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

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Ceftazidime & Avibactam Powder for Concentrate for Solution for Infusion

VERICEFTA **2.5gm**

Single Use Vial For IV Infusion Only

Composition:

Each vial contains:

Ceftazidime Pentahydrate IP eq to Ceftazidime	2.0 gm
Avibactam Sodium eq to Avibactam	0.5 gm

Description:

Ceftazidime pentahydrate is a white to almost white, crystalline powder chemically described as (Z)-7-[2-(2-Amino-1, 3-thiazol-4-yl)-2-(1-carboxy-1-methylethyloxyimino) acetylamino]-3-(1-pyridiniumylmethyl)-3-cephem-4-carboxylate pentahydrate with a molecular formula of $C_{22}H_{32}N_6O_{12}S_2$ (as pentahydrate). Avibactam sodium is a white to pale yellow crystalline powder chemically described as Sodium; [(2S, 5R)-2-carbamoyl-7-oxo-1, 6-diazabicyclo [3.2.1]octan-6-yl] sulfate with a molecular formula of $C_7H_9N_3O_6SNa$.

Pharmacology:

Mechanism of action: Ceftazidime inhibits bacterial peptidoglycan cell wall synthesis following attachment to penicillin binding proteins (PBPs), which leads to bacterial cell lysis and death. This broad-spectrum cephalosporin is active against many important Gram-negative and Gram-positive bacterial pathogens *in vitro*. 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, including extended-spectrum β-lactamases (ESBLs), KPC carbapenemases, and AmpC enzymes. Avibactam also inhibits the class D carbapenemase OXA-48, which does not significantly hydrolyze ceftazidime. Avibactam has no clinically relevant in vitro antibacterial activity. Avibactam did not induce transcription of blaAmpC in Enterobacter cloacae, Citrobacter freundii or Pseudomonas aeruginosa in vitro at concentrations used to treat patients.

Mechanism Mechanism of resistance: Ceftazidime-avibactam is not active against metallo-β-lactamase-producing bacteria. 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, mutated or acquired β-lactamase enzymes insensitive to avibactam and able to hydrolyze ceftazidime.

Cross-resistance: An absence of cross-resistance between ceftazidime-avibactam and fluoroquinolones or aminoglycosides has been demonstrated in vitro using molecularly-characterized clinical isolates. Some isolates resistant to ceftazidime (and other cephalosporins) or to carbapenems are susceptible to ceftazidime-avibactam. There is cross-resistance with β-lactam antibacterial agents, including carbapenems, when the mechanism is production of metallo-β-lactamases, such as VIM-2.

Interaction with other antimicrobial agents: In vitro interaction tests with ceftazidime-avibactam show ceftazidime-avibactam has little potential to antagonize or be antagonized by other antibiotics of various classes (e.g. metronidazole, tobramycin, levofloxacin, vancomycin, linezolid, colistin, tigecycline).

Clinical efficacy against specific pathogens: Efficacy has been demonstrated in clinical studies against the pathogens, listed under each indication, 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.* Ceftazidime-avibactam is active *in vitro* against *Streptococcus pyogenes* and *Streptococcus agalactiae,* but not generally active against other clinically-important Gram-positive bacteria *including methicillin-resistant Staphylococcus aureus* (MRSA).

Pharmacokinetics:

Distribution: The human protein binding of both ceftazidime and avibactam is low, approximately 10% and 8%, respectively. The steady-state volumes of distribution of ceftazidime and avibactam were comparable, about 17 L and 22 L, respectively in healthy adults following multiple doses of 2 g/500 mg ceftazidime-avibactam infused over 2 hours every 8 hours. Pharmacokinetic parameters of ceftazidime and avibactam following single and multiple dose administration of Ceftazidime/Avibactam were like those determined when ceftazidime or avibactam were administered alone. Both ceftazidime and avibactam penetrate into human bronchial epithelial lining fluid (ELF) to the same extent with concentrations around 30% that of plasma, and a similar concentration time profile between ELF and plasma. Ceftazidime and avibactam plasma exposure were comparable across patients with different indications, cIAI, cUTI and NP. Penetration of ceftazidime into the intact blood-brain barrier is poor, resulting in low levels of ceftazidime in the CSF in the absence of inflammation. However, 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. For ceftazidime, concentrations in excess of the MIC of ceftazidime-avibactam for common pathogens can be achieved in tissues such as bone, heart, bile, sputum, aqueous humor, synovial, pleural and peritoneal fluids. Ceftazidime crosses the placenta readily and is excreted in the breast milk. Avibactam penetrates into the subcutaneous tissue at the site of skin infections, with tissue concentrations approximately equal to free drug concentrations in plasma.

Biotransformation: Ceftazidime is not metabolized. No metabolism of avibactam was observed in human liver preparations (microsomes and hepatocytes). Unchanged avibactam was the major drug-related component in human plasma and urine following dosing with [14C]-avibactam

Elimination: The terminal half-life (t½) of both ceftazidime and avibactam is about 2 h after IV 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 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 feces.

Special populations: Patients with renal impairment: Elimination of ceftazidime and avibactam is decreased in patients with moderate or severe renal impairment, and end stage renal disease including patients undergoing hemodialysis; the dose should be reduced in patients with CrCl ≤50 ml/min).

Patients with hepatic impairment: Mild to moderate hepatic impairment had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g IV 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. As ceftazidime and avibactam do not appear to undergo significant hepatic metabolism, the systemic clearance of either drug is not expected to be significantly altered by hepatic impairment. Therefore, no dosage adjustment of ceftazidime-avibactam is recommended for patients with hepatic impairment.

Elderly patients: The reduced clearance observed in elderly patients was primarily due to age-related decrease in renal clearance of ceftazidime. The mean elimination half-life ranged from 3.5 to 4 hours following single or 7 days repeated every 12 hours dosing of 2 g IV bolus injections in elderly patients 80 years or older. Following single dose IV 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. Dosage adjustment for ceftazidime-avibactam is not required in elderly subjects (≥ 65 years of age) with CrCl > 50 ml/min.

Pediatric patients: The pharmacokinetics of ceftazidime and avibactam were evaluated in pediatric 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 Ceftazidime /Avibactam 2.5 g 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 AUC0-t and Cmax values in the two older cohorts (children 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 Ceftazidime/Avibactam 2 g/0.5 g. Data from this study and the two Phase 2 pediatric 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 pediatric 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 Ceftazidime/Avibactam dose of 2 g/0.5 g administered over 2 hours, every 8 hours.

Gender: The pharmacokinetics of ceftazidime-avibactam was similar between males and females. No dose adjustment is required based on sex.

Race: Based on a population pharmacokinetic analysis, no dose adjustment of ceftazidime-avibactam is required based on race.

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 injection 10mL 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 by transferring an appropriately 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 and 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.

Preparation of adult and paediatric doses in INFUSION BAG or in INFUSION SYRINGE.

Threezid-AVDose (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
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 in0use 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 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 injection 10 mg/mL of sterile water for injections
   b) Withdraw the needle and shake the vial to give a clear solution..
   c) Insert 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 9mg/mL (0.9%)vsolution for injection or dextrose 50 mg/mL (5%) solution for injection) to an infusion syringe.

Storage

Store at temperatures not exceeding 30°C. Store in the original package in order to protect from light. After reconstitution: The reconstituted vial should be used immediately. After dilution: Once the intravenous solution is prepared with diluents it should be administered within 12 hours of preparation. The chemical and physical in-use stability has been demonstrated for up to 24 hours at 2-8°C. Once removed from refrigeration the diluted product must be stored at room temperature and used within 12 hours. From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

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