1. NAME OF THE MEDICINAL PRODUCT

Zavicefta (Ceftazidime 2 g/Avibactam 0.5 g) powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ceftazidime (as pentahydrate) equivalent to 2000 mg ceftazidime and avibactam (as sodium salt) equivalent to 500 mg avibactam.

After reconstitution, 1 mL of solution contains 167.3 mg of ceftazidime (CAZ) and 41.8 mg of avibactam (AVI).

Ceftazidime (as pentahydrate) is a white to almost white crystalline powder. It is soluble in acid, alkali and dimethyl sulphoxide and slightly soluble in water, methanol and dimethylformamide.

Avibactam (as sodium) is a crystalline powder. It is freely soluble in water, relatively soluble in methanol and insoluble in ethanol.

Excipients with known effect

Each vial contains approximately 6.44 mmol of sodium (approximately 148 mg).

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

Zavicefta is a white to yellow sterile powder.

The reconstituted solution is a clear and colourless to yellow solution free from visible particulate matter.

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 Special warnings and precautions for use and 5.1 Pharmacodynamic properties):

- Complicated intra-abdominal infection (cIAI), in combination with metronidazole.
- Complicated urinary tract infection (cUTI), including pyelonephritis.

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

- 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, any of the infections listed above.

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zavicefta and other antibiotics, Zavicefta should be used in combination with an antibacterial agent(s) active against Gram-positive and/or anaerobic pathogens when these are known or suspected to be contributing to the infectious process.

4.2 Posology and method of administration

Posology

Dosage in Adults with Creatinine Clearance (CrCL > 50 mL/min)

Table 1 shows the recommended intravenous dose for adults with estimated creatinine clearance (CrCL) > 50 mL/min (see sections 4.4 Special Warnings and Precautions for Use and 5.1 Pharmacodynamic Properties).

Table 1 Recommended dose for adults with estimated CrCL > 50 mL/min[1]

Type of infection	Dose of ceftazidime/avibactam	Frequency	Infusion time	Duration of treatment
cIAI[2,3]	2 g/0.5 g	Every 8 hours	2 hours	5-14 days
cUTI, including pyelonephritis[3]	2 g/0.5 g	Every 8 hours	2 hours	5-10 days[4]
HAP/VAP[3]	2 g/0.5 g	Every 8 hours	2 hours	7-14 days
Bacteraemia associated with, or suspected to be associated with any of the above infections	2 g/0.5 g	Every 8 hours	2 hours	Duration of treatment should be in accordance with the site of infection.

[1]CrCL estimated using the Cockcroft-Gault formula.
[2]To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.
[3]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.
[4]The total duration shown may include intravenous Zavicefta followed by appropriate oral therapy.

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

Table 2 shows the recommended intravenous doses for paediatric patients with estimated creatinine clearance (CrCL) > 50 mL/min/1.73 m^2 (see sections 4.4 Special Warnings and Precautions for Use and 5.1 Pharmacodynamic Properties).

Table 2: Recommended dose for paediatric patients from 3 months of age with estimated CrCL[1] > 50 mL/min/1.73 m²

Type of infection	Age group[7]	Dose of ceftazidime/avibactam[6]	Frequency	Infusion time	Duration of treatment
cIAI[2,3] OR cUTI including pyelonephritis[3]	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[4]: 5 – 14 days
			Every 8 hours	2 hours	
	3 months to <6 months [5]	40 mg/kg/10 mg/kg	Every 8 hours	2 hours	

[1] CrCL estimated using the Schwartz bedside formula.
[2] To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.
[3] 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.
[4] The total treatment duration shown may include intravenous Zavicefta followed by appropriate oral therapy.
[5] There is limited experience with the use of Zavicefta in paediatric patients 3 months to < 6 months (see section 5.2 Pharmacokinetic Properties).
[6] 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 Special precautions for disposal and other handling).
[7] Paediatric patients studied from 3 to 12 months of age were full term (≥37 weeks gestation).

Table 3: Recommended dose for paediatric patients less than 3 months of age[8]

Type of infection	Age group		Dose of **ceftazidime**/avibactam[4]	Frequency	Infusion time	Duration of treatment
cIAI[1,2] OR cUTI including pyelonephritis[2]	Full term neonates and infants	> 28 days to < 3 months	**30 mg/kg**/7.5 mg/kg	Every 8 hours	2 hours	cIAI: 5 – 14 days cUTI[3]: 5 – 14 days
		Birth to ≤ 28 days	**20 mg/kg**/5 mg/kg			
	Preterm neonates and infants[5]	> 44 weeks to < 53 weeks PMA[6]	**30 mg/kg**/7.5 mg/kg	Every 8 hours	2 hours	
		31 to ≤ 44 weeks PMA[6]	**20 mg/kg**/5 mg/kg			
		26 to < 31 weeks PMA[6,7]	**20 mg/kg**/5 mg/kg	Every 12 hours	2 hours	

[1] To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.

