Zavicefta 2 g/0.5 g powder for concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

Zavicefta 2 g/0.5 g powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ceftazidime pentahydrate equivalent to 2 g ceftazidime and avibactam sodium equivalent to 0.5 g avibactam.

After reconstitution, 1 mL of solution contains 167.3 mg of ceftazidime and 41.8 mg of avibactam (see section 6.6).

Excipient with known effect: each vial contains 6.37 mmol of sodium (approximately 146 mg).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

A white to yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zavicefta is indicated in adults and paediatric patients from birth for the treatment of the following infections (see sections 4.4 and 5.1):

- Complicated Intra-Abdominal Infection (cIAI)
- Complicated Urinary Tract Infection (cUTI), including pyelonephritis
- Hospital-acquired Pneumonia (HAP), including ventilator associated pneumonia (VAP)

Treatment of adult patients with bacteraemia that occurs in association with, or is suspected to be associated with cIAI, cUTI, or HAP/VAP.

Consideration should be given to official guidance on the appropriate use of antibacterial agents. For treatment of cIAI use in combination with metronidazole.

4.2 Posology and method of administration

Dosage in adults with creatinine clearance (CrCl >50 mL/min)

The recommended dosage of Zavicefta in adults is 1 vial where each vial contains 2 g ceftazidime and 0.5 g avibactam administered by intravenous (IV) infusion over 2 hours. Treatment is repeated every 8 hours. The duration of treatment is provided in Table 1.

Treatment duration for adult patients

Table 1 Summary of the treatment duration by indication or condition

Indication	Treatment Duration
Complicated Intra-Abdominal Infection (cIAI)[a,b]	5-14 days
Complicated Urinary Tract Infection (cUTI), including Pyelonephritis[b]	5-10 days[c] The total duration of treatment could be increased to 14 days for patients with bacteraemia
Hospital-acquired Pneumonia, including ventilator associated pneumonia (HAP/VAP)[b]	7-14 days
Bacteraemia associated, or suspected to be associated with the above infections	Duration of treatment should be in accordance with the site of infection.

[a] To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.
[b] To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process.
[c] Treatment duration includes intravenous plus oral treatment. The time to switch from intravenous Zavicefta to oral treatment with another antibiotic depends on the clinical situation, but is normally after about 5 days (the minimum duration of treatment with ceftazidime-avibactam in clinical trials was 5 days).

The duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.

Dosage in paediatric patients with creatinine clearance (CrCl) >50 mL/min/1.73 m^2

The recommended dosage of Zavicefta in paediatric patients (from birth to <18 years) is based on the age and weight of the patient. Zavicefta is administered every 8 hours by intravenous infusion over 2 hours, see Table 2 (see also sections 4.4 and 5.1). The duration of therapy should be guided by the severity, site of infection and the patient's clinical and bacteriological progress.

Table 2 Dosage in paediatric patients with CrCl >50 mL/min/1.73 m^{2*}

Type of Infection	Age Group[e]		Dose of Ceftazidime/Avibactam[d]	Frequency	Infusion Time	Duration of Treatment
cIAI[a,b] OR cUTI including pyelonephritis[b] OR HAP/VAP[b]	6 months to <18 years		**50 mg/kg**/12.5 mg/kg **to a maximum of 2 g**/0.5 g	Every 8 hours	2 hours	cIAI: 5-14 days cUTI[c]: 5-14 days HAP/VAP: 7-14 days
	3 months to <6 months		**40 mg/kg**/10 mg/kg	Every 8 hours	2 hours	
	Full term (birth to <3 months)	Birth to ≤28 days	**20 mg/kg**/5 mg/kg	Every 8 hours	2 hours	
		>28 days to <3 months	**30 mg/kg/7.**5 mg/kg			
	Preterm[f] (birth to <3 months)	31 to ≤44 weeks PMA[g]	**20 mg/kg**/5 mg/kg	Every 8 hours	2 hours	
		>44 weeks to <53 weeks PMA[g]	**30 mg/kg/7.**5 mg/kg			

[a] To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.
[b] To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process.
[c] Treatment duration includes intravenous plus oral treatment.

[d] Ceftazidime/avibactam is a combination product in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only (see section 6.6).
[e] Paediatric patients studied from 3 to 12 months of age were full term (≥37 weeks gestation).
[f] Preterm defined as <37 weeks gestation.
[g] Postmenstrual age.
[*]Calculated using the Schwartz bedside formula for paediatric patients (mL/min/1.73 m^2).

Special populations

Elderly patients
No dosage adjustment is considered necessary in elderly patients (≥65 years). The dose regimen should be adjusted if renal impairment is present (see section 5.2).

Patients with renal impairment
The following dose adjustment is recommended in patients with renal impairment (see sections 4.4 and 5.2).

Dose adjustments for Zavicefta for patients with an estimated creatinine clearance (CrCl) ≤50 mL/min are outlined in Table 3 below.

Dosage in adults and paediatric patients (from 2 years to <18 years) with creatinine clearance (CrCl) ≤50 mL/min

Table 3 Recommended dose for patients with renal impairment (CrCl ≤50 mL/min)

Age Group	Estimated CrCl (mL/min)[a]	Dose of Ceftazidime/Avibactam[b,d]	Frequency	Infusion Time
Adults	31-50	**1 g**/0.25 g	Every 8 hours	2 hours
	16-30	**0.75 g**/0.1875 g	Every 12 hours	
	6-15		Every 24 hours	
	ESRD including on haemodialysis[c]		Every 48 hours	
Paediatric patients aged 2 years to <18 years	31-50	**25 mg/kg**/6.25 mg/kg **to a maximum of 1 g**/0.25 g	Every 8 hours	2 hours
	16-30	**18.75 mg/kg**/4.7 mg/kg **to a maximum of 0.75 g**/0.1875 g	Every 12 hours	
	6-15		Every 24 hours	
	ESRD including on haemodialysis[c]		Every 48 hours	

[a] CrCl calculated using the Cockcroft-Gault formula for adults and with the Schwartz bedside formula for paediatric patients (mL/min/1.73 m^2).
[b] Dose recommendations are based on PK modelling.
[c] Both ceftazidime and avibactam are haemodialysable; thus, Zavicefta should be administered after haemodialysis on haemodialysis day.
[d] Ceftazidime/avibactam is a combination product in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only (see section 6.6).

Dosage in paediatric patients 3 months to <2 years of age with creatinine clearance (CrCl) ≤50 mL/min/1.73 m²

Table 4 Recommended dose for paediatric patients with estimated CrCl[a] ≤50 mL/min/1.73 m²

Age Group[d]	Estimated CrCl (mL/min/1.73 m²)	Dose of Ceftazidime/Avibactam[b,c]	Frequency	Infusion Time
3 to <6 months	31-50	**20 mg/kg**/5 mg/kg	Every 8 hours	2 hours
6 months to <2 years		**25 mg/kg**/6.25 mg/kg	Every 8 hours	
3 to <6 months	16-30	**15 mg/kg**/3.75 mg/kg	Every 12 hours	
6 months to <2 years		**18.75 mg/kg**/4.7 mg/kg	Every 12 hours	

[a] Calculated using the Schwartz bedside formula.
[b] Dose recommendations are based on pharmacokinetic modelling (see section 5.2).
[c] Ceftazidime/avibactam is a combination product in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only (see section 6.6).
[d] Paediatric patients studied from 3 to 12 months of age were full term (≥37 weeks gestation).

There is insufficient information to recommend a dosage regimen for paediatric patients from birth to 3 months of age with signs of renal impairment.

There is insufficient information to recommend a dosage regimen for paediatric patients <2 years of age that have a CrCl <16 mL/min/1.73 m².

In patients with impaired renal function, regular monitoring of estimated creatinine clearance is advised as in some patients, especially early in the course of their infection, the creatinine clearance estimated from serum creatinine can change quickly.

Haemodialysis
Both ceftazidime and avibactam are haemodialysable; thus, Zavicefta should be administered after haemodialysis on haemodialysis day.

Haemofiltration
There is insufficient data to make specific dosage adjustment recommendations for patients undergoing continuous veno-venous haemofiltration.

Peritoneal dialysis
There is insufficient data to make specific dosage adjustment recommendations for patients undergoing peritoneal dialysis.

Patients with hepatic impairment
No dosage adjustment is considered necessary in patients with hepatic impairment (see section 5.2). Close clinical monitoring for safety and efficacy is advised.

