For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

Ceftazidime Pentahydrate and Avibactam Sodium

Zavicefta®

1. GENERIC NAME

Ceftazidime Pentahydrate and Avibactam Sodium

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.

Excipient with known effect: each vial contains 6.44 mmol of sodium (approximately 148 mg).

List of Excipients

Sodium carbonate (anhydrous)

3. DOSAGE FORM AND STRENGTH

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

A white to yellow powder.

Ceftazidime pentahydrate equivalent to 2 g ceftazidime and avibactam sodium equivalent to 0.5 g avibactam.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ceftazidime Pentahydrate and Avibactam Sodium is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.2):

- Complicated intra-abdominal infection (cIAI)

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- Complicated urinary tract infection (cUTI), including pyelonephritis
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP) with susceptible gram negative microorganisms

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

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

4.2 Posology and Method of Administration

Posology

Table 1 shows the recommended intravenous dose for patients with estimated creatinine clearance (CrCL) ≥51 mL/min (see sections 4.4 and 5.2).

Table 1: Recommended intravenous dose for patients with estimated CrCL ≥51 mL/min[1]

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

[1] CrCL estimated using the Cockcroft-Gault formula.
[2] To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.
[3] To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process.
[4] The total duration shown may include intravenous Ceftazidime Pentahydrate and Avibactam Sodium followed by appropriate oral therapy.

Special populations

Elderly
No dosage adjustment is required in elderly patients (see section 5.3).

Renal impairment
No dosage adjustment is required in patients with mild renal impairment (estimated CrCL ≥51 - ≤80 mL/min) (see section 5.3).

Table 2 shows the recommended dose adjustments for patients with estimated CrCL ≤50 mL/min (see sections 4.4 and 5.3).

Table 2: Recommended intravenous doses for patients with estimated CrCL ≤50 mL/min[1]

Estimated CrCL (mL/min)	Dose regimen[2,4]	Frequency	Infusion time
31-50	1 g/0.25 g	Every 8 hours	2 hours
16-30	0.75 g/0.1875 g	Every 12 hours	2 hours
6-15	0.75 g/0.1875 g	Every 24 hours	2 hours
ESRD including on haemodialysis[3]	0.75 g/0.1875 g	Every 48 hours	2 hours

[1] CrCL estimated using the Cockcroft-Gault formula.
[2] Dose recommendations are based on pharmacokinetic modelling.
[3] Ceftazidime and avibactam are removed by haemodialysis (see sections 4.9 and 5.3). Dosing of Ceftazidime Pentahydrate and Avibactam Sodium 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 8.4).

Hepatic impairment
No dosage adjustment is required in patients with hepatic impairment (see section 5.3).

Method of administration

Ceftazidime Pentahydrate and Avibactam Sodium is administered by intravenous infusion over 120 minutes in an infusion volume of 100 mL.

For instructions on reconstitution and dilution of the medicinal product before administration see section 8.4.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 2.

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 Ceftazidime Pentahydrate and Avibactam Sodium 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.

Clostridium difficile-associated diarrhoea

Clostridium difficile-associated diarrhoea has been reported with ceftazidime/avibactam and can range in severity from mild to life-threatening. This diagnosis should be considered in patients who present with diarrhoea during or subsequent to the administration of Ceftazidime Pentahydrate and Avibactam Sodium (see section 4.8). Discontinuation of therapy with Ceftazidime Pentahydrate and Avibactam Sodium and the administration of specific treatment for *Clostridium 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 Ceftazidime Pentahydrate and Avibactam Sodium 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 Ceftazidime Pentahydrate and Avibactam Sodium treatment cannot be ruled out. Patients experiencing anaemia during or after treatment with Ceftazidime Pentahydrate and Avibactam Sodium should be investigated for this possibility.

Limitations of the clinical data

Clinical efficacy and safety studies of Ceftazidime Pentahydrate and Avibactam Sodium have been conducted in cIAI, cUTI and HAP (including VAP).

Complicated intra-abdominal infections
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 4.0% had bacteraemia at baseline. Death occurred in 2.1% (18/857) of patients who received Ceftazidime Pentahydrate and Avibactam Sodium 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 Ceftazidime Pentahydrate and Avibactam Sodium 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 Ceftazidime Pentahydrate and Avibactam Sodium than is currently recommended for patients in this sub-group.

Complicated urinary tract infections
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 a single study in patients with nosocomial pneumonia 280/808 (34.7%) had VAP and 40/808 (5.0%) were bacteraemic at baseline.