[2] 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.
[3] The total treatment duration shown may include intravenous Zavicefta followed by appropriate oral therapy.
[4] 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 Special precautions for disposal and other handling).
[5] Preterm defined as < 37 weeks gestation.
[6] Postmenstrual age.
[7] Dose recommendations for patients 26 to < 31 weeks PMA are based on pharmacokinetic modelling only (see section 5.2 Pharmacokinetic Properties).
[8] Patients with serum creatinine at or below the upper limit of normal for age.

Special populations

Elderly

No dosage adjustment is required in elderly patients (see section 5.2 Pharmacokinetic Properties).

Renal impairment

Table 4 shows the recommended dose adjustments for adults with estimated CrCL ≤ 50 mL/min (see sections 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties).

Dosage in adults with CrCL ≤ 50 mL/min

Table 4 Recommended dose for adults with estimated CrCL[1] ≤ 50 mL/min

Age Group	Estimated CrCl (mL/min)	Dose of Ceftazidime/ Avibactam[2,4]	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 to 15		Every 24 hours	
	End Stage Renal Disease including on haemodialysis[3]		Every 48 hours	

[1]CrCL estimated using the Cockcroft-Gault formula.
[2]Dose recommendations are based on pharmacokinetic modelling (see section 5.2 Pharmacokinetic Properties).
[3]Ceftazidime and avibactam are removed by haemodialysis (see sections 4.9 Overdose and Treatment and 5.2 Pharmacokinetic Properties. Dosing of Zavicefta on haemodialysis days should occur after completion of haemodialysis.
[4]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 Special precautions for disposal and other handling).

Table 5 and Table 6 show the recommended dose adjustments for paediatric patients with estimated CrCL ≤ 50 mL/min/1.73 m^2 according to different age groups (see sections 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties).

Dosage in paediatric patients ≥ 2 years of age with CrCl ≤ 50 mL/min/1.73 m²

Table 5: Recommended dose for paediatric patients aged 2 years to < 18 years with estimated CrCL[1] ≤ 50 mL/min/1.73 m²

Age Group	Estimated CrCL (mL/min/1.73 m²)	Dose of ceftazidime/avibactam[2,4]	Frequency	Infusion time
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	
	End Stage Renal Disease including on haemodialysis[3]		Every 48 hours	

[1] CrCL estimated using the Schwartz bedside formula.
[2] Dose recommendations are based on pharmacokinetic modelling (see section 5.2 Pharmacokinetic Properties).
[3] Ceftazidime and avibactam are removed by haemodialysis (see sections 4.9 Overdose and Treatment and 5.2 Pharmacokinetic Properties). Dosing of Zavicefta on haemodialysis days should occur after completion of haemodialysis.
[4] 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 Special precautions for disposal and other handling).

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

Table 6: Recommended dose for paediatric patients aged 3 months to < 2 years with estimated CrCL[1] ≤ 50 mL/min/1.73 m²

Age group[4]	Estimated CrCL (mL/min/1.73 m²)	Dose of **ceftazidime**/avibactam[2,3]	Frequency	Infusion time
6 months to < 2 years	31 to 50	**25 mg/kg**/6.25 mg/kg	Every 8 hours	2 hours
3 to < 6 months		**20 mg/kg**/5 mg/kg	Every 8 hours	
6 months to < 2 years	16 to 30	**18.75 mg/kg**/4.7 mg/kg	Every 12 hours	
3 to < 6 months		**15 mg/kg**/3.75 mg/kg	Every 12 hours	

[1] Calculated using the Schwartz bedside formula.
[2] Dose recommendations are based on pharmacokinetic modelling (see section 5.2 Pharmacokinetic Properties).
[3] 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 Special precautions for disposal and other handling).
[4] 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 < 2 years of age that have a CrCL < 16 mL/min/1.73 m².

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

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

Method of administration
Intravenous use.

Zavicefta is administered by intravenous infusion over 120 minutes in an appropriate infusion volume (see section 6.6 Special precautions for disposal and other handling).

For instructions on reconstitution and dilution of the medicinal product before administration, (see section 6.6 Special precautions for disposal and other handling).

4.3 Contraindications

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

Hypersensitivity to any cephalosporin antibacterial agent.

