ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 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

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, 4.4, and 5.1).

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).

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).

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).

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 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	

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)
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 Abdominal pain	*Clostridium difficile* colitis Gastrointestinal haemorrhage Mouth ulceration	Pseudomembranous colitis Breath odour	
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		

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)
		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.

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 the national reporting system listed in Appendix V.

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 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.
- *Pseudomonas aeruginosa*
- *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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Emblaveo in one or more subsets of the paediatric population for the treatment of infections caused by aerobic Gram-negative bacteria in patients with limited treatment options (see section 4.2 for information on paediatric use).

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

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.

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 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. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Brussels
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1808/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Pfizer Service Company BV
Hoge Wei 10
Zaventem
1930
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Emblaveo 1.5 g/0.5 g powder for concentrate for solution for infusion
aztreonam/avibactam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

This product contains arginine and sodium.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after reconstitution and dilution.
Single use vial

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Read the leaflet for the shelf life of the reconstituted and diluted medicine.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1808/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Emblaveo 1.5 g/0.5 g powder for concentrate
aztreonam/avibactam
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Emblaveo 1.5 g/0.5 g powder for concentrate for solution for infusion
aztreonam/avibactam

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Emblaveo is and what it is used for

What Emblaveo is
Emblaveo is an antibiotic medicine that contains two active substances aztreonam and avibactam.
- Aztreonam belongs to the group of antibiotics called "monobactams". It can kill certain types of bacteria (so-called Gram-negative bacteria).
- Avibactam is a "beta-lactamase inhibitor" that helps aztreonam kill some bacteria that it cannot kill on its own.

What Emblaveo is used for
Emblaveo is used in adults to treat:
- complicated bacterial infections of the abdomen (stomach and gut), where the infection has spread into abdominal cavity (space within the abdomen)
- hospital-acquired pneumonia (a bacterial infection of the lungs that is picked up in hospitals), including ventilator-associated pneumonia (pneumonia that develops in patients on a machine called a ventilator to help them breathe)
- complicated (difficult to treat as it has spread to other parts of the body or the patient has other conditions) urinary tract infections, including pyelonephritis (kidney infection)
- infections caused by Gram-negative bacteria that other antibiotics may not be able to kill.

2. What you need to know before you are given Emblaveo

You should not be given Emblaveo if:
- you are allergic to aztreonam, avibactam or any of the other ingredients of this medicine (listed in section 6).
- you have ever had a severe allergic reaction (swelling of the face, hands, feet, lips, tongue or throat; or difficulty swallowing or breathing; or a severe skin reaction) to other antibiotics belonging to the penicillin, cephalosporin, or carbapenem groups.

Warnings and precautions
Talk to your doctor or nurse before using Emblaveo if:
- you have ever had any allergic reaction (even if only a skin rash) to other antibiotics. Signs of allergic reaction include itching, a rash on the skin or difficulty in breathing.

- you have kidney problems or if you are taking medicines that affect your kidney function, such as other antibiotics known as aminoglycosides (streptomycin, neomycin, gentamicin). If your kidney function is impaired, your doctor may give you a lower dose of Emblaveo and may want to perform regular blood tests during treatment to check your kidney function. In addition, you may be at higher risk of developing serious side effects that affect the nervous system such as encephalopathy (a disorder of the brain that may be caused by disease, injury, medicines or chemicals) due to increased blood levels of Emblaveo unless the dose is reduced. Symptoms of encephalopathy include confusion, seizures and altered mental function (see Section 3: If you use more Emblaveo than you should).
- you have any liver problems. Your doctor may want to perform regular blood tests during treatment to check your liver since increases in liver enzymes have been observed with Emblaveo
- you are taking medicines known as anticoagulants (a medicine that prevents the blood from clotting). Emblaveo can affect blood clotting. Your doctor will monitor your blood levels to check if your dose of anticoagulant needs to be changed during treatment with Emblaveo.

Talk to your doctor if after starting treatment with Emblaveo, you experience:
- severe, prolonged, or bloody diarrhoea. This may be a sign of an inflammation of the large bowel. It may be necessary to interrupt the treatment with Emblaveo and start specific treatment for the diarrhoea (see section 4: Possible side effects).
- other infections. There is a small possibility that you may get a different infection caused by another bacteria during or after treatment with Emblaveo.

Lab tests
Tell your doctor that you are taking Emblaveo if you are going to have any tests. This is because you may get an abnormal result with a test called direct or indirect Coombs test. This test looks for antibodies that fight against your red blood cells.

Children and adolescents
Emblaveo should not be used in paediatric or adolescent patients aged under 18 years. This is because it is not known if the medicine is safe to use in this age group.

Other medicines and Emblaveo
Tell your doctor if you are using, have recently used or might use any other medicines.

Talk to your doctor before using Emblaveo if you are taking any of the following medicines:
- a medicine for gout called probenecid

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

This medicine may harm your unborn child. It should only be used during pregnancy if the doctor considers it necessary and only if the benefit for the mother outweighs the risk for the child.

This medicine may pass into breast milk. If you are breast-feeding a decision must be made whether you should discontinue breast-feeding or abstain from treatment with this medicine, taking into account the benefit of breast-feeding for the child and the benefit of treatment for the woman.

Driving and using machines
Emblaveo may cause side effects, such as dizziness, which can affect your ability to drive and use machines. Do not drive or use tools or machines if you experience side effects such as dizziness (see section 4: Possible side effects).

Emblaveo contains Sodium
This medicine contains approximately 44.6 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 2.2% of the recommended maximum daily dietary intake for sodium for an adult.