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 5.2). 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 5.2).

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.

4.5 Drugs Interactions

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 Use in Special Populations

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 6.1).

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 6.1).

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 Ceftazidime Pentahydrate and Avibactam Sodium (see section 4.8).

4.8 Undesirable Effects

Summary of the safety profile

In seven Phase 2 and Phase 3 clinical trials, 2024 adult patients were treated with Ceftazidime Pentahydrate and Avibactam Sodium. The most common adverse reactions occurring in ≥5% of patients treated with Ceftazidime Pentahydrate and Avibactam Sodium 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 Ceftazidime Pentahydrate and Avibactam Sodium. 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 3: 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)	Clostridium 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; 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	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.

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.

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 Mechanism of Action

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

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.

5.2. Pharmacodynamic Properties

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.

5.3 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 22 L and 18 L, respectively in healthy adults following multiple doses of 2000 mg/500 mg ceftazidime/avibactam infused over 2 hours every 8 hours. Both ceftazidime and avibactam penetrate into human bronchial epithelial lining fluid (ELF) to the same extent with concentrations around 30% of those in plasma. The concentration time profiles are similar for ELF and plasma.

Penetration of ceftazidime into the intact blood-brain barrier is poor. Ceftazidime concentrations of 4 to 20 mg/L or more are achieved in the CSF when the meninges are inflamed. Avibactam penetration of the blood brain barrier has not been studied clinically; however, in rabbits with inflamed meninges, CSF exposures of ceftazidime and avibactam were 43% and 38% of plasma AUC, respectively. Ceftazidime crosses the placenta readily, and is excreted in the breast milk.

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.

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

6. NON-CLINICAL PROPERTIES

6.1. Animal Toxicology or Pharmacology

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.

7. DESCRIPTION

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

A white to yellow powder.

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.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 8.4.

8.2 Shelf-life

Dry powder

3 years.

After reconstitution

The reconstituted vial should be used immediately.

After dilution

If the intravenous solution is prepared with diluents listed in section 8.4 (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 8.4 (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.

8.3 Packaging Information

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

The medicinal product is supplied in packs of 10 vials.

8.4 Storage and Handling Instructions

Store below 30°C in the original package. Protect from light.

Keep out if the sight and reach of children.
For storage conditions of the reconstituted and diluted medicinal product, see section 8.2.

Special Precaution for Use and Handling

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

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.

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 doses in INFUSION BAG:

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.

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):
   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.

Refer to Table 4 below.

Table 4: Preparation of Ceftazidime/avibactam for adult doses in INFUSION BAG.

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

[1] Based on ceftazidime component only.

[2] Dilute to final ceftazidime concentration of 8 mg/mL for in-use stability up to 12 hours at 2 - 8°C, followed by up to 4 hours at not more than 25°C (i.e. dilute 2 g dose of ceftazidime in 250 mL, 1 g dose of ceftazidime in 125 mL, 0.75 g dose of ceftazidime in 93 mL, etc.). All other ceftazidime concentrations (> 8 mg/mL to 40 mg/mL) have in-use stability up to 4 hours at not more than 25°C.

9. PATIENT COUNSELLING INFORMATION

Serious Allergic Reactions
Advise patients, their families, or caregivers that allergic reactions, including serious allergic reactions, could occur that require immediate treatment. Ask them about any previous hypersensitivity reactions to ceftazidime/avibactam, other beta-lactams (including cephalosporins), or other allergens (see section 4.4).

Potentially Serious Diarrhea
Advise patients, their families, or caregivers that diarrhea is a common problem caused by antibacterial drugs. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, tell them to contact his or her healthcare provider (see section 4.4).

Nervous System Reactions
Advise patients, their families, or caregivers that neurological adverse reactions can occur with ceftazidime/avibactam use. Instruct patients their families, or caregivers to inform a healthcare provider at once of any neurological signs and symptoms, including encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures, for immediate treatment, dosage adjustment, or discontinuation of ceftazidime/avibactam (see section 4.4).

Antibacterial Resistance
Counsel patients, their families, or caregivers that antibacterial drugs including ceftazidime/avibactam should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ceftazidime/avibactam is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ceftazidime/avibactam or other antibacterial drugs in the future (see section 4.4).

10. DETAILS OF MANUFACTURER

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11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

IMP-17/2021 dated 12 Feb 2021
IMP-ND-230/2018 dated 1 Oct 2018

12. DATE OF REVISION

June 2025