Severe hypersensitivity (e.g. anaphylactic reaction, severe skin 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

Serious and occasionally fatal hypersensitivity reactions are possible (see sections 4.3 Contraindications and 4.8 Adverse effects (undesirable effects)). In case of hypersensitivity reactions, treatment with Zavicefta must be discontinued immediately and adequate emergency measures must be initiated.

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

Serious and occasionally fatal hypersensitivity reactions [including anaphylactoid and 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)] have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with Zavicefta, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or

other beta-lactam agents. If an allergic reaction occurs, Zavicefta must be discontinued immediately and appropriate alternative therapy instituted.

***Clostridium difficile*-associated diarrhoea**

Clostridium difficile-associated diarrhoea has been reported with ceftazidime/avibactam, and can 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 Zavicefta (see section 4.8 Adverse effects (undesirable effects)). 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.

Nephrotoxicity

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.

Direct antiglobulin test (DAGT or Coombs test) seroconversion and potential risk of haemolytic anaemia

Ceftazidime/avibactam 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 (see section 4.8 Adverse effects (undesirable effects)). While DAGT seroconversion in patients receiving Zavicefta was very common in clinical studies (the estimated range of seroconversion across Phase 3 studies was 3.2% to 20.8% in patients with a negative Coombs test at baseline and at least one follow-up test), there was no evidence of haemolysis in patients who developed a positive DAGT on treatment. However, the possibility that haemolytic anaemia could occur in association with Zavicefta treatment cannot be ruled out. Patients experiencing anaemia during or after treatment with Zavicefta should be investigated for this possibility.

Dermatological adverse events

Severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, Zavicefta should be discontinued immediately and an alternative treatment should be considered. See section 4.8 Adverse effects (undesirable effects).

Spectrum of activity of ceftazidime/avibactam

Ceftazidime has little or no activity against the majority of Gram-positive organisms and anaerobes (see sections 4.2 Posology and method of administration and 5.1 Pharmacodynamic properties). Additional antibacterial agents 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 ceftazidime, 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 (see section 5.1 Pharmacodynamic properties).

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.

Development of drug-resistant bacteria

Prescribing Zavicefta in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria (see section 4.1. Therapeutic indications).

Controlled sodium diet

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. This should be considered when administering Zavicefta to patients who are on a controlled sodium diet.

Neurotoxicity

There have been reports of neurotoxicity associated with cephalosporin treatment. Symptoms of neurotoxicity include encephalopathy, seizures and/or myoclonus. Risk factors for developing neurotoxicity with cephalosporin treatment include being elderly, renal impairment, central nervous system disorders and intravenous administration. Withdrawal of the medicine should be considered if there are signs of neurotoxicity.

Use in renal impairment

Ceftazidime and avibactam are eliminated via the kidneys, therefore the dose should be reduced according to the degree of renal impairment (see section 4.2 Posology and method of administration). Neurological sequelae, including tremor, myoclonus, non-convulsive status epilepticus, convulsion, encephalopathy and coma, have occasionally been reported with ceftazidime when the dose has not been reduced in patients with renal impairment.

In patients with renal impairment, close monitoring of estimated creatinine clearance is advised. In some patients, the creatinine clearance estimated from serum creatinine can change quickly, especially early in the course of treatment for the infection (see sections 5.1 Clinical trials and 5.2 Pharmacokinetic properties, Renal impairment).

Use in the elderly

No dosage adjustment is required in elderly patients (see sections 4.2 Posology and method of

administration and 5.2 Pharmacokinetic properties).

Paediatric use

The safety and efficacy of Zavicefta in paediatric patients (< 3 months old) have not been established.

There is a potential risk of overdosing, particularly for paediatric patients aged from 3 to less than 12 months of age. Care should be taken when calculating the volume of administration of the dose (see sections 4.2 Posology and method of administration and 4.9 Overdose).

Effects on laboratory tests

Ceftazidime may interfere with copper reduction methods (Benedict's, Fehling's, Clinitest) for detection of glycosuria leading to false positive results. Ceftazidime does not interfere with enzyme-based tests for glycosuria.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro, avibactam is a substrate of OAT1 and OAT3 transporters which might contribute to the active uptake of avibactam from the blood compartment and therefore affect 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. Since a clinical interaction study of avibactam and probenecid has not been conducted, co-administration of avibactam with probenecid is not recommended.

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

Clinical data have demonstrated that there is no interaction between ceftazidime and avibactam, and between ceftazidime/avibactam and metronidazole

Other types 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 Special warnings and precautions for use).

