Avitaz™

Ceftazidime 2 gm & Avibactam 0.5 gm

Composition
Avitaz™ 2.5 gm powder for IV Infusion: Each vial contains sterile mixture of 2 gm Ceftazidime (as Ceftazidime Pentahydrate buffered with Sodium Carbonate) and 0.5 gm Avibactam (as Avibactam Sodium) and each ampoule contains 10 ml Water for Injections BP (Sterile).

Description
Avitaz™ 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 Avitaz™ 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 Avitaz™ 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
Indicated for the treatment of the following infections caused by susceptible Gram-negative microorganisms in adult and pediatric patients (which are born having completed at least 31 weeks gestational age):

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

Dosage & Administration
Recommended dose in adult patients:
The recommended dosage of Avitaz™ is 2.5 gram (Ceftazidime 2 grams and Avibactam 0.5 gram) administered every 8 hours by intravenous (IV) infusion over 2 hours in patients 18 years of age and older with CrCl greater than 50 mL/min. For treatment of cIAI, metronidazole should be given concurrently. The guidelines for dosage of Avitaz™ in patients with creatinine clearance (CrCl) greater than 50 mL/min are listed in Table 1.

Table 1. Dosage of Avitaz™ 2.5 grams (Ceftazidime 2 grams and Avibactam 0.5 grams) by Indication in Adult Patients (18 years of age and older)

Infection	Dose	Frequency	Infusion time (hours)	Duration of Treatment
Complicated Intra-abdominal Infections (cIAI)*	2.5 grams	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)				

*Used in conjunction with metronidazole 0.5 g intravenously every 8 hours in adult cIAI patients.

Recommended Dosage in Pediatric Patients
The recommended dosage of Avitaz™ in pediatric patients aged 2 years to less than 18 years and an estimated glomerular filtration rate (eGFR) greater than 50 mL/min/1.73 m^2 and in pediatric patients less than 2 years of age without renal impairment is described in Table 2. Avitaz™ is administered every 8 hours by intravenous infusion over 2 hours. For treatment of cIAI, metronidazole should be given concurrently.

Table 2. Dosage of Avitaz™ (Ceftazidime and Avibactam) in Pediatric Patients

Infection	Age range	Dose	Frequency	Infusion time (hours)	Duration of Treatment
cIAI*, cUTI including Pyelonephritis, and HABP/ VABP	2 years to less than 18 years[a]	Avitaz™ 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 HABP/ VABP: 7 to 14 days
	6 months to less than 2 years	Avitaz™ 62.5 mg/kg (Ceftazidime 50 mg/kg and avibactam 12.5 mg/kg)			
	3 months to less than 6 months	Avitaz™ 50 mg/kg (Ceftazidime 40 mg/kg and avibactam 10 mg/kg)			
	Greater than 28 days[b] to less than 3 months	Avitaz™ 37.5 mg/kg (Ceftazidime 30 mg/kg and avibactam 7.5 mg/kg)			
	Less than or equal to 28 days[c] with GA 31 weeks and older	Avitaz™ 25 mg/kg (Ceftazidime 20 mg/kg and avibactam 5 mg/kg)			

*Avitaz™ was used in conjunction with metronidazole 10 mg/kg intravenously every 8 hours in pediatric cIAI patients.

a. For pediatric patients (aged 2 years and older) with eGFR less than or equal to 50 mL/min/1.73m^2, dosage adjustments are recommended (Table. 3).

b. Includes full-term infants with PNA > 28 days and pre-term infants with corrected age > 28 days. Corrected age is calculated by subtracting the number of weeks born before 40 weeks of gestation from the postnatal age.

c. Includes neonates PNA ≤ 28 days and pre-term infants with corrected age ≤ 28 days.
GA = gestational age and PNA = postnatal age.

Dosage Adjustments in Adult and Pediatric Patients (Aged 2 Years and Older) with Renal Impairment:
The recommended Avitaz™ dosage in adult and pediatric patients aged 2 years and older with varying degrees of renal function is presented in Table 3 and Table 4, respectively. For patients with changing renal function, monitor CrCl in adults or eGFR in pediatric patients at least daily and adjust the dosage of Avitaz™ accordingly. There is insufficient information to recommend a dosing regimen for pediatric patients less than 2 years of age with renal impairment.

Adult Patients

Table 3. Dosage of Avitaz™ in Adult Patients with Renal Impairment

Estimated Creatinine Clearance (mL/minute)[a]	Dose for Avitaz™ (Ceftazidime and avibactam)[b]	Frequency
31 to 50	Avitaz™ 1.25 gm (Ceftazidime 1 gm and avibactam 0.25 gm) intravenously	Every 8 hours
16 to 30	Avitaz™ 0.94 gm (Ceftazidime 0.75 gm and avibactam 0.19 gm) intravenously	Every 12 hours
6 to 15[c]	Avitaz™ 0.94 gm (Ceftazidime 0.75 gm and avibactam 0.19 gm) intravenously	Every 24 hours
Less than or equal to 5[c]	Avitaz™ 0.94 gm (Ceftazidime 0.75 gm and avibactam 0.19 gm) intravenously	Every 48 hours

a. As calculated using the Cockcroft-Gault formula
b. All doses of Avitaz™ are administered over 2 hours
c. Both Ceftazidime and avibactam are hemodialyzable; thus, administer Avitaz™ after hemodialysis on hemodialysis days

Pediatric Patients

Table 4. Dosage of Avitaz™ in Pediatric Patients Aged 2 years and older with Renal Impairment[a]

