aztreonam-avibactam have not been evaluated in pediatric 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) $\geq$ 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/fetal 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 fetal weight and delayed ossification, potentially related to maternal toxicity. Plasma exposure levels at maternal and fetal NOAEL (100 mg/kg/day) indicate moderate to low margins of safety.

In the rat, no adverse effects were observed on embryofetal 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 Special precautions for disposal and other handling.

6.3 Shelf life

Dry powder

2 years.

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 Shelf life.

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, colorless 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, colorless 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 4 below.

Table 4. 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. MANUFACTURER

Hospira Australia Pty Ltd,
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