Chloramphenicol is antagonistic *in vitro* with ceftazidime and other cephalosporins. The clinical relevance of this finding is unknown, but due to the possibility of antagonism *in vivo* this drug combination should be avoided.

4.6 Fertility, pregnancy and lactation

Effects on fertility

The effects of ceftazidime/avibactam on fertility in humans have not been studied. No data are available on animal studies with ceftazidime. Animal studies with avibactam do not indicate harmful effects with respect to male fertility. Studies in female rats showed a dose-related increase in pre-and post-implantation losses and smaller live litter size at ≥500 mg/kg/day (≥3 times the human therapeutic exposure at 500 mg three times a day, based on AUC).

Use in pregnancy - Pregnancy Category B3.

Ceftazidime

The safety of ceftazidime in pregnancy has not been established, although animal studies have not produced evidence of embryopathic or teratogenic effects attributable to ceftazidime.

Avibactam

Animal studies with avibactam have shown reproductive toxicity without evidence of teratogenic effects.

In pregnant rabbits administered avibactam at 300 and 1000 mg/kg/day (5-21 times the human therapeutic exposure based on AUC), there was a dose-related lower mean fetal weight and delayed ossification, associated with maternal toxicity (decreased food consumption and body weight gain). Plasma exposure levels at maternal and fetal NOAEL (100 mg/kg/day) indicate low margins of safety (1.5 times the human therapeutic exposure based on AUC).

In the rat, no adverse effects were observed on embryofetal development at up to 1000 mg/kg/day (6 times the human therapeutic exposure based on AUC). 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 ≥450 mg/kg/day (greater than or equal to approximately 3 times the human therapeutic exposures based on AUC). Ceftazidime/avibactam should only be used during pregnancy if the potential benefit outweighs the possible risk.

Use in lactation

Ceftazidime is excreted in human milk in small quantities.

It is unknown whether avibactam is excreted in human milk. Avibactam was excreted in rat milk (~20% of plasma C_{max}), and very low levels were detected in pup plasma (<0.03% of nonclinical maternal plasma C_{max}) as a result of exposure from milk.

A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast feeding or to discontinue/abstain from ceftazidime/avibactam therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines following administration of Zavicefta (see section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

In seven Phase 2 and Phase 3 clinical trials, 2024 adult patients were treated with Zavicefta. The table below lists the adverse events (regardless of causality) occurring in ≥1% of patients treated with Zavicefta with or without metronidazole or comparator from Phase 2 and Phase 3 clinical trials.

Table 7: Adverse events (regardless of causality) reported by ≥1% adult patients up to the last visit

	CAZ-AVI or CAZ-AVI+MTZ (N = 2024)	**Comparator (N=2026)**
Any AE	**996 (49.2)**	**965 (47.6)**
Infections and infestations		
Pneumonia	21 (1.0)	26 (1.3)
Urinary tract infection	21 (1.0)	23 (1.1)
Blood and lymphatic system disorders		
Anaemia	46 (2.3)	38 (1.9)
Metabolism and nutrition disorders		
Hypokalaemia	57 (2.8)	45 (2.2)
Psychiatric disorders		
Anxiety	23 (1.1)	18 (0.9)
Insomnia	25 (1.2)	35 (1.7)
Nervous systems disorders		
Headache	83 (4.1)	97 (4.8)
Dizziness	21 (1.0)	14 (0.7)
Cardiac disorders		
Tachycardia	20 (1.0)	13 (0.6)
Vascular disorders		
Hypotension	26 (1.3)	25 (1.2)
Hypertension	47 (2.3)	56 (2.8)
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	20 (1.0)	18 (0.9)
Dyspnoea	20 (1.0)	18 (0.9)
Cough	30 (1.5)	29 (1.4)
Gastrointestinal disorders		
Diarrhoea	150 (7.4)	126 (6.2)

Constipation	62 (3.1)	66 (3.3)
Abdominal pain	39 (1.9)	30 (1.5)
Lower abdominal pain	22 (1.1)	13 (0.6)
Nausea	102 (5.0)	64 (3.2)
Vomiting	78 (3.9)	50 (2.5)
Skin and subcutaneous tissue disorders		
Rash	20 (1.0)	27 (1.3)
Musculoskeletal and connective tissue disorders		
Back pain	20 (1.0)	13 (0.6)
General disorders and administration site conditions		
Pyrexia	65 (3.2)	71 (3.5)
Asthenia	20 (1.0)	15 (0.7)
Oedema peripheral	36 (1.8)	26 (1.3)
Investigations		
Alanine aminotransferase increased	35 (1.7)	43 (2.1)
Aspartate aminotransferase increased	37 (1.8)	41 (2.0)

CAZ-AVI = ceftazidime-avibactam; MTZ = metronidazole; Comparator = meropenem, doripenem or best available therapy.