Paediatric patients
Safety and efficacy in paediatric patients <18 years of age have not been established for HAP/VAP and is based on extrapolation (see section 4.4).

Method of administration

Zavicefta is administered to adults by intravenous infusion over 2 hours in an appropriate infusion volume (see section 6.6). For paediatric patients, the infusion volume may be adjusted (see section 6.6).

Constitution and compatibility

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.

Hypersensitivity to the cephalosporin class of antibacterials.

Immediate and severe hypersensitivity (e.g., anaphylactic reaction) to any other type of β-lactam antibacterial agent (e.g., penicillins, monobactams or carbapenems).

4.4 Special warnings and precautions for use

Hypersensitivity reactions
As with all β-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with Zavicefta must be discontinued immediately and adequate emergency measures must be initiated.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in patients receiving ceftazidime treatment (see section 4.8). If a severe skin reaction occurs, Zavicefta should be discontinued and appropriate therapy should be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to ceftazidime, to other cephalosporins or to any other type of β-lactam agent. Caution should be used if ceftazidime-avibactam is given to patients with a history of non-severe hypersensitivity to other β-lactam agents.

Limitation of the clinical data
No clinical studies have been conducted in paediatric patients with nosocomial pneumonia. The efficacy of ceftazidime/avibactam for the treatment of paediatric patients ≥3 months of age with HAP/VAP is extrapolated from adults and is based on analyses of the pharmacokinetic-pharmacodynamic relationship for ceftazidime/avibactam and on paediatric experience with ceftazidime alone (see section 5.2).

Clostridium difficile-associated diarrhoea
Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all anti-bacterial agents, including ceftazidime-avibactam, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of Zavicefta (see section 4.8). Discontinuation of therapy with Zavicefta and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Patients with renal impairment
Ceftazidime and avibactam are eliminated via the kidneys, therefore the dose should be reduced according to the degree of renal impairment. Patients with renal impairment should be closely monitored for both safety and efficacy. Neurological sequelae, including tremor, myoclonus, nonconvulsive status epilepticus, convulsion, encephalopathy and coma, have occasionally been reported with ceftazidime when the dose has not been reduced in patients with renal impairment (see section 4.2).

Concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products such as aminoglycosides or potent diuretics (e.g., furosemide) may adversely affect renal function.

Non-susceptible organisms
Prolonged use may result in the overgrowth of non-susceptible organisms (e.g., enterococci, fungi), which may require interruption of treatment or other appropriate measures.

Non-drug interference
Ceftazidime does not interfere with enzyme-based tests for glycosuria, but slight interference (false-positive) may occur with copper reduction methods (Benedict's, Fehling's, Clinitest).

Ceftazidime does not interfere in the alkaline picrate assay for creatinine.

Direct antiglobulin test (DAGT or Coombs test) seroconversion and potential risk of haemolytic anaemia
Cephalosporin use may cause development of a positive direct antiglobulin test (DAGT, or Coombs test), which may interfere with the cross-matching of blood and/or may cause drug induced immune haemolytic anaemia. While DAGT seroconversion in patients receiving ceftazidime-avibactam (CAZ-AVI) was frequent in clinical studies, there was no evidence of haemolysis in patients who developed a positive DAGT on treatment (see section 4.8). However, the possibility that haemolytic anaemia could occur in association with CAZ-AVI treatment cannot be ruled out. Patients experiencing anaemia during or after treatment with CAZ-AVI should be investigated for this possibility.

Controlled sodium diet
For patients who are on a controlled sodium diet, the following important information about the ingredients of ceftazidime and avibactam should be considered:

Each vial contains approximately 6.37 mmol of sodium per vial. This total is the combined sodium from avibactam sodium and the excipient sodium carbonate.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products such as aminoglycosides or potent diuretics (e.g., furosemide) may adversely affect renal function (see section 4.4).

Chloramphenicol is antagonistic *in vitro* with ceftazidime and other cephalosporins. The clinical relevance of this finding is unknown, but if concurrent administration of ceftazidime-avibactam with chloramphenicol is proposed, the possibility of antagonism should be considered.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited clinical data from the use of ceftazidime-avibactam in pregnant women. Animal embryofetal development studies conducted with ceftazidime or avibactam do not indicate harmful effects at exposures equivalent to therapeutic concentrations. Following administration of avibactam throughout pregnancy and lactation in the rat at maternal exposures greater than or equal to approximately 1.5 times human therapeutic exposures, there were minor changes in the morphology of the kidney and ureters in the rat pups (see section 5.3).

Ceftazidime-avibactam should not be used during pregnancy unless clearly necessary and only if the potential benefit outweighs the possible risk.

Lactation
There are no data on human milk excretion of ceftazidime-avibactam. Ceftazidime is excreted in human milk in small quantities. It is unknown whether avibactam is excreted in human milk. Women who are breast-feeding should be treated with ceftazidime-avibactam only if clearly indicated. Interruption of breast-feeding is recommended.

Fertility
The effects of ceftazidime-avibactam on fertility in humans have not been studied. Animal studies with ceftazidime 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

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g., dizziness), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

In seven Phase 2 and Phase 3 clinical trials, 2024 adults were treated with CAZ-AVI. The most common adverse drug reactions occurring in ≥5% of patients treated with CAZ-AVI were Coombs direct test positive, nausea, and diarrhoea. These were usually mild or moderate in intensity. No clinically significant differences were observed in the safety profile across indications.

The following adverse drug reactions have been reported with ceftazidime alone and/or identified during all Phase 2 and Phase 3 clinical trials with CAZ-AVI (N=2024).

Table 5 ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC

System Organ Class	**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**	**Frequency not known (cannot be estimated from the available data)**
Infections and infestations		Candidiasis (including Vulvovaginal candidiasis and Oral candidiasis)	Pseudomembranous colitis *Clostridium difficile* colitis			
Blood and lymphatic system disorders	Coombs direct test positive[+]	Eosinophilia Thrombocytosis Thrombocytopenia	Neutropenia Leukopenia Lymphocytosis			Agranulocytosis Haemolytic anaemia
Immune system disorders						Anaphylactic reaction Kounis syndrome[++]
Nervous system disorders		Dizziness Headache	Paraesthesia			
Gastrointestinal disorders		Vomiting Nausea Diarrhoea Abdominal pain	Dysgeusia			

System Organ Class	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	Frequency not known (cannot be estimated from the available data)
Hepatobiliary disorders		Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphatase increased Gamma-glutamyltransferase increased Blood lactate dehydrogenase increased				Jaundice
Skin and subcutaneous tissue disorders		Urticaria Pruritus Rash maculo-papular				Toxic epidermal necrolysis[+] Angioedema Stevens-Johnson syndrome[+] Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [+] Acute generalised exanthematous pustulosis[+] Erythema multiforme
Renal and urinary disorders			Acute kidney injury Blood creatinine increased Blood urea increased		Tubulo-interstitial nephritis	
General disorders and administration site conditions		Infusion site thrombosis Infusion site phlebitis				

System Organ Class	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	Frequency not known (cannot be estimated from the available data)
		Pyrexia				

[+] See section 4.4.
[++] Acute coronary syndrome associated with an allergic reaction.

Paediatric population

From birth to less than 3 months of age

The safety assessment in neonates and infants less than 3 months of age is based on the safety data from one clinical trial in which 46 patients (from birth to less than 3 months of age) received Zavicefta. Overall, the adverse reactions reported in these 46 paediatric patients were consistent with the known safety profile of Zavicefta in older populations (i.e., paediatric patients from 3 months of age and adults).

3 months of age and older

The safety assessment in paediatric patients from 3 months of age and older is based on the safety data from two trials in which 61 patients with cIAI (aged from 3 years to less than 18 years) and 67 patients with cUTI (aged from 3 months to less than 18 years) received Zavicefta. Overall, the safety profile in these 128 paediatric patients was similar to that observed in the adult population with cIAI and cUTI.

4.9 Overdose

Overdosage of ceftazidime-avibactam is unlikely, although overdosing could potentially occur in patients with moderate to severe renal impairment, and in end stage renal disease including patients undergoing haemodialysis (see sections 4.4 and 5.2). Overdosing with ceftazidime-avibactam can lead to neurological sequelae including encephalopathy, convulsions and coma, due to the ceftazidime component.

