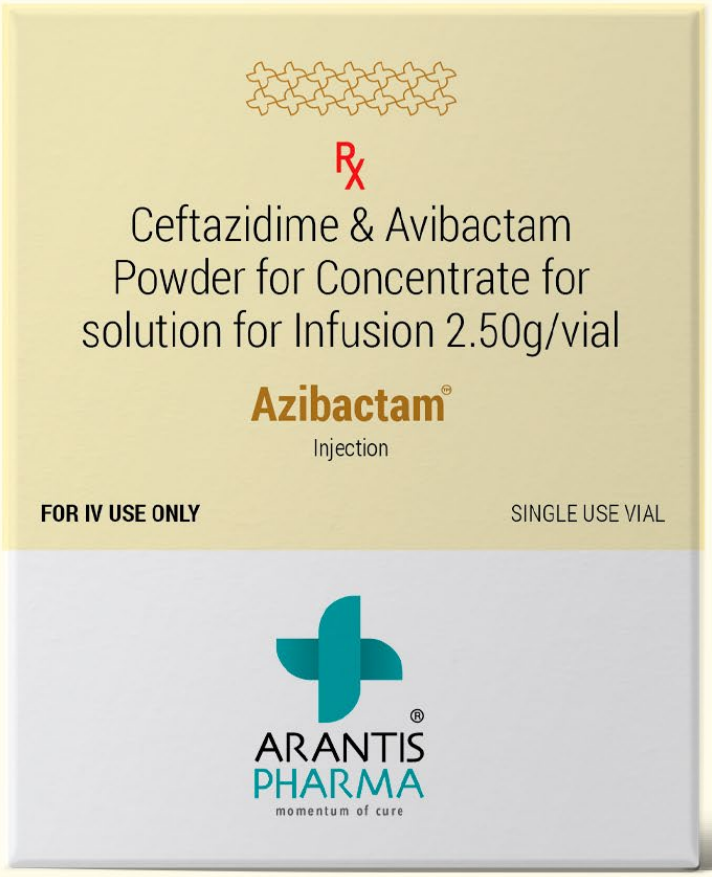



**PRODUCT MONOGRAPH FOR**

# AZIBACTAM IINJ IV

## (Ceftazidime2000 mg/Avibactam 500 mg)

Ceftazidime is a third-generation cephalosporin &Avibactam is a beta-lactamase inhibitor.

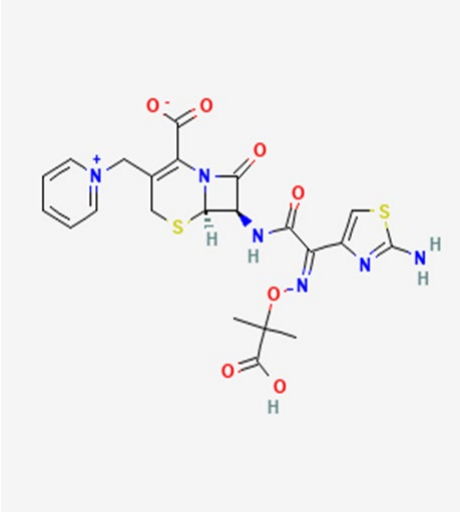
## IUPAC NAME:

6R,7R)-7-[[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-(2-carboxypropan-2-yloxyimino)acetyl]amino]-8-oxo-3-(pyridin-1-ium-1-ylmethyl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

**MOLECULAR FORMULA:** C22H22N6O7S2

**MOLECULAR WEIGHT:** 546.6 G/MOL

**STRUCTURAL FORMULA:**



Avibactam sodium is an organic sodium salt that is the monosodium salt of avibactam. Used in combination with ceftazidime pentahydrate for the treatment of complicated urinary tract infections including pyelonephritis. It has a role as an EC 3.5.2.6 (beta-lactamase) inhibitor, an antibacterial drug and an antimicrobial agent.