The most common adverse reactions occurring in ≥5% of patients treated with Zavicefta were Coombs direct test positive, nausea, and diarrhoea. Nausea and diarrhoea were usually mild or moderate in intensity. No clinically significant differences were observed in the safety profile across indications.

The following adverse reactions have been reported with ceftazidime alone and/or identified during the Phase 2 and Phase 3 clinical trials with Zavicefta. Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are derived from adverse reactions and/or potentially clinically significant laboratory abnormalities.

Table 8: Frequency of adverse reactions by system organ class

System Organ Class	Very Common (≥10%)	Common (≥1% and <10%)	Uncommon (≥0.1% and <1%)	Very Rare (≥0.01% and <0.1%)	Unknown (cannot be estimated from available data)
Infections and infestations		Candidiasis (including Vulvovaginal candidiasis and Oral candidiasis)	*Clostridium difficile* colitis Pseudomembranous colitis		
Blood and lymphatic system disorders	Coombs direct test positive[+]	Eosinophilia Thrombocytosis Thrombocytopenia	Neutropenia Leukopenia Lymphocytosis		Agranulocytosis Haemolytic anemia

Table 8: Frequency of adverse reactions by system organ class					
System Organ Class	**Very Common (≥10%)**	**Common (≥1% and <10%)**	**Uncommon (≥0.1% and <1%)**	**Very Rare (≥0.01% and <0.1%)**	**Unknown (cannot be estimated from available data)**
Immune system disorders					Anaphylactic reaction Kounis syndrome[++]
Nervous system disorders		Headache Dizziness	Paraesthesia		
Gastrointestinal disorders		Diarrhoea Abdominal pain Nausea Vomiting	Dysgeusia		
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		Rash maculo-papular Urticaria Pruritus			Toxic epidermal necrolysis[+] Stevens-Johnson syndrome[+] Erythema multiforme Angioedema Drug Reaction with Eosinophilia and Systemic

Table 8: Frequency of adverse reactions by system organ class					
System Organ Class	**Very Common (≥10%)**	**Common (≥1% and <10%)**	**Uncommon (≥0.1% and <1%)**	**Very Rare (≥0.01% and <0.1%)**	**Unknown (cannot be estimated from available data)**
					Symptoms (DRESS) Acute generalised exanthematous pustulosis (AGEP)[+]
Renal and urinary disorders			Blood creatinine increased Blood urea increased Acute kidney injury	Tubulointerstitial nephritis	
General disorders and administration site conditions		Infusion site thrombosis Infusion site phlebitis 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 Special Warnings and Precautions for Use and 5.2

Pharmacokinetic Properties). Overdose with ceftazidime/avibactam can lead to neurological sequelae including encephalopathy, convulsions and coma, due to the ceftazidime component.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, ceftazidime, combinations, ATC code: J01DD52.

Mechanism of action

Ceftazidime inhibits bacterial peptidoglycan cell wall synthesis following binding to penicillin binding proteins (PBPs), which leads to bacterial cell lysis and death. 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, and some class D enzymes including extended-spectrum β-lactamases (ESBLs), KPC and OXA-48 carbapenemases, and AmpC enzymes. Avibactam does not inhibit class B enzymes (metallo-β-lactamases) and is not able to inhibit many class D enzymes.

Mechanism of resistance

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, and β-lactamase enzymes refractory to inhibition by avibactam and able to hydrolyze ceftazidime.

Cross-resistance

An absence of cross-resistance between ceftazidime-avibactam and fluoroquinolones or aminoglycosides has been demonstrated *in vitro* using molecularly-characterized 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.

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
Complicated intra-abdominal infections
Gram-negative micro-organisms

- *Citrobacter freundii*
- *Enterobacter cloacae*
- *Escherichia coli*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*

Complicated urinary-tract infections

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).

Susceptibility testing interpretive criteria (breakpoints)

EUCAST Reference Information

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.				

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Quality control microorganisms are specific strains with intrinsic biological properties relating to resistance mechanisms and their genetic expression within the microorganism; 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.		

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.

Interaction with other antimicrobial agents
In vitro interaction tests with ceftazidime-avibactam show ceftazidime-avibactam has little potential to antagonize or be antagonized 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.