Treatment for overdose should follow local standard medical practice. Both ceftazidime and avibactam can be partially removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Ceftazidime inhibits bacterial peptidoglycan cell wall synthesis following attachment to penicillin binding proteins (PBPs), which leads to bacterial cell lysis and death. This broad spectrum cephalosporin is active against many important Gram-negative and Gram-positive bacterial pathogens *in vitro*. Avibactam is a non β-lactam, β-lactamase inhibitor that acts by forming a covalent adduct with the enzyme that is stable to hydrolysis. It inhibits both Ambler class A and class C β-lactamases, including extended-spectrum β-lactamases (ESBLs), KPC carbapenemases, and AmpC enzymes. Avibactam also inhibits the class D carbapenemase OXA-48, which does not significantly hydrolyse ceftazidime. Avibactam has no clinically relevant *in vitro* antibacterial activity. Avibactam did not induce transcription of bla_{AmpC} in *Enterobacter cloacae*, *Citrobacter freundii* or *Pseudomonas aeruginosa in vitro* at concentrations used to treat patients.

Mechanism of resistance
Ceftazidime-avibactam is not active against metallo-β-lactamase-producing bacteria. Bacterial resistance mechanisms that could potentially affect ceftazidime-avibactam include mutant or acquired PBPs, decreased outer membrane permeability to either compound, active efflux of either compound, mutated or acquired β-lactamase enzymes insensitive to avibactam and able to hydrolyse ceftazidime.

Cross-resistance
An absence of cross-resistance between ceftazidime-avibactam and fluoroquinolones or aminoglycosides has been demonstrated *in vitro* using molecularly-characterised clinical isolates. Some isolates resistant to ceftazidime (and other cephalosporins) or to carbapenems are susceptible to ceftazidime-avibactam. There is cross-resistance with β-lactam antibacterial agents, including carbapenems, when the mechanism is production of metallo-β-lactamases, such as VIM-2.

Pharmacokinetic/pharmacodynamic relationship
The antimicrobial activity of ceftazidime-avibactam against specific pathogens has been shown to best correlate with the percent time of free-drug concentration above the ceftazidime-avibactam minimum inhibitory concentration over the dose interval (%*f*T >MIC of ceftazidime-avibactam) for ceftazidime, and the percent time of the free drug concentration above a threshold concentration over the dose interval (% *f*T>C_T) for avibactam.

Clinical efficacy against specific pathogens
This list is provided based on clinical efficacy and pharmacokinetic/pharmacodynamic data from clinical studies. The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. Efficacy has been demonstrated in clinical studies against the pathogens, listed under each indication, that were susceptible to ceftazidime-avibactam *in vitro*.

Susceptibility
<u>Complicated intra-abdominal infections</u> Gram-negative micro-organisms • *Citrobacter freundii* • *Enterobacter cloacae* • *Escherichia coli* • *Klebsiella oxytoca* • *Klebsiella pneumoniae* • *Pseudomonas aeruginosa*
<u>Complicated urinary-tract infections</u> Gram-negative micro-organisms • *Escherichia coli* • *Klebsiella pneumoniae* • *Proteus mirabilis* • *Enterobacter cloacae* • *Pseudomonas aeruginosa*

Hospital-acquired pneumonia including ventilator-associated pneumonia
Gram-negative micro-organisms
- *Enterobacter cloacae*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Serratia marcescens*
- *Pseudomonas aeruginosa*

Clinical efficacy has not been established against the following pathogens that are relevant to the approved indications although *in vitro* studies suggest that they would be susceptible to ceftazidime-avibactam in the absence of acquired mechanisms of resistance.

Gram-negative micro-organisms
- *Citrobacter koseri*
- *Enterobacter aerogenes*
- *Morganella morganii*
- *Proteus vulgaris*
- *Providencia rettgeri*

Ceftazidime-avibactam is active *in vitro* against *Streptococcus pyogenes* and *Streptococcus agalactiae*, but not generally active against other clinically-important Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA).

Interaction with other antimicrobial agents
In vitro interaction tests with ceftazidime-avibactam show ceftazidime-avibactam has little potential to antagonise or be antagonised by other antibiotics of various classes (e.g., metronidazole, tobramycin, levofloxacin, vancomycin, linezolid, colistin, tigecycline).

Susceptibility testing
The prevalence of acquired resistance may vary geographically and with time for selected species. Local information on resistance is desirable, particularly when treating severe infections.

The susceptibility to ceftazidime-avibactam of a given clinical isolate should be determined by standard methods. Interpretations of test results should be made in accordance with local infectious diseases and clinical microbiology guidelines.

Susceptibility testing interpretive criteria (breakpoints)
European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints are based on the dosages below. Alternative dosing regimens may result in equivalent exposure. The table should not be used as a guidance for dosing in clinical practice as dosages can vary widely by indication. It does not replace specific national, regional or local dosing guidelines. However, if national practices significantly differ from those listed below, EUCAST breakpoints may not be valid. Situations where less antibiotic is given as standard or high dose should be discussed locally or regionally.

The EUCAST Breakpoint Tables v. 14.0 2024 indicates that the standard dosage on which breakpoints are based is (2 g ceftazidime + 0.5 g avibactam) x 3 iv over 2 hours. For inhibition zone determination, the disks contain 10 µg ceftazidime and 4 µg avibactam.

The EUCAST breakpoints for ceftazidime-avibactam are listed in the following table:

EUCAST Susceptibility Interpretive Criteria for Ceftazidime-Avibactam				
	Minimal Inhibitory Concentration (mg/L of Ceftazidime)[a]		**Disk Diffusion Inhibition Zone (mm Diameter)**	
Pathogen	S≤	R>	S≥	R<
Enterobacterales	8	8	13	13
Pseudomonas aeruginosa	8	8	17	17

Sources:
EUCAST Clinical Breakpoint Table v. 14.0, 1 January, 2024.
S = Susceptible. R = Resistant.
[a] For MIC determination, avibactam is present at a fixed concentration of 4 mg/L.

Standardised susceptibility test procedures require the use of quality control micro-organisms to control the technical aspects of the test procedures. Quality control micro-organisms are specific strains with intrinsic biological properties relating to resistance mechanisms and their genetic expression within the micro-organism; the specific strains used for susceptibility test quality control are not clinically significant.

Quality control ranges for EUCAST susceptibility breakpoints are listed in the following table.

Quality Control Ranges for Ceftazidime-Avibactam to be Used in Conjunction with EUCAST Susceptibility Test Interpretive Criteria		
	Minimal Inhibitory Concentration (mg/L of Ceftazidime)[a]	**Disk Diffusion Inhibition Zone (mm Diameter)**
Quality Control Strain		
Escherichia coli ATCC 25922	0.06-0.25	24-30
Pseudomonas aeruginosa ATCC 27853	0.5-4	21-27
Klebsiella pneumoniae ATCC 700603	0.25-2	18-24

Source: The European Committee on Antimicrobial Susceptibility Testing. Routine and extended internal quality control for MIC determination and disk diffusion as recommended by EUCAST. Version 14.0, 2024.
[a] For MIC determination, avibactam is present at a fixed concentration of 4 mg/L.

Clinical efficacy and safety

Complicated intra-abdominal infections

A total of 1058 adults with complicated intra-abdominal infections (defined as infections that require surgical intervention and extend beyond the hollow viscus into the intraperitoneal space) were randomised and received treatment in two identical randomised, multi-centre, multinational, double-blind studies (RECLAIM 1 and RECLAIM 2) comparing ceftazidime-avibactam (2 g of ceftazidime and 0.5 g of avibactam) administered intravenously over 2 hours every 8 hours plus metronidazole (0.5 g) to meropenem (1 g) administered intravenously over 30 minutes. Treatment duration was 5 to 14 days. The modified intent-to-treat (MITT) population included all patients who met the disease definition of cIAI and

received at least 1 dose of the study drug. The clinically evaluable (CE) population included patients who had an appropriate diagnosis of cIAI and excluded patients with a bacterial species typically not expected to respond to both study drugs (i.e. *Acinetobacter baumannii* or *Stenotrophomonas* spp.) and/or who had an important protocol deviation impacting the assessment of efficacy.

The primary efficacy endpoint was the clinical response at the Test of Cure (TOC) visit in the co-primary populations of the CE and MITT patients in Table 6 below.