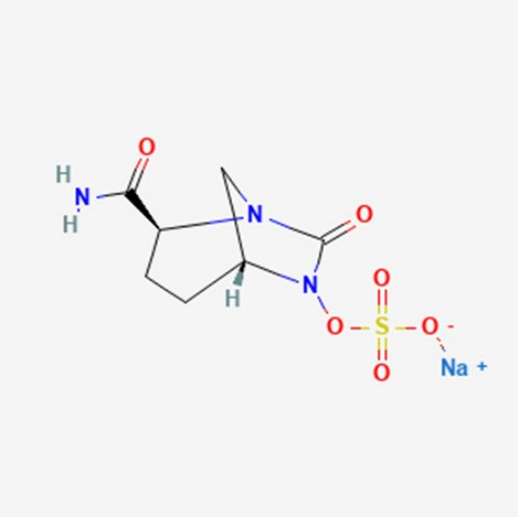
## IUPAC NAME

sodium ;[(2S,5R)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl] sulphate.

**MOLECULAR FORMULA: C7H10N3NaO6S**

**MOLECULAR WEIGHT: 287.23/G MOL**

**STRUTURAL FORMULA:**



## Indications:

Ceftazidime + Avibactam is indicated for complicated urinary tract infections (cUTI), including pyelonephritis and complicated intra-abdominal infections (cIAI) used in combination with metronidazole who have limited or no alternative treatment options.

• Active against Gram-negative pathogens, including *Pseudomonas*, *Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus* spp., *Providencia stuartii*, *Citrobacter koseri, Citrobacter freundii, Enterobacter aerogenes,* and *Enterobacter cloaca.*

• Activity against Gram-positive pathogens, *(has not been published yet)*

• Anaerobic activity is limited to *Bacteroides fragilis, Clostridium perfringens, Prevotella* spp., *and Porphyromonas* spp.

## Clinical Pharmacology:

Mechanism of action -Ceftazidime, like other b-lactams, inhibits peptidoglycan synthesis by inhibiting penicillin-binding proteins (PBPs). Inactivation of a sufficient fraction of the PBPs leads to an unstable peptidoglycan cell wall, ultimately resulting in cell death. Avibactam is a potent inhibitor of Ambler class A and class D beta- lactamases, both chromosomal and mobile Ambler class C beta-lactamases, and KPC carbapenemases. It forms a carbon bond between the C-7 of avibactam and the active-site serine that forms an acyl bond with beta-lactams. Avibactam does not restore the activity of ceftazidime against organisms producing metallobeta-lactamases and some OXA beta-lactamase

## PHARMACOKINETICS:

**ABSORPTION:** Available as IV Infusion only

**DISTRIBUTION:** Vdss:17-22.5 L

**PROTIEN BINDING:** 10-17%

**METABOLISM:** 80-90% of the Ceftazidime&Avibactam are eliminated through urine. None of them are substrate for cytochrome P 450.

**BIOAVAILABILITY:**
**HALF LIFE OF ELIMINATION:** 17.20-2.1 HRS
**TIME TO PEAK:** 1.01-1.1 HRS

**EXCRETION:**
Both Ceftazidime&Avibactam undergo<95% renal elimination by active tubular secretion.
***Comparative Efficacy:***
**Lucasti C, Popescu I, Ramesh MK, et al. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of**

**complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind Phase II trial. *J Antimicrob Chemother.* 2013; 68(5):1183-92.**