Complicated intra-abdominal infections (cIAI)
In two identical randomised, multi-centre, multinational, double-blind studies (RECLAIM 1 and RECLAIM 2), a total of 1058 adults with cIAI were randomised to receive treatment comparing Zavicefta (2000 mg of CAZ and 500 mg of AVI) administered intravenously over 120 minutes every 8 hours plus metronidazole (500 mg) to meropenem (1000 mg) administered intravenously over 30 minutes. Treatment duration was 5 to 14 days. cIAI (defined as infections that require surgical intervention and extend beyond the hollow viscus into the intraperitoneal space) included appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, perforation of the intestine, and other causes of intra-abdominal abscesses and peritonitis.

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 the table below.

Table 9: 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)

Abbreviations: CAZ/AVI = ceftazidime/avibactam; MTZ = metronidazole.

Clinical cure rates at TOC by pathogen in the microbiologically Modified Intent to Treat (mMITT) population for Gram-negative aerobes are shown in Table 10 below.

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

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

Abbreviations: CAZ/AVI = ceftazidime/avibactam; MTZ = metronidazole

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 below).

Table 11: Clinical cure rates at TOC (RECLAIM3 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)

Abbreviations: CAZ/AVI = ceftazidime/avibactam

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

Table 12: Clinical cure rates at TOC by common (combined frequency of ≥7) Gram- negative baseline pathogen (RECLAIM3 mMITT analysis set)						
	Number of patients					
	CAZ/AVI + MTZ (N = 143)			**Meropenem (N = 152)**		
Pathogen	**Cure rate (%)**	**Number of clinical cures**	**N**	**Cure rate (%)**	**Number of clinical cures**	**N**
Enterobacterales (Enterobacteriaceae)	80.9	93	115	92.7	115	124
C. freundii complex	62.5	5	8		0	0
E. cloacae	100	5	5	66.7	2	3
E. coli	83.3	70	84	94.4	84	89
K. oxytoca	100	5	5	100	5	5
K. pneumoniae	82.1	23	28	88.6	31	35
P. mirabilis	66.7	2	3	100	5	5
P. aeruginosa	82.4	14	17	85.0	17	20

Abbreviations: CAZ/AVI = ceftazidime/avibactam; MTZ = metronidazole.

Among patients with baseline bacteraemia who were enrolled in any of the phase 3 cIAI studies (RECLAIM, RECLAIM3 or REPRISE), clinical response 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 3/4 (75.0%) CAZ-AVI- and 2/2 (100.0%) comparator-treated patients with *P. aeruginosa* bacteraemia.

Complicated urinary tract infections (cUTI)

A total of 1020 adults with documented 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. cUTI included acute pyelonephritis and complicated lower urinary tract infections. Treatment was with either ceftazidime/avibactam (2000 mg/500 mg) IV over 120 mins every 8 hours or doripenem 500 mg 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. Patients with CrCL <30 mL/min were excluded.

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

Table 13: 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)

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

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

Table 14: 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 (Enterobacteriaceae)	78.3	299	382	70.6	281	398
E. cloacae	54.5	6	11	69.2	9	13
E. coli	78.4	229	292	71.9	220	306
K. pneumoniae	75.0	33	44	62.5	35	56
P. mirabilis	94.1	16	17	69.2	9	13
P. aeruginosa	66.7	12	18	75.0	15	20

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

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 (HAP)

In a phase III double-blind, comparative study, a total of 808 adults with nosocomial pneumonia

(280/808, 34.7% with VAP and 40/808 (5.0%) were bacteraemic at baseline) were randomised to receive treatment of ceftazidime/avibactam (2000 mg/500 mg) IV over 120 mins every 8 hours or meropenem 1 g IV over 30 mins every 8 hours. Treatment duration was 7 to 14 days. Nosocomial pneumonia was defined as an onset of relevant signs and symptoms ≥48 hours after admission or <7 days after discharge from an inpatient acute or chronic care facility, and a new or worsening infiltrate on chest X-ray obtained within 48 hours prior to randomisation. Patients with infections only due to Gram-positive organisms were excluded from the trial, when this could be determined before enrollment. Following randomisation, patients in both treatment groups could receive empiric open-label linezolid or vancomycin to cover for Gram-positive pathogens while awaiting culture results. Treatment with Gram-positive coverage continued in patients with Gram-positive pathogens.

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 the table below.

Table 15: 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)

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

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 15 and 16.