Table 6 Clinical cure rate at TOC (RECLAIM MITT and CE analysis sets)

Analysis set	Number (%) of patients		
Response	CAZ-AVI + MTZ	Meropenem	Difference (%) 95% CI
MITT	(N=520)	(N=523)	
Clinical cure	429 (82.5)	444 (84.9)	-2.4 (-6.90, 2.10)
CE	(N=410)	(N=416)	
Clinical cure	376 (91.7)	385 (92.5)	-0.8 (-4.61, 2.89)

Clinical cure rates at TOC by pathogen in the microbiologically Modified Intent to Treat (mMITT) population for Gram-negative aerobes are shown in Table 7 below.

Table 7 Clinical cure rate at TOC by common (combined frequency of ≥10) Gram-negative baseline pathogen (RECLAIM mMITT analysis set)

Pathogen	Number of patients CAZ-AVI + MTZ (N=413)			Meropenem (N=410)		
	Cure rate (%)	Number of clinical cures	N	Cure rate (%)	Number of clinical cures	n
Enterobacterales	81.4	272	334	86.4	305	353
Citrobacter freundii complex	77.8	14	18	75.0	9	12
Enterobacter aerogenes	80.0	4	5	100	5	5
Enterobacter cloacae	84.6	11	13	84.2	16	19
Escherichia coli	80.4	218	271	87.0	248	285
Klebsiella oxytoca	77.8	14	18	80.0	12	15
Klebsiella pneumoniae	78.4	40	51	75.5	37	49
Proteus mirabilis	62.5	5	8	77.8	7	9
Gram-negative other than *Enterobacterales*						
Pseudomonas aeruginosa	85.7	30	35	94.4	34	36

A further 432 adults with complicated intra-abdominal infections were randomised and received treatment in a multi-centre, double-blind study (RECLAIM 3) conducted in 3 Asian countries (China, Republic of Korea and Vietnam). The patient population and key aspects of the study design were identical to RECLAIM apart from the primary efficacy endpoint of clinical response at the TOC visit being solely in the CE population (see Table 8 below).

Table 8 Clinical cure rates at TOC (RECLAIM 3 CE at TOC analysis set)

	Number (%) of patients		
	CAZ-AVI + MTZ	Meropenem	Difference (%) 95% CI
	(N=177)	(N=184)	
Clinical cure	166 (93.8)	173 (94.0)	-0.2 (-5.53, 4.97)

Clinical cure rates at TOC by pathogen in the microbiologically modified Intent to Treat (mMITT) population for Gram-negative aerobes are shown in Table 9 below.

Table 9 Clinical cure rates at TOC by common (combined frequency of ≥7) Gram-negative baseline pathogen (RECLAIM 3 mMITT analysis set)

Pathogen	Number of patients CAZ-AVI + MTZ (N=143) Cure rate (%)	Number of clinical cures	N	Meropenem (N=152) Cure rate (%)	Number of clinical cures	n
Enterobacterales	80.9	93	115	92.7	115	124
Citrobacter freundii complex	62.5	5	8		0	0
Enterobacter cloacae	100	5	5	66.7	2	3
Escherichia coli	83.3	70	84	94.4	84	89
Klebsiella oxytoca	100	5	5	100	5	5
Klebsiella pneumoniae	82.1	23	28	88.6	31	35
Proteus mirabilis	66.7	2	3	100	5	5
Gram-negative other than *Enterobacterales*						
Pseudomonas aeruginosa	82.4	14	17	85.0	17	20

Among patients with baseline bacteraemia who were enrolled in any of the phase 3 cIAI studies (RECLAIM, RECLAIM 3 or REPRISE), clinical cure at TOC in the subset of patients with bacteraemia due to aerobic Gram-negative pathogens was observed in 9/11 (81.8%) patients treated with CAZ-AVI + MTZ and 9/10 (90.0%) patients treated with comparators (meropenem or best-available therapy). The most common Gram-negative baseline pathogens isolated from the blood were *E. coli* and *P. aeruginosa*. A favourable per-pathogen microbiological response at TOC was reported in 9/11 (81.8%) CAZ-AVI and 6/6 (100.0%) comparator-treated patients with *E. coli* bacteraemia; and ¾ (75.0%) CAZ-AVI and 2/2 (100.0%) comparator-treated patients with *P. aeruginosa* bacteraemia.

Complicated urinary tract infections

A total of 1020 adults with documented complicated urinary tract infection (cUTI) (737 with acute pyelonephritis and 283 with cUTI without acute pyelonephritis) were randomised and received treatment in a phase III multicentre, double-blind, comparative study. Treatment was with either ceftazidime-avibactam (2 g/0.5 g) IV over 2 hours every 8 hours or doripenem 0.5 g IV over 60 mins every 8 hours. There was an optional switch to oral therapy for patients who had clinical improvement as defined in the study protocol after a minimum of 5 days IV treatment. Total duration of antibiotic therapy (IV plus oral) was 10 days (optionally up to 14 if bacteraemic). The mMITT population included all patients with a confirmed cUTI diagnosis, received at least 1 dose of study treatment and had a study-qualifying pre-treatment urine culture containing 10^5 CFU/mL of a Gram-negative pathogen and no more than 2 species of microorganisms. Any patient with a Gram-positive pathogen, or a bacterial species not expected to respond to both study drugs was excluded.

The primary efficacy endpoint was per-patient microbiological response at the TOC visit in the mMITT analysis set.

Table 10 Favourable per-patient microbiological response rate at TOC (RECAPTURE mMITT analysis set)

		CAZ-AVI (N=393)	Doripenem (N=417)	Difference (%) (95% CI)
Per patient microbiological response	Favourable	304 (77.4)	296 (71.0)	6.4 (0.33, 12.36)

Favourable microbiological response rates at TOC by pathogen in the mMITT population are shown in Table 11 below.

Table 11 Favourable per-pathogen microbiological response rate at TOC by common (combined frequency of ≥10) baseline pathogen (RECAPTURE mMITT)

	Number of patients					
	CAZ-AVI (N=393)			Doripenem (N=417)		
Pathogen	**Favourable response rate (%)**	**Number of favourable responses**	**N**	**Favourable response rate (%)**	**Number of favourable responses**	**n**
Enterobacterales	78.3	299	382	70.6	281	398
Enterobacter cloacae	54.5	6	11	69.2	9	13
Escherichia coli	78.4	229	292	71.9	220	306
Klebsiella pneumoniae	75.0	33	44	62.5	35	56
Proteus mirabilis	94.1	16	17	69.2	9	13
Gram-negative other than *Enterobacterales*						
Pseudomonas aeruginosa	66.7	12	18	75.0	15	20

Among patients with baseline bacteraemia who were enrolled in any of the phase 3 cUTI studies (RECAPTURE or REPRISE), clinical cure at TOC in the subset of patients with bacteraemia due to aerobic Gram-negative pathogens was observed in 28/28 (100.0%) patients treated with CAZ-AVI and 25/29 (86.2%) patients treated with comparators (doripenem or best-available therapy). For the endpoint of per-patient microbiological response at TOC, a favourable response at TOC was reported in 26/28 (92.9%) patients treated with CAZ-AVI and 20/29 (69.0%) patients treated with comparator. The most commonly isolated pathogen was *E. coli.* A total of 21/23 (91.3%) patients in the CAZ-AVI group and 19/23 (82.6%) in the comparator group had a favourable per-pathogen microbiological response for *E. coli*, which was the most common pathogen.

Hospital-acquired pneumonia

A total of 808 adults with nosocomial pneumonia (35% with VAP) were randomised and received treatment in a phase III double-blind, comparative study of ceftazidime-avibactam (2 g/0.5 g) IV over 2 hours every 8 hours or meropenem 1 g IV over 30 mins every 8 hours. Treatment duration was 7 to 14 days. The clinically modified intent to treat (cMITT) population included patients who met the minimum disease criteria, received at least 1 dose of study treatment and who had properly obtained baseline respiratory or blood cultures demonstrating Gram-negative pathogens excluding patients with monomicrobial Gram-negative infections with species not expected to respond to both study drugs (e.g., *Acinetobacter* species or *Stenotrophomonas* species). The cMITT also included patients in whom no etiologic pathogens were identified from respiratory or blood cultures at baseline. The CE at TOC analyses set was the clinically evaluable subset of the cMITT.

The primary efficacy endpoint was the clinical response at the TOC visit in the co-primary populations of the cMITT and CE at TOC. See Table 12 below.

