Ziditam™

Ceftazidime and Avibactam

Presentation
Ziditam™IV Infusion: Each vial contains Ceftazidime and Avibactam Sodium for injection INN equivalent to Ceftazidime 2 gm and Avibactam 0.5 gm.

Description
Ziditam™ is an antibacterial combination product consisting of the semisynthetic cephalosporin ceftazidime pentahydrate and the beta-lactamase inhibitor avibactam sodium for intravenous administration.

Pharmacology
The ceftazidime component of Ziditam™ is a cephalosporin antibacterial drug with in vitro activity against certain gram-negative and gram-positive bacteria. The bactericidal action of ceftazidime is mediated through binding to essential penicillin-binding proteins (PBPs). The avibactam component of Ziditam™ is a non-beta-lactam beta-lactamase inhibitor that inactivates certain beta-lactamases that degrade ceftazidime. Avibactam does not decrease the activity of ceftazidime against ceftazidime-susceptible organisms.

Indications
- Complicated Intra-abdominal Infections (cIAI)
- Complicated Urinary Tract Infections (cUTI), including Pyelonephritis
- Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

Dosage and Administration
Recommended Dosage in Adult Patient

Dosage in Adult Patients with Creatinine Clearance (CrCl) greater than 50 ml/min				
Infection	**Dose**	**Frequency**	**Infusion Time (hours)**	**Duration of Treatment**
Complicated Intra-abdominal Infections [used in combination with metronidazole] (cIAI)	2.5 gm	Every 8 hours	2	cIAI: 5 to 14 days cUTI: 7 to 14 days HABP/VABP: 7 to 14 days
Complicated Urinary Tract Infections including Pyelonephritis (cUTI)				
Hospital-acquired Bacterial Pneumonia and Ventilator- associated Bacterial Pneumonia (HABP/VABP)				

Dosage in Adult Patients with Creatinine Clearance (CrCl) less than 50 mL/min		
Estimated Creatinine Clearance (ml /minute)[a]	**Dose[b]**	**Frequency**
31 to 50	Ziditam™ 1.25 grams (ceftazidime 1 gram and avibactam 0.25 grams) intravenously	Every 8 hours
16 to 30	Ziditam™ 0.94 grams (ceftazidime 0.75 grams and avibactam 0.19 grams) intravenously	Every 12 hours
6 to 15[c]	Ziditam™ 0.94 grams (ceftazidime 0.75 grams and avibactam 0.19 grams) intravenously	Every 24 hours
Less than or equal to 5[c]	Ziditam™ 0.94 grams (ceftazidime 0.75 grams and avibactam 0.19 grams) intravenously	Every 48 hours
a As calculated using the Cockcroft-Gault formula, b All doses of Ziditam™ are administered over 2 hours, c Both ceftazidime and avibactam are hemodialyzable; thus, administer Ziditam™ after hemodialysis on hemodialysis days.		

Recommended Dosage in Pediatric Patients with cIAI or cUTI

Dosage in Patients 3 months to < 18 years					
Infection	**Age Range**	**Dose**	**Frequency**	**Infusion Time (Hours)**	**Duration of Treatment**
cIAI* and cUTI including Pyelonephritis	2 years to less than 18 years	Ziditam™ 62.5 mg/kg to a maximum of 2.5 grams (Ceftazidime 50 mg/kg and avibactam 12.5 mg/kg to a maximum dose of ceftazidime 2 grams and avibactam 0.5 grams)	Every 8 hours	2	cIAI: 5 to 14 days cUTI: 7 to 14 days
	6 months to less than 2 years	Ziditam™ 62.5 mg/kg (Ceftazidime 50 mg/kg and avibactam 12.5 mg/kg)			
	3 months to less than 6 months	Ziditam™ 50 mg/kg (Ceftazidime 40 mg/kg and avibactam 10 mg/kg)			
a For pediatric patients (2 years or older) with eGFR less than or equal to 50 ml/min/1.73m^2, dosage adjustments are recommended * Ziditam™ was used in combination with metronidazole in cIAI pediatric patients					

In Pediatric Patients 2 to < 18 years with Renal Impairment		
Estimated eGFR[b] (ml/min/1.73m^2)	**Dose**	**Frequency**
31 to 50	Ziditam™ 31.25 mg/kg to a maximum of 1.25 grams (Ceftazidime 25 mg/kg and avibactam 6.25 mg/kg to a maximum dose of ceftazidime 1 gram and avibactam 0.25 grams)	Every 8 hours
16 to 30	Ziditam™ 23.75 mg/kg to a maximum of 0.94 grams (Ceftazidime 19 mg/kg and avibactam 4.75 mg/kg to a maximum dose of ceftazidime 0.75 grams and avibactam 0.19 grams)	Every 12 hours
6 to 15[c]	Ziditam™ 23.75 mg/kg to a maximum of 0.94 grams (Ceftazidime 19 mg/kg and avibactam 4.75 mg/kg to a maximum dose of ceftazidime 0.75 grams and avibactam 0.19 grams)	Every 24 hours
Less than or equal to 5[d]	Ziditam™ 23.75 mg/kg to a maximum of 0.94 grams (Ceftazidime 19 mg/kg and avibactam 4.75 mg/kg to a maximum dose of ceftazidime 0.75 grams and avibactam 0.19 grams)	Every 48 hours
Dosing was derived based on the population PK modeling, which assumed similar proportional effects of renal impairment in adults and pediatric patients 2 years and older, b As calculated using the Schwartz bedside formula, c All doses of Ziditam™ are administered over 2 hours, d Both ceftazidime and avibactam are hemodialyzable; thus, administer Ziditam™ after hemodialysis on hemodialysis days.		

