

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZAVITA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A. Qualitative Composition

Each vial Contains:
Ceftazidime Pentahydrate USP
Eq. Ceftazidime.....2.0 g
Avibactam Sodium
Eq. Avibactam.....0.5g

3. PHARMACEUTICAL FORM

Powder for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZAVITA is indicated in adults and paediatric patients aged 3 months and older for the treatment of the following infections

- 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, any of the infections listed above.

ZAVITA is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults and paediatric patients aged 3 months and older with limited treatment options Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

It is recommended that ZAVITA should be used to treat infections due to aerobic Gram-negative organisms in adults and paediatric patients aged 3 months and older with limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases .

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 .

Table: 1 Recommended dose for adults with estimated CrCL > 50 mL/min¹

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.
Infections due to aerobic Gramnegative organisms in patients with limited treatment options ^{2,3}	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 ZAVITA followed by appropriate oral therapy.

⁵ There is very limited experience with the use of ZAVITA for more than 14 days.

Dosage in paediatric patients with creatinine clearance (CrCL) >50 mL/min/1.73 m²

Table 2 shows the recommended intravenous doses for paediatric patients with estimated creatinine clearance (CrCL) > 50 mL/min/1.73 m².

Table 2: Recommended dose for paediatric patients with estimated CrCL¹ > 50 mL/min/1.73 m²

Type of infection	Age group	Dose of ceftazidime/avibactam ⁷	Frequency	Infusion time	Duration of treatment
cIAI ^{2,3} OR	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 ² : 5 – 14 days HAP/VAP: 7 – 14 days

² The total treatment duration shown may include intravenous ZAVITA followed by appropriate oral therapy.

cUTI including pyelonephritis ¹ OR HAP/VAP ³ OR Infections due to aerobic Gram-negative organisms in patients with limited treatment options (LTO) ^{2,3}	3 months to <6 months ⁴⁵	40 mg/kg/ 10 mg/kg	Every 8 hours	2 hours	LTO: Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress ³
			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.

Special populations

Elderly

No dosage adjustment is required in elderly patients .

Renal impairment

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

Table 3 shows the recommended dose adjustments for adults with estimated CrCL ≤ 50 mL/min .

Dosage in adults with CrCL ≤ 50 mL/min

Table 3: Recommended dose for adults with estimated CrCL¹ ≤ 50 mL/min

Age Group	Estimated CrCL (mL/min)	Dose of ceftazidime /avibactam ^{2,4}	Frequency	Infusion time
	31-50	1 g/0.25 g	Every 8 hours	

¹ 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 There is limited experience with the use of ZAVITA in paediatric patients 3 months to < 6 months..

⁵ Ceftazidime/avibactam is a combination product in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only .

³ There is very limited experience with the use of ZAVITA for more than 14 days.

Adults	16-30	0.75 g/0.1875 g	Every 12 hours	2 hours
	6-15		Every 24 hours	
	End Stage Renal Disease including on haemodialysis ³		Every 48 hour	

¹ CrCL estimated using the Cockcroft-Gault formula.

² Dose recommendations are based on pharmacokinetic modelling .³ Ceftazidime and avibactam are removed by haemodialysis Dosing of ZAVITA 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 .

Table 4 and Table 5 show the recommended dose adjustments for paediatric patients with estimated CrCL ≤ 50 mL/min/1.73 m² according to different age groups .

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

Table 4: Recommended dose for paediatric patients with estimated CrCL¹ ≤ 50 mL/min/1.73 m²

Age Group	Estimated CrCL (mL/min/1.73 m ²)	Dose of ceftazidime/avibactam ^{2,3}	Frequency	Infusion time	
3 to < 6 months	31 to 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 to 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		
¹ Calculated using the Schwartz bedside formula					
² Dose recommendations are based on pharmacokinetic modelling .					
³ Ceftazidime/avibactam is a combination product in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only					

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.

Hepatic impairment

No dosage adjustment is required in patients with hepatic impairment .

Paediatric population

The safety and efficacy of ZAVITA in paediatric patients < 3 months old have not been established. No data are available.

Method of administration

Intravenous use.

ZAVITA is administered by intravenous infusion over 120 minutes in an appropriate infusion volume. For instructions on reconstitution and dilution of the medicinal product before administration.

4.3 Contraindications

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

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. In case of hypersensitivity reactions, treatment with ZAVITA 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.

***Clostridioides difficile*- associated diarrhoea**

Clostridioides 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 ZAVITA. Discontinuation of therapy with ZAVITA and the administration of specific treatment for *Clostridioides difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Renal impairment

Ceftazidime and avibactam are eliminated via the kidneys, therefore, the dose should be reduced according to the degree of renal impairment. 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.