Table 12 Clinical cure rates at TOC (REPROVE cMITT and CE at TOC analysis sets)

		Number (%) of patients		
Analysis set	**Response**	**CAZ-AVI**	**Meropenem**	**Difference (%) 95% CI**
cMITT		(N=356)	(N=370)	
	Clinical cure	245 (68.8)	270 (73.0)	-4.2 (-10.76, 2.46)
CE at TOC		(N=257)	(N=270)	
	Clinical cure	199 (77.4)	211 (78.1)	-0.7 (-7.86, 6.39)

All-cause mortality rates at Day 28 (cMITT) was 8.4% (30/356) and 7.3% (27/370) ceftazidime-avibactam and meropenem treated patients, respectively.

Clinical cure rate and favourable microbiological response rate at TOC by pathogen in mMITT for Gram-negative aerobes are shown in Tables 13 and 14.

Table 13 Clinical cure rate at TOC by common (combined frequency of ≥10) Gram-negative baseline pathogen (REPROVE mMITT)

	Number of patients					
	CAZ-AVI (N=171)			Meropenem (N=184)		
Pathogen	**Cure rate (%)**	**Number of clinical cures**	**N**	**Cure rate (%)**	**Number of clinical cures**	**n**
Enterobacterales	73.6	89	121	75.4	104	138
Enterobacter aerogenes	62.5	5	8	50.0	4	8
Enterobacter cloacae	92.3	24	26	54.5	12	22
Escherichia coli	64.7	11	17	75.0	15	20
Klebsiella pneumoniae	72.9	43	59	77.5	55	71
Proteus mirabilis	85.7	12	14	75.0	9	12
Serratia marcescens	73.3	11	15	92.3	12	13
Gram-negative other than *Enterobacterales*						
Pseudomonas aeruginosa	60.3	35	58	74.5	35	47
Haemophilus influenzae	81.3	13	16	80.0	20	25

Table 14 Per-pathogen microbiological response at TOC by common (combined frequency of ≥10) Gram-negative baseline pathogen (REPROVE mMITT)

	Number of patients					
	CAZ-AVI (N=171)			Meropenem (N=184)		
Pathogen	**Favourable response rate (%)**	**Number of favourable responses**	**N**	**Favourable response rate (%)**	**Number of favourable responses**	**n**
Enterobacterales						
Enterobacter aerogenes	62.5	5	8	62.5	5	8
Enterobacter cloacae	80.8	21	26	59.1	13	22
Escherichia coli	76.5	13	17	80.0	16	20
Klebsiella pneumoniae	62.7	37	59	74.6	53	71
Proteus mirabilis	78.6	11	14	66.7	8	12
Serratia marcescens	66.7	10	15	61.5	8	13
Gram-negative other than *Enterobacterales*						
Pseudomonas aeruginosa	37.9	22	58	38.3	18	47
Haemophilus influenzae	87.5	14	16	92.0	23	25

For HAP/VAP patients enrolled with baseline bacteraemia, clinical cure at TOC in the subset of patients with bacteraemia due to aerobic Gram-negative pathogens was observed in 10/15 (66.7%) patients treated with CAZ-AVI and 5/8 (62.5%) patients treated with meropenem.

Although patient numbers were small for any given pathogen, favourable per-pathogen microbiological response rates in this sub-group were broadly similar to those of the overall population.

Among patients enrolled with baseline bacteraemia in the Phase 3 program across all indications combined (cIAI, cUTI or HAP/VAP), clinical cure at TOC in the subset of patients with bacteraemia due to aerobic Gram-negative pathogens was observed in 47/54 (87.0%) patients treated with CAZ-AVI ± MTZ and 39/47 (83.0%) patients treated with comparators. For the two most commonly occurring pathogens in this sub-group, a favourable per-pathogen microbiological response at TOC was reported in 32/37 (86.5%) CAZ-AVI ± MTZ and 29/33 (87.9%) comparator-treated patients with *E. coli* bacteraemia; and 6/11 (54.5%) CAZ-AVI ± MTZ and 3/6 (50.0%) comparator-treated patients with *P. aeruginosa* bacteraemia.

Paediatric population

From birth to less than 3 months of age

Ceftazidime-avibactam has been evaluated in paediatric patients from birth to less than 3 months of age in a Phase 2a, 2-part, open-label, non-randomised clinical study in patients with suspected or confirmed infections due to Gram-negative pathogens. Part A used a single dose to assess the pharmacokinetic (PK) profile and evaluate safety and tolerability of ceftazidime/avibactam. Part B used multiple doses to evaluate the safety and tolerability, PK profile, and efficacy. Clinical cure or clinical improvement rate in Part B were 81.0% (17/21) at TOC (ITT) and 75.0% (12/16) at TOC (modified-ITT). The microbiological eradication or presumed eradication rate at TOC (micro-ITT) was 80% (8/10).

3 months of age and older

Ceftazidime-avibactam has been evaluated in paediatric patients aged 3 months to <18 years in two Phase 2 single-blind, randomised, comparative clinical studies, one in patients with cIAI and one in patients with cUTI (Doses provided in Table 2). Patients aged ≥3 months to <1 year must have been born at term (defined as gestational age ≥37 weeks). Patients treated with ceftazidime-avibactam in the cIAI trial also received metronidazole (administered per local label; suggested dose: 10 mg/kg every 8 hours, administered IV over 20 to 30 minutes). The primary objective in each study was to assess safety and tolerability of ceftazidime-avibactam (+/- metronidazole). Secondary objectives included assessment of PK and efficacy; efficacy was a descriptive endpoint in both studies.

cIAI

A total of 83 paediatric patients (≥3 months) with cIAI were randomised (3:1) and received treatment with either ceftazidime-avibactam plus metronidazole (n=61) (doses provided in Table 2), or meropenem (n=22), 20 mg/kg IV every 8 hours. The paediatric age groups who received CAZ-AVI plus metronidazole were as follows: 12 to <18 years (n=22), 6 to <12 years (n=33), 3 to <6 years (n=6). No patients less than 2 years of age received CAZ-AVI plus metronidazole. After a minimum of 72 hours of IV treatment, there was an optional switch to oral therapy for patients who had clinical improvement, as defined in the study protocol. The total duration of antibiotic therapy (IV plus oral) was between 7 and 15 days. TOC assessments were performed 8 to 15 days after the last dose of study drug (IV or oral).

The majority of patients (87%) had appendiceal perforation or peri-appendiceal abscess (52/61, 85.2% ceftazidime-avibactam plus metronidazole; 20/22, 90.9% meropenem). The CE population included patients who had a confirmed diagnosis of cIAI and received a

minimum duration of IV study drug, and excluded patients who had a clinical response of indeterminate and/or an important protocol deviation impacting the assessment of efficacy. The microbiological intent-to treat (micro-ITT) population included 69 patients (50 ceftazidime-avibactam plus metronidazole, 19 meropenem) who had at least one baseline intra-abdominal pathogen. Favourable clinical response rates at TOC are presented in Table 15.

Table 15 Favourable clinical response rates at TOC

Analysis Population	Number (%) of patients CAZ-AVI + MTZ[a] n/N (%)	Meropenem[b] n/N (%)
ITT	56/61 (91.8)	21/22 (95.5)
CE	52/56 (92.9)	19/20 (95.0)
Micro-ITT	45/50 (90.0)	18/19 (94.7)
ME	36/40 (90.0)	14/15 (93.3)

Favourable clinical outcome (for which the count is indicated by n) was defined as clinical cure, sustained clinical cure, or clinical improvement, such that no further antimicrobial therapy was required.
CE = clinically evaluable.
ITT = intent-to-treat; the ITT analysis set included all patients who were randomised to treatment.
ME = microbiologically evaluable analysis; the ME analysis set included randomised patients with confirmed cIAI who received a minimum duration of study drug, had a microbiological response other than indeterminate, had no protocol deviations that would impact assessment of efficacy and had a typically IAI bacterial pathogen susceptible to both study agents.
[a] CAZ-AVI doses as per Table 2 + metronidazole 10 mg/kg IV every 8 hours.
[b] 20 mg/kg IV every 8 hours.

The predominant pathogens isolated at baseline were *E. coli* (55/69, 79.7%) and *P. aeruginosa* 23/69 (33.3%). Favourable clinical response rates at TOC by baseline pathogen in the micro-ITT population are presented in Table 16.

