ZAVICEFTA
(Ceftazidime-Avibactam)

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 Instructions for use, handling and disposal**).

For a full list of excipients, see section **6.1. List of excipients**.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

A white to pale yellow sterile powder.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Zavicefta is indicated in adults and paediatric patients aged 3 months and older 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)
- 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 aged 3 months and older with limited treatment options (see sections **4.2 Posology and method of administration**, **4.4 Special warnings and precautions for use** and **5.1 Pharmacodynamic properties**).

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 aged 3 months and older with limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases (see section **4.4 Special warnings and precautions for use**).

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.
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 Special warnings and precautions for use** and **5.1 Pharmacodynamic properties**).

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

Type of infection	Age group	Dose of ceftazidime/avibactam[7]	Frequency	Infusion time	Duration of treatment
cIAI[2,3] OR cUTI including pyelonephritis[3] OR HAP/VAP[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	
OR Infections due to aerobic Gram-negative organisms in patients with limited treatment options (LTO)[2,3]	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 Pharmacokinetic properties**).

[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. Instructions for use, handling and disposal**).

Special populations

Elderly
No dosage adjustment is required in elderly patients (see section **5.2 Pharmacokinetic properties**).

Renal impairment
No dosage adjustment is required in patients with mild renal impairment (estimated CrCL > 50 - ≤ 80 mL/min) (see section **5.2 Pharmacokinetic properties**).

Table 3 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 3: 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 Pharmacokinetic properties**).

[3] Ceftazidime and avibactam are removed by haemodialysis (see sections **4.9 Overdose** 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. Instructions for use, handling and disposal**).

Table 4 and Table 5 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 m^2

Table 4: Recommended dose for paediatric patients 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 Pharmacokinetic properties**).
[3] Ceftazidime and avibactam are removed by haemodialysis (see sections **4.9 Overdose** 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. Instructions for use, handling and disposal**).

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

Table 5: Recommended dose for paediatric patients with estimated CrCL[1] ≤ 50 mL/min/1.73 m²

Age Group	Estimated CrCL (mL/min/1.73 m²)	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 (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. Instructions for use, handling and disposal**).

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 (see section **5.2 Pharmacokinetic properties**).

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

Method of administration

Intravenous use.

Zavicefta is administered by intravenous infusion over 120 minutes in an appropriate infusion volume (see section **6.6 Instructions for use, handling and disposal**).

For instructions on reconstitution and dilution of the medicinal product before administration see section **6.6 Instructions for use, handling and disposal**.

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 Undesirable effects**). 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 Undesirable effects**).

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 Zavicefta (see section **4.8 Undesirable effects**). 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 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.

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 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.

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 Pharmacodynamic properties**).

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.

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 Instructions for use, handling and disposal**) 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 (see sections **4.9 Overdose** and **6.6 Instructions for use, handling and disposal**).

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

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 Preclinical safety data**).

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 Preclinical safety data**).

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 Undesirable effects**).

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)
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**	**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			Jaundice

System Organ Class	Very common	Common	Uncommon	Very rare	Not known
		Blood lactate dehydrogenase Increased			
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 Symptoms (DRESS)
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			

[*] ADR identified post-marketing.

[a] Acute coronary syndrome associated with an allergic reaction.

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 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 authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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

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

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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Zavicefta in one or more subsets of the paediatric population in the treatment of cIAI, cUTI, pneumonia and Gram-negative bacterial infections (see section **4.2 Posology and method of administration** for information on paediatric use).

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 (0.05 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 Posology and method of administration**.

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-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.

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

Sterile sodium carbonate (anhydrous)

6.2. INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section **6.6 Instructions for use, handling and disposal**.

6.3. SHELF LIFE

Pack (Nature & Content of Container)	Shelf-life	Storage Conditions

20 mL, clear, Type I glass vials with fluorinated polymer coated halobutyl rubber injection stoppers.	36 months	Do not store above 30ºC, protect from light.

After reconstitution.
The reconstituted vial should be used immediately.

After dilution.

Infusion bags
If the intravenous solution is prepared with diluents listed in section **6.6 Instructions for use, handling and disposal** (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 Instructions for use, handling and disposal** (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
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, 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 1 vial.
Filled vials are packed in cartons to provide light protection.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

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

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

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

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 aged 3 to 12 months**, detailed steps to prepare a 20 mg/mL concentration (sufficient for most scenarios) are also provided.

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 7 below.

Table 7: Preparation of Zavicefta for adult and paediatric doses in INFUSION BAG.

Zavicefta Dose (ceftazidime)[1]	**Volume to withdraw from reconstituted vial**	**Final volume after dilution in infusion bag[2]**	**Final volume in infusion syringe**
2 g	Entire contents (approximately 12 mL)	50 mL to 250 mL	50 mL
1g	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

Zavicefta Dose (ceftazidime)[1]	**Volume to withdraw from reconstituted vial**	**Final volume after dilution in infusion bag[2]**	**Final volume in infusion syringe**
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.

Preparation of Zavicefta for use in paediatric patients aged 3 to 12 months of age in INFUSION SYRINGE:

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 8, 9, or 10 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 utilized to estimate the approximate volume to verify the calculation.

Table 8: 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	4	160	1	7.4

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 **40 mg/kg of ceftazidime**	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 9: 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 10: 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

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)
	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.

6.7. DRUG PRODUCT SPECIFICATIONS

Pfizer Specs.

7. MARKETING AUTHORIZATION HOLDER

Marketed by:
Pfizer Pakistan Limited,
B-2, S.I.T.E., Karachi Pakistan.

7.1 MANUFACTURER

Name of Manufacturing site	Address of site	Manufacturing step (if applicable)
M/s ACS Dobfar	S.p.A. Via Alessandro Fleming 2, Verona, 1-37135, Italy.	Production, Primary and Secondary Packaging, Batch Release

8. REGISTRATION NUMBER:

106848

9. DATE FROM WHICH MARKETING IS AUTHORIZED:

06-May-2021

10. DATE OF REVISION OF THE TEXT:

June 2024

Zavicefta/LPD/PK-03
According to EMA approved SmPC dated 19 February 2024 and approved information in Pakistan

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*