Table 16: 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 (Enterobacteriaceae)	73.6	89	121	75.4	104	138
E. aerogenes	62.5	5	8	50.0	4	8
E. cloacae	92.3	24	26	54.5	12	22
E. coli	64.7	11	17	75.0	15	20
K. pneumoniae	72.9	43	59	77.5	55	71
P. mirabilis	85.7	12	14	75.0	9	12
Serratia marcescens	73.3	11	15	92.3	12	13
P. aeruginosa	60.3	35	58	74.5	35	47
H. influenzae	81.3	13	16	80.0	20	25

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

Table 17: 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 (Enterobacteriaceae)						
E. aerogenes	62.5	5	8	62.5	5	8
E. cloacae	80.8	21	26	59.1	13	22
E. coli	76.5	13	17	80.0	16	20
K. pneumoniae	62.7	37	59	74.6	53	71
P. mirabilis	78.6	11	14	66.7	8	12
S. marcescens	66.7	10	15	61.5	8	13
P. aeruginosa	37.9	22	58	38.3	18	47
H. influenzae	87.5	14	16	92.0	23	25

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

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
Zavicefta has been evaluated in paediatric patients from birth to less than 3 months of age in a Phase 2a, 2-part (Part A and B), 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 (primary objective) and evaluate safety and tolerability (secondary objective) of ceftazidime/avibactam. Part B used multiple doses to evaluate the safety and tolerability (primary objective) while the PK profile and efficacy were secondary objectives. Efficacy was only a descriptive endpoint. Clinical cure or clinical improvement rates 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
Zavicefta 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. The primary objective in each study was to assess safety and tolerability of ceftazidime-avibactam (+/- metronidazole). Secondary objectives included assessment of pharmacokinetics and efficacy; efficacy was a descriptive endpoint in both studies. Clinical cure rate at TOC (ITT) was 91.8% (56/61) for Zavicefta compared to 95.5% (21/22) for meropenem in paediatric patients with cIAI. Microbiological eradication rate at TOC (micro-ITT) was 79.6% (43/54) for Zavicefta compared to 60.9% (14/23) for cefepime in paediatric patients with cUTI.

Limitations of clinical trial data

Patients with evidence of significant immunocompromise were excluded from the Phase 2 and 3 clinical trials.

5.2 Pharmacokinetic properties

Distribution

The human protein binding of both ceftazidime and avibactam is, approximately 10% and 8%,

respectively. The steady-state volumes of distribution of ceftazidime and avibactam were, about 17 L and 22 L, respectively in healthy adults following multiple doses of 2000 mg/500 mg ceftazidime-avibactam infused over 2 hours every 8 hours. Both ceftazidime and avibactam penetrate into human bronchial epithelial lining fluid (ELF) to the same extent with concentrations around 30% of those in plasma. The concentration time profiles are similar for ELF and plasma.

Penetration of ceftazidime into the intact blood-brain barrier is poor. Ceftazidime 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. Ceftazidime crosses the placenta readily, and is excreted in the breast milk.

Metabolism

Ceftazidime is not metabolized. 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.

Excretion

The terminal half-life (t½) of both ceftazidime and avibactam is about 2 h after intravenous 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 avibactam 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 (50 mg to 2000 mg) for a single intravenous administration. No appreciable accumulation of ceftazidime or avibactam was observed following multiple intravenous infusions of 2000 mg/500 mg of ceftazidime/avibactam administered every 8 hours for up to 11 days in healthy adults with normal renal function.

Pharmacokinetic/pharmacodynamic relationship(s)

The antimicrobial activity of ceftazidime 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 avibactam the PK-PD index is the percent time of the free drug concentration above a threshold concentration over the dose interval (% *f*T >C_T).

Renal impairment

Adults

Ceftazidime is eliminated almost solely by the kidneys; its serum half-life is significantly prolonged in patients with impaired renal function. The clearance of avibactam was significantly decreased in subjects with mild (CrCL >50 to 80 mL/min, n = 6), moderate (CrCL 30 to 50 mL/min, n = 6), and severe (≤CrCL 30 mL/min, not requiring haemodialysis; n = 6) renal impairment compared to healthy subjects with normal renal function (CrCL ≥80 mL/min, n = 6) following administration of a single 100 mg intravenous dose of avibactam. The slower clearance resulted in increases in systemic exposure (AUC) of avibactam of 2.6-fold, 3.8-fold and 7-fold in subjects with mild, moderate and severe renal impairment, respectively.

A single 100 mg dose of avibactam was administered to subjects with ESRD (n = 6) either 1 hour before or after haemodialysis. The avibactam AUC following the post-haemodialysis infusion was 19.5-fold the AUC of healthy subjects with normal renal function. Avibactam was extensively removed by haemodialysis, with an extraction coefficient of 0.77 and a mean haemodialysis clearance of 9.0 L/h. Approximately 55% of the avibactam dose was removed during a 4-hour haemodialysis session.