Table 16 Favourable clinical response rates at TOC by baseline pathogen, paediatric cIAI (micro-ITT population)

Pathogen	Number (%) of patients CAZ-AVI + MTZ[a] n/N (%)	Meropenem[b] n/N (%)
Enterobacterales	38/42 (90.5)	13/14 (92.9)
E. coli	38/42 (90.5)	12/13 (92.3)
Pseudomonas aeruginosa	12/14 (85.7)	8/9 (88.9)

[a] CAZ-AVI doses as per Table 2 + metronidazole 10 mg/kg IV every 8 hours.
[b] 20 mg/kg IV every 8 hours.

cUTI

A total of 95 paediatric patients (≥3 months) with cUTI were randomised (3:1) and received treatment with either ceftazidime-avibactam (n=67) (doses provided in Table 2), or cefepime (n=28), dosed per local prescribing information (maximum dose 2 g). The paediatric age groups who received CAZ-AVI were as follows: 12 to <18 years (n=13), 6 to <12 years (n=17), 2 to <6 years (n=11), 1 to <2 years (n=12), and 3 months to <1 year of age (n=14). After a minimum of 72 hours of IV treatment, there was an optional switch to oral therapy for patients who had clinical improvement, as defined in the study protocol. The total duration of antibiotic therapy (IV plus oral) was between 7 and 14 days. TOC assessments were performed 8 to 15 days after the last dose of study drug (IV or oral).

The majority of patients (83.2%) had acute pyelonephritis (55/67, 82.1% ceftazidime-avibactam; 24/28, 85.7% cefepime). The micro-ITT population included 77 randomised patients (54 ceftazidime-avibactam, 23 cefepime) who had at least 1 Gram-negative typical pathogen known to cause cUTI and no Gram-positive pathogen in the urine at baseline. Favourable clinical, microbiological and combined clinical and microbiological response rates at TOC in the micro-ITT population are presented in Table 17.

Table 17 Favourable clinical and microbiological response rates, paediatric cUTI trial, micro-ITT population

Study Endpoint	Ceftazidime-avibactam[a] n/N (%)	Cefepime[b] n/N (%)
Combined favourable clinical and microbiological response	39/54 (72.2)	14/23 (60.9)
Favourable clinical response	48/54 (88.9)	19/23 (82.6)
Favourable microbiological response	43/54 (79.6)	14/23 (60.9)

[a] Ceftazidime- avibactam doses as per Table 2.
[b] Dosed per local prescribing information, with maximum of 2 g.
Favourable clinical response was defined as a resolution of all acute signs and symptoms of cUTI or improvement to such an extent that no further antimicrobial therapy was required. Favourable microbiological response was defined as eradication of the baseline pathogen.

The predominant baseline pathogen was *E. coli* (71/77, 92.2%). Favourable microbiological response rates by baseline pathogen at TOC in the micro-ITT population are presented in Table 18.

Table 18 Microbiological response rates by baseline pathogen at TOC in the paediatric cUTI trial, micro-ITT population

Aerobic Gram-negative pathogen	Ceftazidime-avibactam[a] n/N (%)	Cefepime[b] n/N (%)
Enterobacterales	43/54 (79.6)	14/23 (60.9)
Escherichia coli	39/49 (79.6)	13/22 (59.1)

[a] Ceftazidime- avibactam doses as per Table 2.
[b] Dosed per local prescribing information, with maximum of 2 g.

5.2 Pharmacokinetic properties

Distribution

The human protein binding of both ceftazidime and avibactam is low, approximately 10% and 8%, respectively. The steady-state volumes of distribution of ceftazidime and avibactam were comparable, about 17 L and 22 L, respectively in healthy adults following multiple doses of 2 g/0.5 g ceftazidime-avibactam infused over 2 hours every 8 hours. Pharmacokinetic parameters of ceftazidime and avibactam following single and multiple dose administration of CAZ-AVI were similar to those determined when ceftazidime or avibactam were administered alone. Both ceftazidime and avibactam penetrate into human bronchial epithelial lining fluid (ELF) to the same extent with concentrations around 30% that of plasma, and a similar concentration time profile between ELF and plasma.

Ceftazidime and avibactam plasma exposure were comparable across patients with different indications, cIAI, cUTI and NP.

Penetration of ceftazidime into the intact blood-brain barrier is poor, resulting in low levels of ceftazidime in the CSF in the absence of inflammation. However, concentrations of 4 to

20 mg/L or more are achieved in the CSF when the meninges are inflamed. Avibactam penetration of the blood brain barrier has not been studied clinically, however, in rabbits with inflamed meninges, CSF exposures of ceftazidime and avibactam were 43% and 38% of plasma AUC, respectively. For ceftazidime, concentrations in excess of the MIC for common pathogens can be achieved in tissues such as bone, heart, bile, sputum, aqueous humour, synovial, pleural and peritoneal fluids. Ceftazidime crosses the placenta readily, and is excreted in the breast milk. Avibactam penetrates into the subcutaneous tissue at the site of skin infections, with tissue concentrations approximately equal to free drug concentrations in plasma.

Biotransformation
Ceftazidime is not metabolised. 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-life (t½) of both ceftazidime and avibactam is about 2 h after IV administration. Ceftazidime is excreted unchanged into the urine by glomerular filtration; approximately 80 - 90% of the dose is recovered in the urine within 24 h. 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; approximately 97% of the dose is recovered in the urine, 95% within 12 h. Less than 1% of ceftazidime is excreted via the bile and less than 0.25% of avibactam is excreted into faeces.

Linearity/non-linearity
The pharmacokinetics of both ceftazidime and avibactam are approximately linear across the dose range studied (0.05 g to 2 g) for a single IV administration. No appreciable accumulation of ceftazidime or avibactam was observed following multiple IV infusions of 2 g/0.5 g of ceftazidime-avibactam administered every 8 hours for up to 11 days in healthy adults with normal renal function.

Special populations

Patients with renal impairment
Elimination of ceftazidime and avibactam is decreased in patients with moderate or severe renal impairment, and end stage renal disease including patients undergoing haemodialysis; the dose should be reduced in patients with CrCl ≤50 mL/min) (see section 4.2).

Patients with hepatic impairment
Mild to moderate hepatic impairment had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g IV every 8 hours for 5 days, provided renal function was not impaired. The pharmacokinetics of ceftazidime in patients with severe hepatic impairment has not been established. The pharmacokinetics of avibactam in patients with any degree of hepatic impairment has not been studied.

As ceftazidime and avibactam do not appear to undergo significant hepatic metabolism, the systemic clearance of either drug is not expected to be significantly altered by hepatic impairment. Therefore, no dosage adjustment of ceftazidime-avibactam is recommended for patients with hepatic impairment (see section 4.2).

Elderly patients
The reduced clearance observed in elderly patients was primarily due to age-related decrease in renal clearance of ceftazidime. The mean elimination half-life ranged from 3.5 to 4 hours following single or 7 days repeated every 12 hours dosing of 2 g IV bolus injections in elderly patients 80 years or older.

Following single dose IV administration of 0.5 g avibactam as a 30-minute IV infusion, the elderly had a slower terminal half-life of avibactam, which may be attributed to age related decrease in renal clearance. Dosage adjustment for ceftazidime-avibactam is not required in elderly subjects (≥65 years of age) with CrCl >50 mL/min.

Paediatric patients
The pharmacokinetics of ceftazidime and avibactam were evaluated in paediatric patients from 3 months to <18 years of age with suspected or confirmed infections following a single dose of ceftazidime 50 mg/kg and avibactam 12.5 mg/kg for patients weighing <40 kg or Zavicefta 2 g/0.5 g (ceftazidime 2 grams and avibactam 0.5 grams) for patients weighing ≥40 kg. Plasma concentrations of ceftazidime and avibactam were similar across all four age cohorts in the study (3 months to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <18 years). Ceftazidime and avibactam AUC_{0-t} and C_{max} values in the two older cohorts (children from 6 to <18 years), which had more extensive pharmacokinetic sampling, were similar to those observed in healthy adult subjects with normal renal function that received Zavicefta 2 g/0.5 g. Data from this study and the two Phase 2 paediatric studies in patients with cIAI and cUTI were pooled with PK data from adults (Phase 1 to Phase 3) to update the population PK model, which was used to conduct simulations to assess PK/PD target attainment. Results from these simulations demonstrated that the recommended dose regimens for paediatric patients with cIAI, cUTI and HAP/VAP, including dose adjustments for patients with renal impairment, result in systemic exposure and PK/PD target attainment values that are similar to those in adults at the approved Zavicefta dose of 2 g/0.5 g administered over 2 hours, every 8 hours.