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 . While DAGT seroconversion in patients receiving ZAVITA 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 ZAVITA treatment cannot be ruled out. Patients experiencing anaemia during or after treatment with ZAVITA should be investigated for this possibility.

Limitations of the clinical data

Clinical efficacy and safety studies of ZAVITA have been conducted in cIAI, cUTI and HAP (including VAP).

Complicated intra-abdominal infections in adults

In two studies in patients with cIAI, the most common diagnosis (approximately 42%) was appendiceal perforation or peri-appendiceal abscess. Approximately 87% of patients had APACHE II scores of ≤ 10 and 4% had bacteraemia at baseline. Death occurred in 2.1% (18/857) of patients who received ZAVITA and metronidazole and in 1.4% (12/863) of patients who received meropenem.

Among a subgroup with baseline CrCL 30 to 50 mL/min death occurred in 16.7% (9/54) of patients who received ZAVITA and metronidazole and 6.8% (4/59) of patients who received meropenem. Patients with CrCL 30 to 50 mL/min received a lower dose of ZAVITA than is currently recommended for patients in this sub-group.

Complicated urinary tract infections in adults

In two studies in patients with cUTI, 381/1091 (34.9%) patients were enrolled with cUTI without pyelonephritis while 710 (65.1%) were enrolled with acute pyelonephritis (mMITT population). A total of 81 cUTI patients (7.4%) had bacteraemia at baseline.

Hospital-acquired pneumonia (including ventilator-associated pneumonia) in adults

In a single study in patients with nosocomial pneumonia 280/808 (34.7%) had VAP and 40/808 (5%) were bacteraemic at baseline.

Patients with limited treatment options

The use of ceftazidime/avibactam to treat patients with infections due to Gram-negative aerobic pathogens who have limited treatment options is based on experience with ceftazidime alone and on analyses of the pharmacokinetic-pharmacodynamic relationship for ceftazidime/avibactam

Spectrum of activity of ceftazidime/avibactam

Ceftazidime has little or no activity against the majority of Gram-positive organisms and anaerobes). 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 .

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.

Interference with 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.

Controlled sodium diet

This medicinal product contains approximately 146 mg sodium per vial, equivalent to 7.3% of the WHO recommended maximum daily intake (RDI) of 2 g sodium for an adult.

The maximum daily dose of this product is equivalent to 22% of the WHO recommended maximum daily intake for sodium. ZAVITA is considered high in sodium.

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

ZAVITA may be diluted with sodium-containing solutions and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

Paediatric population

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 .

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 . 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 Pregnancy, Lactation and Fertility**Pregnancy**

Animal studies with ceftazidime do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Animal studies with avibactam have shown reproductive toxicity without evidence of teratogenic effects.

Ceftazidime/avibactam should only be used during pregnancy if the potential benefit outweighs the possible risk.

Lactation

Ceftazidime is excreted in human milk in small quantities. It is unknown whether avibactam is excreted in human 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..

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 fertility

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 ZAVITA

4.8 Undesirable effects

Summary of the safety profile

In seven Phase 2 and Phase 3 clinical trials, 2024 adults were treated with ZAVITA. The most common adverse reactions occurring in ≥ 5% of patients treated with ZAVITA were Coombs direct test positive, nausea, and diarrhoea. Nausea and diarrhoea were usually mild or moderate in intensity.

Tabulated list of adverse reactions

The following adverse reactions have been reported with ceftazidime alone and/or identified during the Phase 2 and Phase 3 trials with . 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, and are defined according to the following conventions:

- Very common (≥1/10)
- Common (≥1/100 and <1/10)
- Uncommon (≥1/1,000 and <1/100)
- Rare (≥1/10,000 and <1/1000)
- Very rare (<1/10,000)
- Unknown (cannot be estimated from the available data)

Table 6: Frequency of adverse reactions by system organ class

System Organ Class	Very common	common	Uncommon	Very rare	Unknown
Infections and infestations		Candidiasis (including Vulvovaginal candidiasis and Oral candidiasis)	Clostridioides difficile colitis Pseudomembranous colitis		
Blood and lymphatic system disorders	Coombs direct test positive	Eosinophilia Thrombocytosis Thrombocytopenia	Neutropenia Leukopenia Lymphocytosis		Agranulocytosis Haemolytic anaemia

Immune system disorders					Anaphylactic reaction
Nervous system disorders		Headache Dizziness	Paraesthesia		
Gastrointestinal disorders		Diarrhoea	Dysgeusia		

		Abdominal pain Nausea Vomiting			
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 maculopapular Urticaria Pruritus			Toxic epidermal necrolysis StevensJohnson syndrome Erythema multiforme Angioedema Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Renal and urinary disorders			Blood creatinine increased Blood urea	Tubulointersti tial nephritis	
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			increased Acute kidney injury		
General disorders and administration site conditions		Infusion site thrombosis Infusion site phlebitis Pyrexia			

Paediatric population

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

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system.