Method of Administration
Ziditam™ is supplied as a dry powder, which must be constituted and subsequently diluted, using aseptic technique prior to intravenous infusion.

Reconstitution Direction
a) Constitute the powder in the Ziditam™ vial with 10 ml of one of the following solutions:
- Sterile water for injection, USP
- 0.9% of sodium chloride injection, USP (normal saline)
- 5% of dextrose injection, USP
- All combinations of dextrose injection and sodium chloride injection, USP, containing up to 2.5% dextrose, USP, and 0.45% sodium chloride, USP, or
- Lactated Ringer's injection, USP

b) Mix gently and ensure that the contents are dissolved completely. The constituted Ziditam™ solution will have an approximate ceftazidime concentration of 167 mg/ml and an approximate avibactam concentration of 42 mg/ml. The final volume is approximately 12 ml. The constituted solution is not for direct injection. The constituted solution must be diluted before intravenous infusion.
c) Prepare the required dose for intravenous infusion by withdrawing the appropriate volume determined from the following table from the constituted vial.

Preparation of Ziditam™ Doses for Adult and Pediatric Patients (Weighing 40 kg or More)	
Dose	**Volume to Withdraw from Constituted Vial for Further Dilution to 50 to 250[a] ml**
2.5 grams (2 grams and 0.5 grams)	12 ml (entire contents)
1.25 grams (1 gram and 0.25 grams)	6 ml
0.94 grams (0.75 grams and 0.19 grams)	4.5 ml
a. Dilution to 250 ml should only be used for the 2.5 gram dose	

d) Before infusion, dilute the withdrawn volume of the constituted Ziditam™ solution further with the same diluent used for constitution of the powder (except sterile water for injection), to achieve a ceftazidime concentration of 8 to 40 mg/mL and an avibactam concentration of 2 to 10 mg/mL in an infusion bag. If sterile water for injection was used for constitution, use any of the other appropriate constitution diluents for dilution.
e) Mix gently and ensure that the contents are dissolved completely. Visually inspect the diluted Ziditam™ solution (for administration) for particulate matter and discoloration prior to administration (the color of the Ziditam™ infusion solution for administration ranges from clear to light yellow).
f) Use the diluted Ziditam™ solution in the infusion bags within 12 hours when stored at room temperature.
g) The diluted Ziditam™ solution in the infusion bags may be stored under refrigeration at 2 to 8 °C up to 24 hours following dilution and used within 12 hours of subsequent storage at room temperature.

Overdosage
In the event of overdose, discontinue Ziditam™ and institute general supportive treatment. Ceftazidime and avibactam can be removed by hemodialysis.

Contraindications
Ziditam™ is contraindicated in patients with known serious hypersensitivity to the components of Ziditam™ (ceftazidime and avibactam), avibactam-containing products or other members of the cephalosporin class.

Warning and Precautions
Decreased efficacy in adult cIAI patients with baseline CrCl of 30 to less than or equal to 50 ml/ min: Monitor CrCl at least daily in adult and pediatric patients with changing renal function and adjust the dose of Ziditam™ accordingly.
Hypersensitivity reactions: Includes anaphylaxis and serious skin reactions. Cross-hypersensitivity may occur in patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue Ziditam™.
Clostridium difficile-associated diarrhea (CDAD): CDAD has been reported with nearly all systemic antibacterial agents, including Ziditam™.Evaluate if diarrhea occurs.
Central Nervous System Reactions: Seizures and other neurologic events may occur, especially in patients with renal impairment. Adjust dose in patients with renal impairment.

Side Effects
Adult cIAI, cUTI and HABP/VABP Patients: The most common adverse reactions in cIAI (≥ 5%, when used with metronidazole) patients are diarrhea, nausea and vomiting. The most common adverse reactions (3%) in cUTI patients are diarrhea and nausea. The most common adverse reactions (≥ 5%) in HABP/VABP patients were diarrhea and vomiting.
Pediatric cIAI and cUTI Patients: The most common adverse reactions (> 3%) in pediatric patients were vomiting, diarrhea, rash, and infusion site phlebitis.

Drug Interactions
Clinical interaction study of Ziditam™ or avibactam alone with probenecid has not been conducted, co-administration of Ziditam™ with probenecid is not recommended.

Use in Pregnancy and Lactation
Pregnancy: There are no adequate and well-controlled studies of ceftazidime or avibactam in pregnant women. Lactation: No information is available on the effects of ceftazidime and avibactam on the breast-fed child or on milk production.

Storage Condition
Do not store above 30 ^{0}C. Keep away from light and out of the reach of children.

Commercial Pack
Ziditam™IV Infusion: Each box contains one blister strip containing one vial of 2.5 gm injection with one ampoule of 10 ml water for injection.

Manufactured by
Incepta Pharmaceuticals Ltd
Savar, Dhaka, Bangladesh
™ Trademark