There is limited experience with the use of ceftazidime plus avibactam in the paediatric groups of 3 months to <6 years. The recommended dosing regimens are based on simulations conducted using the final population PK models. Simulations demonstrated that the recommended dose regimens result in comparable exposures to other age groups with PK/PD target attainment >90%. Based on data from the completed paediatric clinical trials, at the recommended dose regimens, there was no evidence of over or under exposure in the subjects aged 3 months to <6 years.

In addition, there is very limited data in paediatric patients aged 3 months to <2 years with impaired renal function (CrCl ≤50 mL/min/1.73 m^2), with no data in severe renal impairment from the completed paediatric clinical trials. Population PK models for ceftazidime and avibactam were used to conduct simulations for patients with impaired renal function.

The pharmacokinetics of ceftazidime and avibactam were evaluated in 45 paediatric patients from birth to less than 3 months of age with suspected or confirmed infections following single and multiple doses of ceftazidime 20 mg/kg and avibactam 5 mg/kg for patients from birth to 28 days (including preterm neonates) or ceftazidime 30 mg/kg and avibactam 7.5 mg/kg for patients one month to less than 3 months. Plasma concentrations of ceftazidime and avibactam were similar across all age cohorts. Data from this study was used to update the previous population PK model and perform simulations to assess PK/PD target

attainment. Results from these simulations demonstrated that the recommended dose regimens for term (GA ≥37 weeks) and preterm neonates (GA >26 weeks to <37 weeks) is 20 mg/kg ceftazidime and 5 mg/kg avibactam q8h as a 2-hour infusion, and for infants age >28 days to <3 months is 30 mg/kg ceftazidime and 7.5 mg/kg avibactam q8h as a 2-hour infusion, result in systemic exposures and PK/PD target attainment values that are similar to those in adults.

Gender
The pharmacokinetics of ceftazidime-avibactam was similar between males and females. No dose adjustment is required based on sex.

Race
Based on a population pharmacokinetic analysis, no dose adjustment of ceftazidime-avibactam is required based on race.

5.3 Preclinical safety data

Genetic toxicology

For ceftazidime a mouse Micronucleus test and an Ames test were both negative for mutagenic effects. Carcinogenicity studies have not been conducted. In genotoxicity assays with avibactam, there was no induction of gene mutation in the *in vitro* bacterial reverse mutation tests, nor were there any indications of genotoxicity in an *in vitro* unscheduled DNA synthesis test in rat liver cells or an *in vitro* micronucleus test in mouse lymphoma cells. In cultured human lymphocytes, statistically significant increases in chromosomal aberrations were observed under a single treatment condition (44h harvest time, -S9). As these findings were not replicated in an independent study, the results are considered to be of limited biological relevance. When administered up to the limit dose of 2 g/kg IV, avibactam was negative in a rat *in vivo* micronucleus assay. Carcinogenicity studies have not been conducted. No genetic toxicology studies have been conducted on ceftazidime-avibactam.

Reproductive toxicology

Reproduction studies have been performed with ceftazidime in mice and rats at doses up to 40 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus. A slightly increased post-implantation loss was observed at avibactam dose of 1000 mg/kg/day and lower mean fetal weight with slightly retarded ossification of a small number of bones was observed at avibactam doses of 300 mg/kg/day and above in pregnant rabbits. 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 1.5 times human therapeutic exposures. No reproductive toxicology studies have been conducted on ceftazidime-avibactam.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate (anhydrous)

6.2 Incompatibilities

The compatibility of Zavicefta with other medicines has not been established. Zavicefta should not be mixed with or physically added to solutions containing other medicinal products except diluents mentioned in section 6.6.

6.3 Shelf life

Dry powder

3 years

Storage conditions: Do not store above 30°C, protect from light.

After reconstitution

The reconstituted vial should be used immediately.

After dilution

Infusion bags:
If the intravenous solution is prepared with diluents listed in section 6.6 (ceftazidime concentration 8 mg/mL), the chemical and physical in-use stability has been demonstrated (from initial vial puncture) for up to 12 hours at 2-8°C, followed by up to 4 hours at room temperature.

If the intravenous solution is prepared with diluents listed in section 6.6 (ceftazidime concentration >8 mg/mL to 40 mg/mL), the chemical and physical in-use stability has been demonstrated (from initial vial puncture) for up to 4 hours at room temperature.

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 above.

Infusion syringes:
If the intravenous solution is prepared with diluents listed in section 6.6 (ceftazidime concentration ≥8 mg/mL to 40 mg/mL), the chemical and physical in-use stability has been demonstrated (from initial vial puncture) for up to 6 hours at room temperature 15-25°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 6 hours at room temperature 15-25°C.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

20 mL glass vial (type 1) closed with a rubber (Bromobutyl) 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. The reconstituted solution must be used to prepare the final infusion solution within 30 minutes from initial vial puncture. The reconstituted solution is a pale yellow solution that is free of any particles.

Zavicefta (ceftazidime/avibactam) is a combination product; each vial contains 2 g of ceftazidime and 0.5 g of avibactam in a fixed 4:1 ratio. Dosage recommendations are based on the ceftazidime component only.

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

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

Each vial is for single use only.

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

<u>Instructions for preparing adult and paediatric doses in INFUSION BAG or INFUSION SYRINGE</u>

NOTE: The following procedure describes the steps to prepare an infusion solution with a final concentration of 8-40 mg/mL of ceftazidime. All calculations should be completed prior to initiating these steps.

- For **paediatric patients 3 to 12 months of age**, detailed steps to prepare a 20 mg/mL concentration (sufficient for most scenarios) are provided below.
- For **paediatric patients from birth (including preterm) to <3 months of age**, detailed steps to prepare a **10 mg/mL concentration** (sufficient for most scenarios) are provided below.

1. Prepare the **reconstituted solution** (**167.3 mg/mL** of ceftazidime):
    a) Insert the syringe needle through the vial closure and inject 10 mL of sterile water for injections.

b) Withdraw the needle and shake the vial to give a clear solution.
c) Insert a gas relief needle through the vial closure **after** the product has dissolved to relieve the internal pressure (this is important to preserve product sterility).

2. Prepare the **final solution** for infusion (final concentration must be **8-40 mg/mL** of ceftazidime):
    a) 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 9 mg/mL (0.9%) solution for injection, dextrose 50 mg/mL (5%) solution for injection, or Lactated Ringer's solution.
    b) Infusion syringe: Further dilute the reconstituted solution by transferring an appropriately calculated volume of the reconstituted solution combined with a sufficient volume of diluent (sodium chloride 9 mg/mL (0.9%) solution for injection or dextrose 50 mg/mL (5%) solution for injection) to an infusion syringe.

Refer to Table 19 below.

Table 19 Preparation of Zavicefta for adult and paediatric doses in INFUSION BAG or in INFUSION SYRINGE

Zavicefta dose (ceftazidime)[a]	**Volume to withdraw from reconstituted vial**	**Final volume after dilution in infusion bag[b]**	**Final volume in infusion syringe[3]**
2 g	Entire contents (approximately 12 mL)	50 mL to 250 mL	50 mL
1 g	6 mL	25 mL to 125 mL	25 mL to 50 mL
0.75 g	4.5 mL	19 mL to 93 mL	19 mL to 50 mL
All other doses	Volume (mL) calculated based on dose required: **Dose (mg ceftazidime) ÷ 167.3 mg/mL ceftazidime**	Volume (mL) will vary based on infusion bag size availability and preferred final concentration (must be 8-40 mg/mL of ceftazidime)	Volume (mL) will vary based on infusion syringe size availability and preferred final concentration (must be 8-40 mg/mL of ceftazidime)

[a] Based on ceftazidime component only.
[b] Dilute to final ceftazidime concentration of 8 mg/mL for in-use stability up to 12 hours at 2-8°C, followed by up to 4 hours at room temperature (i.e. dilute 2 g dose of ceftazidime in 250 mL, 1 g dose of ceftazidime in 125 mL, 0.75 g dose of ceftazidime in 93 mL, etc.). All other ceftazidime concentrations (>8 mg/mL to 40 mg/mL) have in-use stability up to 4 hours at room temperature.
[3] Dilute to final ceftazidime concentration ≥8 mg/mL to 40 mg/mL for in-use stability up to 6 hours at room temperature 15-25°C.