4.9 Overdose

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

Serum levels of ceftazidime can be reduced by haemodialysis or peritoneal dialysis. During a 4-hour haemodialysis period, 55% of the avibactam dose was removed.

5. Pharmacological properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group : Antibacterial, beta-lactam for systemic use **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.

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 hydrolyse ceftazidime.

Antibacterial activity in combination with other antibacterial agents

No synergy or antagonism was demonstrated in *in vitro* drug combination studies with ceftazidime/avibactam and metronidazole, tobramycin, levofloxacin, vancomycin, linezolid, colistin and tigecycline.

Susceptibility testing breakpoints

Minimum Inhibitory Concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for ceftazidime/avibactam are as follows:

Organisms	Susceptible	Resistant
<i>Enterobacteriales</i>	≤8 mg/L	>8 mg/L
<i>Pseudomonas aeruginosa</i>	≤8 mg/L	>8 mg/L

Pharmacokinetic/pharmacodynamic relationship

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).

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against the following pathogens that were susceptible to ceftazidime/avibactam *in vitro*.

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*

In-vitro data indicate that the following species are not susceptible to ceftazidime/avibactam.

- *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant)
- Anaerobes
- *Enterococcus* spp.
- *Stenotrophomonas maltophilia*
- *Acinetobacter* spp.

Paediatric population

ZAVITA has been evaluated in paediatric patients aged 3 months to < 18 years in two Phase 2 singleblind, 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 ceftazidimeavibactam (+/- 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 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 compared to 60.9% (14/23) for cefepime in paediatric patients with cUTI.

The European Medicines Agency has deferred the obligation to submit the results of studies with in one or more subsets of the paediatric population in the treatment of cIAI, cUTI, pneumonia and Gramnegative bacterial infections .

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 2 g/0.5 g 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.

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 [¹⁴C]-avibactam.

Elimination

The terminal half-life ($t_{1/2}$) 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 (0.05 g to 2 g) for a single intravenous administration. No appreciable accumulation of ceftazidime or avibactam was observed following multiple intravenous 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

Renal impairment Elimination of ceftazidime and avibactam is decreased in patients with moderate or severe renal impairment. The average increases in avibactam AUC are 3.8-fold and 7-fold in subjects with moderate and severe renal impairment, see section 4.2.

Hepatic impairment Mild to moderate hepatic impairment had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g 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.

Elderly patients (≥65 years)

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 2 g every 12 hours in elderly patients aged 80 years or older.

Following a 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 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 (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 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 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 months. 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 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 m²), 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.

Gender and race

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

5.3 Preclinical safety data

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

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

Reproduction toxicity In pregnant rabbits administered avibactam at 300 and 1000 mg/kg/day, there was a dose-related lower mean foetal weight and delayed ossification, potentially related to maternal toxicity. Plasma exposure levels at maternal and foetal NOAEL (100 mg/kg/day) indicate moderate to low margins of safety.

In the rat, no adverse effects were observed on 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.

6. PharmaceuticalParticulars

6.1 List of Excipients

NOT Applicable

6.2 Incompatibilities

The compatibility of ZAVITA with other medicines has not been established. should not be mixed with or physically added to solutions containing other medicinal products.

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

6.3 Shelf Life

Dry powder

24 months

6.4 Special Precautions for Storage

Store at a temperature below 30°C.
Protect from light & moisture.
Keep out of reach of children.

6.5 Nature and Contents of container

A white powder filled in clear glass vial sealed with gray butyl rubber stopper & 20 mm flip of seal

6.6 Special precautions for disposal and other handling

=== Not Applicable ===

7. MARKETING AUTHORISATION HOLDER & MANUFACTURING SITE ADDRESS

Vellinton Healthcare

Address: Vllage-Rampur Jattan, Trilokpur Road

Kala Amb Sirmour (H.P), 173030

8. MARKETING AUTHORISATION NUMBER

H2025/CTD11805/26043

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

18/02/2026

10. DATE OF REVISION OF THE TEXT

18/02/2026