Estimated eGFR[b] (mL/min/1.73m^2)	Dose for Avitaz™ (Ceftazidime and avibactam)[c]	Frequency
31 to 50	Avitaz™ 31.25 mg/kg to a maximum of 1.25 gm (Ceftazidime 25 mg/kg and avibactam 6.25 mg/kg to a maximum dose of Ceftazidime 1 gm and avibactam 0.25 gm)	Every 8 hours
16 to 30	Avitaz™ 23.75 mg/kg to a maximum of 0.94 gm (Ceftazidime 19 mg/kg and avibactam 4.75 mg/ kg to a maximum dose of Ceftazidime 0.75 gm and avibactam 0.19 gm)	Every 12 hours
6 to 15	Avitaz™ 23.75 mg/kg to a maximum of 0.94 gm (Ceftazidime 19 mg/kg and avibactam 4.75 mg/ kg to a maximum dose of Ceftazidime 0.75 gm and avibactam 0.19 gm)	Every 24 hours
Less than or equal to 5[d]	Avitaz™ 23.75 mg/kg to a maximum of 0.94 gm (Ceftazidime 19 mg/kg and avibactam 4.75 mg/ kg to a maximum dose of Ceftazidime 0.75 gm and avibactam 0.19 gm)	Every 48 hours

a. Dosing was derived based on the population PK modeling, which assumed similar proportional effects of renal impairment in adults and pediatric patients aged 2 years and older
b. As calculated using the Schwartz bedside formula
c. All doses of Avitaz™ are administered over 2 hours
d. Both Ceftazidime and avibactam are hemodialyzable; thus, administer Avitaz™ after hemodialysis on hemodialysis days

Method of administration
Avitaz™ 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 Avitaz™ 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 Avitaz™ 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 Table 5 from the constituted vial. To prepare doses for pediatric patients weighing less than 40 kg, follow the constitution instruction above to yield a solution with a final Avitaz™ concentration of approximately 209 mg/ml (Ceftazidime concentration of 167 mg/mL and an avibactam concentration of 42 mg/ml). Use these concentrations to calculate the volume of Avitaz™ required to prepare the prescribed dose.

Table 5. Preparation of Avitaz™ Doses for Adult and Pediatric Patients (Weighing 40 kg or More)

Avitaz™ (Ceftazidime and avibactam) Dose	Volume to Withdraw from Constituted Vial for Further Dilution to 50 to 250[a] ml
2.5 gm (2 gm and 0.5 gm)	12 ml (entire contents)
1.25 gm (1 gm and 0.25 gm)	6 ml
0.94 gm (0.75 gm and 0.19 gm)	4.5 ml

a. Dilution to 250 mL should only be used for the 2.5 gm dose

d) Before infusion, dilute the withdrawn volume of the constituted Avitaz™ 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 Avitaz™ solution (for administration) for particulate matter and discoloration prior to administration (the color of the Avitaz™ infusion solution for administration ranges from clear to light yellow).

f) Use the diluted Avitaz™ solution in the infusion bags within 12 hours when stored at room temperature.

g) The diluted Avitaz™ solution in the infusion bags may be stored under refrigeration at 2 to 8°C (36 to 46°F) up to 24 hours following dilution and used within 12 hours of subsequent storage at room temperature.

Drug compatibility
The Avitaz™ solution for administration at the range of diluted concentrations of Ceftazidime 8 mg/ml and avibactam 2 mg/ml to Ceftazidime 40 mg/ml and avibactam 10 mg/ml is compatible with the more commonly used intravenous infusion fluids in infusion bags (including Baxter® Mini-Bag Plus™) such as:
- ✓ 0.9% sodium chloride injection, USP
- ✓ 5% 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
- ✓ lactated ringer's injection, USP, and
- ✓ Baxter® Mini-Bag Plus™ containing 0.9% sodium chloride injection or 5% dextrose injection

Storage of Constituted Solutions
Upon constitution with appropriate diluent, the constituted Avitaz™ solution may be held for no longer than 30 minutes prior to transfer and dilution in a suitable infusion bag. Following dilution of the constituted solutions with the appropriate diluents, Avitaz™ solutions in the infusion bags are stable for 12 hours when stored at room temperature. Following dilution of the constituted solutions with the appropriate diluents, Avitaz™ solutions in the infusion bags may also be refrigerated at 2 to 8°C (36 to 46°F) for up to 24 hours; and then should be used within 12 hours of subsequent storage at room temperature.

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

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

Warning & Precautions
- ✓ Decreased Clinical Response 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 dosage of Avitaz™ accordingly.
- ✓ Hypersensitivity Reactions: Includes anaphylaxis and serious skin reactions. Cross sensitivity may occur in patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue Avitaz™.
- ✓ Clostridioides difficile-associated Diarrhea (CDAD): CDAD has been reported with nearly all systemic antibacterial agents, including Avitaz™. 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.

Adverse effects
- Adult 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 Patients (aged 3 months to less than 18 years): The most common adverse reactions (> 3%) in pediatric patients aged 3 months and older were vomiting, diarrhea, rash, and infusion site phlebitis.
- Pediatric Patients (less than 3 months of age): The most common adverse reactions (>3 %) in pediatric patients less than 3 months of age were vomiting and increased transaminases.

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

Use in Pregnancy and Lactation
Pregnancy: There are no adequate and well-controlled studies of Avitaz™, 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 conditions
Store below 25 °C. Protect from light & moisture.

How supplied
Avitaz™ 2.5 gm powder for IV Infusion: Each box contains 1 vial of 2.5 gm (Ceftazidime 2 gm and avibactam 0.5 gm) with 1 ampoule of 10 ml Water for Injections BP (sterile).

Manufactured by-
SQUARE PHARMACEUTICALS PLC.
Kaliakoir, Gazipur, Bangladesh

Scan for more information

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