Paediatric patients 3 to 12 months of age

NOTE: The following procedure describes the steps to prepare an infusion solution with a final concentration of 20 mg/mL of ceftazidime (sufficient for most scenarios). Alternative concentrations may be prepared, but must have a final concentration range of 8-40 mg/mL of ceftazidime.

1. Prepare the **reconstituted solution (167.3 mg/mL** of ceftazidime):
    a) Insert the syringe needle through the vial closure and inject 10 mL of sterile water for injections.
    b) Withdraw the needle and shake the vial to give a clear solution.
    c) Insert a gas relief needle through the vial closure **after** the product has dissolved to relieve the internal pressure (this is important to preserve product sterility).

2. Prepare the **final solution** for infusion to a final concentration of **20 mg/mL** of ceftazidime:
    a) Further dilute the reconstituted solution by transferring an appropriately calculated volume of the reconstituted solution combined with a sufficient volume of diluent (sodium chloride 9 mg/mL (0.9%) solution for injection or dextrose 50 mg/mL (5%) solution for injection) to an infusion syringe.
    b) Refer to Table 20, 21 and 22 below to confirm the calculations. Values shown are approximate as it may be necessary to round to the nearest graduation mark of an appropriately sized syringe. Note that the tables are NOT inclusive of all possible calculated doses but may be utilised to estimate the approximate volume to verify the calculation.

Table 20 Preparation of Zavicefta (final concentration of 20 mg/mL of ceftazidime) in paediatric patients 3 to 12 months of age with creatinine clearance (CrCl) >50 mL/min/1.73 m^2

Age and Zavicefta dose (mg/kg)[a]	Weight (kg)	Dose (mg ceftazidime)	Volume of reconstituted solution to be withdrawn from vial (mL)	Volume of diluent to add for mixing (mL)
6 months to 12 months **50 mg/kg of ceftazidime**	5	250	1.5	11
	6	300	1.8	13
	7	350	2.1	15
	8	400	2.4	18
	9	450	2.7	20
	10	500	3	22
	11	550	3.3	24
	12	600	3.6	27
3 months to <6 months **40 mg/kg of ceftazidime**	4	160	1	7.4
	5	200	1.2	8.8
	6	240	1.4	10
	7	280	1.7	13
	8	320	1.9	14
	9	360	2.2	16
	10	400	2.4	18

[a] Based on ceftazidime component only.

Table 21 Preparation of Zavicefta (final concentration of 20 mg/mL of ceftazidime) in paediatric patients 3 to 12 months of age with creatinine clearance (CrCl) 31-50 mL/min/1.73 m^2

Age and Zavicefta dose (mg/kg)[a]	Weight (kg)	Dose (mg ceftazidime)	Volume of reconstituted solution to be withdrawn from vial (mL)	Volume of diluent to add for mixing (mL)
6 months to 12 months **25 mg/kg of ceftazidime**	5	125	0.75	5.5
	6	150	0.9	6.6
	7	175	1	7.4
	8	200	1.2	8.8
	9	225	1.3	9.6
	10	250	1.5	11
	11	275	1.6	12
	12	300	1.8	13

Age and Zavicefta dose (mg/kg)[a]	Weight (kg)	Dose (mg ceftazidime)	Volume of reconstituted solution to be withdrawn from vial (mL)	Volume of diluent to add for mixing (mL)
3 months to <6 months **20 mg/kg of ceftazidime**	4	80	0.48	3.5
	5	100	0.6	4.4
	6	120	0.72	5.3
	7	140	0.84	6.2
	8	160	1	7.4
	9	180	1.1	8.1
	10	200	1.2	8.8

[a] Based on ceftazidime component only.

Table 22 Preparation of Zavicefta (final concentration of 20 mg/mL of ceftazidime) in paediatric patients 3 to 12 months of age with creatinine clearance (CrCl) 16-30 mL/min/1.73 m^2

Age and Zavicefta dose (mg/kg)[a]	Weight (kg)	Dose (mg ceftazidime)	Volume of reconstituted solution to be withdrawn from vial (mL)	Volume of diluent to add for mixing (mL)
6 months to 12 months **18.75 mg/kg of ceftazidime**	5	93.75	0.56	4.1
	6	112.5	0.67	4.9
	7	131.25	0.78	5.7
	8	150	0.9	6.6
	9	168.75	1	7.4
	10	187.5	1.1	8.1
	11	206.25	1.2	8.8
	12	225	1.3	9.6
3 months to <6 months **15 mg/kg of ceftazidime**	4	60	0.36	2.7
	5	75	0.45	3.3
	6	90	0.54	4
	7	105	0.63	4.6
	8	120	0.72	5.3
	9	135	0.81	6
	10	150	0.9	6.6

[a] Based on ceftazidime component only.

<u>Paediatric patients from birth (including preterm) to <3 months of age</u>

NOTE: The following procedure describes the steps to prepare a stock infusion solution with a final concentration of 10 mg/mL of ceftazidime appropriate for administering doses under 250 mg to paediatric patients from birth (including preterm) to <3 months of age. Alternative concentrations may be prepared, but must have a final concentration range of 8-40 mg/mL of ceftazidime.

1. Prepare the **reconstituted solution** (**167.3 mg/mL** of ceftazidime):
    a) Insert the syringe needle through the vial closure and inject 10 mL of sterile water for injections.
    b) Withdraw the needle and shake the vial to give a clear solution.
    c) Insert a gas relief needle through the vial closure **after** the product has dissolved to relieve the internal pressure (this is important to preserve product sterility).

2. Prepare the **final stock solution** for infusion to a final concentration of **10 mg/mL** of ceftazidime:
    a) Further dilute the reconstituted solution by transferring 3 mL of the reconstituted solution to an infusion bag or a syringe containing 47 mL of diluent (sodium chloride 9 mg/mL (0.9%) solution for injection or dextrose 50 mg/mL (5%) solution for injection) to provide a final volume of 50 mL.
    b) Mix thoroughly (e.g. gently invert the infusion bag or using a syringe connector gently pass the solution back and forth at least 5 times between 2 syringes).
    c) Transfer an appropriate volume of the **10 mg/mL** of ceftazidime stock solution to an infusion syringe. Refer to Table 23 below for the volume of the stock solution to transfer to the infusion syringe to be administered. Values shown are approximate as it may be necessary to round to the nearest graduation mark of an appropriately sized syringe. Note that the tables are NOT inclusive of all possible calculated doses but may be utilised to estimate the approximate volume to verify the calculation.

Table 23 Zavicefta dosing in paediatric patients from birth (including preterm) to <3 months of age using a 50 mL stock solution of Zavicefta (final concentration of 10 mg/mL of ceftazidime) prepared with 3 mL reconstituted solution withdrawn from the vial and added to 47 mL diluent

Age and Zavicefta dose (mg/kg)[a]	**Weight (kg)**	**Dose (mg ceftazidime)**	**Volume of 10 mg/mL (ceftazidime) stock solution to be administered (mL)**
Full term infants (gestation ≥37 weeks) from >28 days to <3 months OR Preterm infants from >44 weeks to <53 weeks PMA **30 mg/kg of ceftazidime**	3	90	9
	3.5	105	10.5
	4	120	12
	4.5	135	13.5
	5	150	15
	5.5	165	16.5
	6	180	18
	6.5	195	19.5
	7	210	21
	7.5	225	22.5
	8	240	24
Full term neonates (gestation ≥37 weeks) from birth to ≤28 days OR Preterm neonates and infants from 31 to ≤44 weeks PMA **20 mg/kg of ceftazidime**	0.8	16	1.6
	1	20	2
	1.2	24	2.4
	1.4	28	2.8
	1.6	32	3.2
	1.8	36	3.6
	2	40	4
	2.2	44	4.4
	2.4	48	4.8
	2.6	52	5.2
	2.8	56	5.6
	3	60	6
	3.5	70	7
	4	80	8
	4.5	90	9

Age and Zavicefta dose (mg/kg)[a]	Weight (kg)	Dose (mg ceftazidime)	Volume of 10 mg/mL (ceftazidime) stock solution to be administered (mL)
	5	100	10
	5.5	110	11
	6	120	12

[a] Based on ceftazidime component only.

7. PRODUCT OWNER

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