Study characteristics, Primary and Secondary Endpoints, Population and Methods: o This was a Phase II, prospective, double-blind, multi-center, randomized, active-controlled trial conducted in Eastern Europe, Russia, India, Lebanon and the United States, and was designed to assess patient clinical and microbiological responses to and the safety of ceftazidime/avibactam plus metronidazole compared with those of meropenem. Hospitalized adults with complicated intra-abdominal infections (cIAIs) that required surgical intervention were randomized (1:1) and stratified by APACHE score (<10 and 10-25) to receive IV ceftazidime/avibactam (2.5 g [containing 2,000 mg ceftazidime and 500 mg avibactam] every 8 h [q8h]) with IV metronidazole (500 mg q8h) or IV meropenem (1 g q8h) for 5 to 14 days.
o The primary endpoint was the clinical response at the test-of-cure (TOC) visit in the microbiologically evaluable (ME) population.
o Secondary measures included the patients' microbiological response and safety at both the TOC and late follow-up (LFU) visits.
o Hospitalized patients were eligible for inclusion if they had the following diagnoses: cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall; diverticular disease with perforation or abscess; appendiceal perforation or peri-appendiceal abscess; acute gastric and duodenal perforation (surgery >24 h after perforation); traumatic perforation of the intestines (>12 h after perforation); secondary peritonitis (but not spontaneous peritonitis associated with cirrhosis and chronic ascites); or intra-abdominal abscess with evidence of intraperitoneal involvement. Patients were excluded if they were unlikely to respond to treatment, if they were unlikely to survive the study period, if they were immunosuppressed, had an APACHE score >25, had renal or liver dysfunction at baseline, bowel obstruction, abdominal wall abscess, concomitant infection, or had been treated with antibiotics within the past 72 hours.

- Results: o For the primary endpoint in the ME population, a favourable outcome at the TOC was observed in 91.2% (62/68) and 93.4% (71/76) of the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively.
- Secondary endpoints were similar between the two groups with very high rates of favourable clinical response at the end of IV therapy in the ME population (97.1% versus 97.4% in the ceftazidime/avibactam and meropenem groups) and at TOC (92% [80/87] versus 94.4% [85/90]) and the end of IV therapy (96.6% versus 97.8%) in the clinically evaluable population. >90% of all patients had a favourable microbiological response in both treatment groups.
- Safety analysis revealed that serious adverse events (SAEs) occurred in 8.9% [9/101] and 10.8% [11/102] of patients in the ceftazidime/avibactam and meropenem groups respectively. The overall incidences of AEs that were reported after the start of therapy with the study drug were similar between patients in the ceftazidime/avibactam and those in the meropenem groups (64.4% [65/101] versus 57.8% [59/102], respectively). Three deaths occurred in the ceftazidime/avibactam group and two deaths occurred in the meropenem group. None of the deaths were thought to be related to the study drug.

- This effectiveness of ceftazidime/avibactam in treating cIAIs may be comparable to that of meropenem and according to the authors would be a viable alternative for the treatment of cIAIs.

**Vasquez JA, Patzán LD, Stricklin D, et al. Efficacy and safety of ceftazidime–avibactam versus imipenem–cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. *Curr Med Res Opin*. 2012; 28(12):1921-31.**

- Study characteristics, Primary and Secondary Endpoints, Population and Methods: o A Phase II global, prospective, blinded, randomized clinical trial in 135 patients was conducted to assess the efficacy and safety of intravenous ceftazidime 500 mg plus avibactam125 mg every 8 hours versus imipenem–cilastatin 500 mg every 6 hours in serious complicated urinary tract infections (cUTI). Patients meeting pre-specified improvement criteria after 4 days could be switched to oral ciprofloxacin (500 mg every 12 hours). Patients were treated for a total of 7–14 days.
- The primary efficacy endpoint was a favourable microbiological response at the test-of-cure (TOC) visit, 5–9 days after the last dose of the study therapy, in the microbiologically evaluable (ME) population.
- Secondary endpoints included microbiological response at the end of IV therapy and at the late follow-up (LFU) visit, 4–6 weeks post-therapy in the ME population.
- Adults between the ages of 18-90 were eligible if diagnosed with acute pyelonephritis or other cUTI due to Gram-negative pathogens that was judged serious enough by the investigator to require IV therapy. Notable exclusions included those patients not likely to survive the study period.
- Results: o Favourable microbiological response was observed in 19/27 (70.4%) patients in the ceftazidime/avibactam arm and 25/35 (71.4%) patients in the imipenem/cilastatin arm (observed difference -1.1% [95% CI: -27.2%, 25.0%]).
- Secondary outcomes were similar between the two groups, with favourable microbiological response rates at the end of IV therapy being 25/26 (96.2%) and 34/34 (100%) in the ceftazidime– avibactam and imipenem–cilastatin arms, respectively, and 15/26 (57.7%) and 18/30 (60.0%) at the LFU visit.
o Safety results were similar between groups. Drug-related AEs were less common in the ceftazidime/avibactam group (24/68, 35.3%) as compared to the imipenem/cilastatin group (34/67, 50.7%). SAEs were reported in 6/68 (8.8%) patients in the ceftazidime/avibactam group and 2/67 (3.0%) of the imipenem/cilastatin group. Three of the six SAEs in the ceftazidime/avibactam group were considered drug related, including an accidental overdose of 2000 mg ceftazidime and 1000 mg avibactam. While this was a SAE, there were no lab abnormalities or adverse events associated with the overdose in the two-week period following the event.
o While this study wasn't powered to demonstrate non-inferiority, the results were similar in both pyelonephritis and other cUTIs, prompting the authors to suggest that these two treatment options may be similar in terms of both efficacy and safety. Exclusion of patients not likely to survive may have eliminated septic patients, so it remains to be seen if this therapy will be as effective in that population.