3. How to use Emblaveo

Emblaveo will be given to you by a doctor or a nurse.

How much to use

Emblaveo is given as a drip directly into a vein ('intravenous infusion'). The usual dose is one vial (containing 1.5 g aztreonam and 0.5 g avibactam) every 6 hours. The first dose is higher (2 g aztreonam and 0.67 g avibactam). The infusion will last 3 hours. A course of treatment usually lasts from 5 to up to 14 days, depending on the type of infection you have and how you respond to treatment.

People with kidney problems
If you have kidney problems your doctor may lower your dose and increase the time between the doses. This is because Emblaveo is removed from your body by the kidneys. If your kidney function is impaired your blood levels of Emblaveo may be increased.

If you are given more Emblaveo than you should be given
Emblaveo will be given to you by a doctor or a nurse, so it is unlikely you will be given too much of this medicine. However, if you have side effects or think you have been given too much Emblaveo, tell your doctor or nurse straight away. You must tell your doctor if you experience confusion, altered mental function, movement problems, or seizure.

If a dose of Emblaveo has been forgotten
If you think you have missed a dose, tell your doctor or nurse straight away.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:
- Swelling of the face, lips, eyes, tongue, and/or throat, hives and with difficulty in swallowing or breathing. These may be signs of an allergic reaction or angioedema which may be life-threatening.
- Severe, persistent, or bloody diarrhoea (which may be associated with stomach pain or fever). This may occur during or after treatment with antibiotics and can be a sign of serious bowel inflammation. If this happens do not take medicines that stop or slow bowel movement.
- Sudden onset of a severe rash or blistering or peeling skin, possibly accompanied by a high fever or joint pain (these may be signs of more serious medical conditions such as toxic epidermal necrolysis, dermatitis exfoliative, erythema multiforme).

These serious side effects are uncommon (may affect up to 1 in 100 people).

Other side effects
Tell your doctor or nurse if you notice any of the following side effects:

Common: (may affect up to 1 in 10 people)
- Decrease in the number of red blood cells – shown in blood tests
- Change in the number of some types of blood cells (called “platelets”) – shown in blood tests
- Confusion
- Dizziness
- Diarrhoea
- Feeling sick (nausea) or being sick (vomiting)
- Stomach pain
- Increase in certain liver enzymes – shown in blood tests
- Rash
- Inflammation of a vein
- Inflammation of a vein associated with a blood clot
- Pain or swelling at the site of the injection
- Fever

Uncommon: (may affect up to 1 in 100 people)
- Increase in the number of some types of white blood cells (called “eosinophils” and “leucocytes”) – shown in blood tests
- Difficulty falling and staying asleep
- Encephalopathy (a condition that affects the brain and causes altered mental state and confusion)
- Headache
- Reduced sensation to touch, pain and temperature in the mouth
- Taste disturbance
- Extra heartbeats
- Bleeding
- Reduced blood pressure
- Reddening of the face
- Excessive contraction of the airway muscles causing breathing difficulty
- Stomach bleeding
- Mouth ulcers
- Increase in the levels of some substances in your blood (Gamma-glutamyltransferase, Blood alkaline phosphatase, Creatinine)
- Itching
- purple patches like bruising, small red spots
- Excessive sweating
- Chest pain
- Weakness

Rare: (may affect up to 1 in 1 000 people)
- Fungal infections of the vagina
- Low levels of blood cells (pancytopenia)
- Significant decrease in the type of white blood cells (called “neutrophils”) used to fight infection - shown in blood tests
- Lengthening of the time it takes for a cut to stop bleeding
- Spontaneous bruising
- Abnormal result with a test called direct or indirect Coombs test. This test looks for antibodies that fight against your red blood cells.
- Seizure
- Sensations like numbness, tingling, pins and needles
- Double vision
- A spinning sensation
- Ringing or buzzing in the ears
- Difficulty breathing

- Breath sounds abnormal (wheezing)
- Sneezing
- Blocked nose (nasal congestion)
- Bad breath
- Inflammation of the liver
- Yellowing of the skin and eyes
- Muscle pain
- Breast tenderness
- Feeling generally unwell

Not known: (cannot be estimated from the available data)
- Superinfection (a new infection that occurs after you are treated for your current infection)

Sudden chest pain, which may be a sign of a potentially serious allergic reaction called Kounis syndrome has been noted with other medicines of the same type. If this happens talk to a doctor or nurse immediately.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Emblaveo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and carton after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Emblaveo contains
- The active substances are aztreonam and avibactam. Each vial contains 1.5 g aztreonam and avibactam sodium equivalent to 0.5 g avibactam (see section 2: Emblaveo contains sodium).
- The other ingredient is arginine.

What Emblaveo looks like and contents of the pack
Emblaveo is a white to slightly yellow powder for concentrate for solution for infusion in a glass vial with a rubber stopper and aluminium seal with flip-off cap. It is available in packs containing 10 vials.

Marketing Authorisation Holder
Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Brussels
Belgium

Manufacturer
Pfizer Service Company BV
Hoge Wei 10
Zaventem
1930
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Pfizer Luxembourg SARL filialas Lietuvoje
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This leaflet was last revised in MM/YYYY

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Important: Please refer to the Summary of Product Characteristics before prescribing.

This medicinal product must not be mixed with other medicinal products except sodium chloride (0.9%) solution for injection, glucose (5%) solution for injection, or Lactated Ringer's solution as mentioned below.

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.

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.

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.

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 1 below.

Table 1: 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[1,2]**
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)

1 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.

2 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.

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.

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