Zavicefta®

Ceftazidime pentahydrate, Avibactam sodium

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

Reference Market: EU

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Excipient with known effect:

Zavicefta contains approximately 146 mg sodium per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

A white to yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Complicated intra-abdominal infection (cIAI)
- Complicated urinary tract infection (cUTI), including pyelonephritis
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)

Treatment of adult patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Zavicefta is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults and paediatric patients from birth with limited treatment options (see sections 4.2, 4.4 and 5.1).

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

4.2 Posology and method of administration

It is recommended that Zavicefta should be used to treat infections due to aerobic Gram-negative organisms in adults and paediatric patients from birth with limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases (see section 4.4).

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 and 5.1).

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.
Infections due to aerobic Gram-negative organisms in patients with limited treatment options[2,3]	2 g/0.5 g	Every 8 hours	2 hours	Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress[5]

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

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 and 5.1).

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

Type of infection	Age group[8]	Dose of **ceftazidime**/avibactam[7]	Frequency	Infusion time	Duration of treatment
cIAI[2,3] OR cUTI including pyelonephritis[3] OR HAP/VAP[3] OR Infections due to aerobic Gram-negative organisms in patients with limited treatment options (LTO)[2,3]	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 HAP/VAP: 7 – 14 days LTO: Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress[5]
			Every 8 hours	2 hours	
	3 months to < 6 months[6]	**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 very limited experience with the use of Zavicefta for more than 14 days.
[6] There is limited experience with the use of Zavicefta in paediatric patients 3 months to < 6 months (see section 5.2).
[7] 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).
[8] 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[9]

Type of infection	Age group		Dose of **ceftazidime**/avibactam[5]	Frequency	Infusion time	Duration of treatment
cIAI[1,2] OR cUTI including pyelonephritis[2] OR HAP/VAP[2] OR Infections due to aerobic Gram-negative organisms in patients with limited treatment options (LTO)[1,2]	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 HAP/VAP: 7 – 14 days LTO: Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress[4]
		Birth to ≤ 28 days	**20 mg/kg**/5 mg/kg			
	Preterm neonates and infants[6]	> 44 weeks to < 53 weeks PMA[7]	**30 mg/kg**/7.5 mg/kg	Every 8 hours	2 hours	
		31 to ≤ 44 weeks PMA[7]	**20 mg/kg**/5 mg/kg			
		26 to < 31 weeks PMA[7,8]	**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] There is very limited experience with the use of Zavicefta for more than 14 days.
[5] 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).
[6] Preterm defined as < 37 weeks gestation.
[7] Postmenstrual age.
[8] Dose recommendations for patients 26 to < 31 weeks PMA are based on pharmacokinetic modelling only (see section 5.2).
[9] 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).

Renal impairment

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

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	
	6-15		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).
[3] Ceftazidime and avibactam are removed by haemodialysis (see sections 4.9 and 5.2). 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).

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 and 5.2).

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

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

Age group	Estimated CrCL (mL/min/1.73 m^2)	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).

[3] Ceftazidime and avibactam are removed by haemodialysis (see sections 4.9 and 5.2). 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).

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).
[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).
[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 aged 3 months to < 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).

Method of administration

Intravenous use.

Zavicefta is administered by intravenous infusion over 120 minutes in an appropriate infusion volume (see section 6.6).

For instructions on reconstitution and dilution of the medicinal product before administration see section 6.6.

4.3 Contraindications

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

Hypersensitivity to 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 and 4.8). In case of hypersensitivity reactions, treatment with Zavicefta must be discontinued immediately and adequate emergency measures must be initiated.

There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8).

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.

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported with unknown frequency in association with ceftazidime treatment (see section 4.8).

Patients should be advised of the signs and symptoms and monitored closely for skin reactions.

If signs and symptoms suggestive of these reactions appear, Zavicefta should be withdrawn immediately, and an alternative treatment considered.

If the patient has developed a serious reaction such as SJS, TEN, DRESS or AGEP with the use of ceftazidime, treatment with Zavicefta must not be restarted in this patient at any time.

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 Zavicefta (see section 4.8). Discontinuation of therapy with Zavicefta 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 (see section 4.2). 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 (see section 4.8). 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.

Limitations of the clinical data

Clinical efficacy and safety studies of Zavicefta 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 Zavicefta 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 Zavicefta 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 Zavicefta 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 (see section 5.1).