Dosage adjustment of Zavicefta is recommended in patients with moderate and severe renal impairment and end-stage renal disease. Population PK models for ceftazidime and avibactam were used to conduct simulations for patients with impaired renal function. Simulations demonstrated that the recommended dose adjustments provide comparable exposures of ceftazidime and avibactam in patients with moderate and severe renal impairment and end-stage renal disease to those in patients with normal renal function or mild renal impairment. For patients with changing renal function, CrCL should be monitored at least daily and the dose of Zavicefta adjusted accordingly (see sections 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use, Use in renal impairment).

Hepatic impairment

Mild to moderate hepatic impairment had no effect on the pharmacokinetics of ceftazidime in individuals administered 200 mg intravenously 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 active substance is not expected to be significantly altered by hepatic impairment.

Use in the elderly

Reduced clearance of ceftazidime was observed in elderly patients which was primarily due to age-related decrease in renal clearance of ceftazidime. The mean elimination half-life of ceftazidime ranged from 3.5 to 4 hours following intravenous bolus dosing with 2000 mg every 12 hours in elderly patients aged 80 years or older.

Following single intravenous administration of 500 mg 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.

Paediatric population

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 2g/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 (paediatric patients 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 and cUTI, 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 2g/0.5g 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 months. The recommended dosing regimens are based on simulations conducted using the final population PK models. Simulations demonstrated that the recommended dose regimens result incomparable 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 months.

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. These simulations demonstrated that the recommended dose regimens for term neonates (gestational age [GA] ≥ 37 weeks), preterm neonates (GA 26 weeks to < 31 weeks and GA 31 to < 37 weeks) and infants aged 28 days to < 3 months, 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 no data in pre-term infants under 31 weeks GA from the completed paediatric clinical trials and dose recommendations in this age group are exclusively based on pharmacokinetic modelling.

Gender and race

The pharmacokinetics of ceftazidime/avibactam is not significantly affected by gender or race.

5.3 Preclinical safety data

Genotoxicity

For ceftazidime a mouse Micronucleus test and an Ames test were both negative for mutagenic effects. 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* 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. No genetic toxicology studies have been conducted on ceftazidime-avibactam.

Carcinogenicity

Carcinogenicity studies have not been conducted with ceftazidime-avibactam.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous sodium carbonate.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2 Posology and method of administration.

6.3 Shelf-life

Dry powder

3 years.

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 Special precautions for disposal and other handling (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 not more than 25°C.

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 not more than 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 those stated above.

Infusion syringes

If the intravenous solution is prepared with diluents listed in section 6.6 Special precautions for disposal and other handling (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 not more than 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 not more than 25°C.

6.4 Special precautions for storage

Store below 30°C.

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 Shelf-life.

6.5 Nature and contents of container

20 mL glass vial (Type 1) closed with a rubber (halobutyl) stopper and aluminium seal with flip-off cap.

The medicinal product is supplied in packs of 10 vials.

"Some product strengths or pack sizes may not be available in your country".

6.6 Special precautions for disposal and other handling

The powder must be reconstituted with water for injections and the resulting concentrate must then be immediately diluted prior to use. The reconstituted solution is a pale yellow solution and is free of 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.

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

<u>Instructions for preparing adult and paediatric doses in INFUSION BAG or in 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 18 below.

Table 18: Preparation of Zavicefta for adult and paediatric doses in INFUSION BAG or in INFUSION SYRINGE

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

[1] Based on ceftazidime component only.

[2] 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 not more than 25°C (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 not more than 25°C.

[3] Dilute to final ceftazidime concentration ≥ 8 mg/mL to 40 mg/mL for in-use stability up to 6 hours at not more than 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 19, 20 or 21 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 19: 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)[1]	**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

[1] Based on ceftazidime component only.

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

Age and Zavicefta Dose (mg/kg)[1]	**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	5	125	0.75	5.5
	6	150	0.9	6.6
	7	175	1	7.4

25 mg/kg of ceftazidime	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
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

[1] 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 CrCL 16 to 30 mL/min/1.73 m^2

Age and Zavicefta Dose (mg/kg) [1]	**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

[1] 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 22 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 22: 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)[1]	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 26 to ⩽ 44 weeks PMA	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

20 mg/kg of ceftazidime	2.6	52	5.2
	2.8	56	5.6
	3	60	6
	3.5	70	7
	4	80	8
	4.5	90	9
	5	100	10
	5.5	110	11
	6	120	12

[1] Based on ceftazidime component only.

7. MANUFACTURER

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