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 and 5.1). 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).

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

Zavicefta may be diluted with sodium-containing solutions (see section 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

Paediatric population

There is a potential risk of overdosing, particularly for paediatric patients from birth to less than 12 months of age. Care should be taken when calculating the volume of administration of the dose (see sections 4.9 and 6.6).

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).

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

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 (see section 5.3).

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

Breast-feeding

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 (see section 5.3).

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).

4.8 Undesirable effects

Summary of the safety profile

In seven Phase 2 and Phase 3 clinical trials, 2024 adults were treated with Zavicefta. 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.

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 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, 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)
Not known (cannot be estimated from the available data)

Table 7: Frequency of adverse reactions by system organ class

System organ class	Very common	Common	Uncommon	Very rare	Not known
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		
Cardiac disorders					Kounis syndrome[a,*]
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

System organ class	Very common	Common	Uncommon	Very rare	Not known
					Erythema multiforme Angioedema Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Acute generalised exanthematous pustulosis (AGEP)*
Renal and urinary disorders			Blood creatinine increased Blood urea increased Acute kidney injury	Tubuloint erstitial nephritis	
General disorders and administration site conditions		Infusion site thrombosis Infusion site phlebitis Pyrexia			

* ADR identified post-marketing.
[a] 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 (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 Zavicefta. 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 marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local requirements.

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: Antibacterials for systemic use, other beta-lactam antibacterials, third-generation cephalosporins, 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 can be viewed on the following website:

https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

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

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.

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 [^{14}C]-avibactam.

Elimination

The terminal half-life ($t_{½}$) 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 (0.5 g to 2 g for ceftazidime and 0.05 g to 2 g for avibactam) 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 Zavicefta 2 g/0.5 g (ceftazidime 2 grams and avibactam 0.5 grams) for patients weighing ≥ 40 kg. Plasma concentrations of ceftazidime and avibactam were similar across all four age cohorts in the study (3 months to < 2 years, 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years). Ceftazidime and avibactam $AUC_{0\text{-}t}$ 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, cUTI and HAP/VAP, including dose adjustments for patients with renal impairment, result in systemic exposure and PK/PD target attainment values that are similar to those in adults at the approved Zavicefta dose of 2 g/0.5 g administered over 2 hours, every 8 hours.

There is limited experience with the use of ceftazidime plus avibactam in the paediatric groups of 3 months to < 6 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 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

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. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate (anhydrous)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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

6.3 Shelf life

Do not use Zavicefta after the expiry date which is stated on the Vial label after EXP:. The expiry date refers to the last day of that month.

After reconstitution

The reconstituted vial should be used immediately.

After dilution

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

Don’t store above 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.

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.

6.6 Special precautions for disposal and other handling

Keep out of the sight and reach of children.

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.

Instructions for preparing adult and paediatric doses in INFUSION BAG or in INFUSION SYRINGE

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 8 below.

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

[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.

<u>Paediatric patients 3 to 12 months of age</u>

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 9, 10, or 11 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 9: 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 10: 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 **25 mg/kg of ceftazidime**	5	125	0.75	5.5
	6	150	0.9	6.6
	7	175	1	7.4
	8	200	1.2	8.8
	9	225	1.3	9.6
	10	250	1.5	11
	11	275	1.6	12
	12	300	1.8	13
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 11: 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.

Paediatric patients from birth (including preterm) to < 3 months of age:

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 12 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 12: 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 **20 mg/kg of ceftazidime**	0.8	16	1.6
	1	20	2
	1.2	24	2.4
	1.4	28	2.8
	1.6	32	3.2
	1.8	36	3.6
	2	40	4
	2.2	44	4.4
	2.4	48	4.8
	2.6	52	5.2
	2.8	56	5.6
	3	60	6
	3.5	70	7
	4	80	8
	4.5	90	9
	5	100	10
	5.5	110	11
	6	120	12

[1] Based on ceftazidime component only.

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER

Pfizer Ireland Pharmaceuticals Unlimited Company
Operations Support Group
Ringaskiddy, County Cork
Ireland

Manufacturer, Packager and Batch Releaser
ACS Dobfar S.p.A.
Via Alessandro Fleming 2
Verona 37135
Italy

8. DATE OF REVISION OF THE TEXT

May 2025

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach and sight of children

Council of Arab Health Ministers
Union of Arabic Pharmacists