**Safety:**

***Contraindications/Warnings/Precautions1:***

Ceftazidime/avibactam is contraindicated in patients with known serious hypersensitivity to ceftazidime/avibactam, other avibactam-containing products, ceftazidime, or other members of the cephalosporin class. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions can occur; therefore, use cautiously in with patients' previous hypersensitivity reactions to
other cephalosporins, penicillins, or other beta-lactams as cross-sensitivity has occurred. If a reaction occurs, discontinue infusion and initiate appropriate care.

Ceftazidime/avibactam should be used with caution in patients with renal impairment, end-stage renal disease (ESRD), or those receiving dialysis. Dosage adjustment recommendations are available for various stages of renal impairment and for patients with ESRD on haemodialysis. In a subgroup analysis, there was a decrease in efficacy in patients with a baseline creatinine clearance (CrCl) of 30 to ≤ 50 mL/min.

*Clostridium difficile*-associated diarrhoea (CDAD) has been reported for nearly all systemic antibacterial agents, including ceftazidime/avibactam. Severity may range from mild diarrhoea to fatal colitis. Evaluate patient if diarrhoea occurs after administration. If CDAD is confirmed, discontinue all antibacterials not directed against *C. difficile* if possible.

Seizures, nonconvulsive status epilepticus, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia have been reported in patients treated with ceftazidime, particularly in the setting of renal impairment.

Prescribing ceftazidime/avibactam in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

***Specific Populations:***

• Ceftazidime/avibactam is Pregnancy Category B per manufacturer's prescribing information. Ceftazidime is excreted in human milk in low concentrations. It is not known whether avibactam is excreted in human milk, though it was shown to be excreted in the milk of rats in a dose-dependent manner. .

• Safety and efficacy in paediatric patients have not been established.

• Approximately 11% of patients treated with ceftazidime/avibactam in the cIAI and cUTI Phase II studies were 65 years old or older. Owing to limited data, it is not known if differences in outcomes or specific risks are present in this population. Healthy elderly subjects had a 17% increase in avibactam exposure relative to healthy young subjects. Due to substantial excretion of the drug by the kidney, risk of adverse reactions may be greater in patients with impaired renal function. Elderly patients are more likely to have a decrease in renal function; therefore, caution should be taken in dose selection for this population and regular monitoring of renal function should occur.

## *Adverse Drug Reactions1:*

The most common adverse reactions occurring in patients receiving ceftazidime/avibactam were nausea, vomiting, anxiety, and constipation. Other adverse reactions occurring in 1% or greater of patients receiving ceftazidime/avibactam in Phase II clinical trials include abdominal pain, insomnia, increased ALT, increased AST, increased gamma-glutamyl transferase, prolonged prothrombin time, eosinophilia, thrombocytosis, dizziness, hypokalaemia, acute renal failure, renal impairment, and rash.

### *Drug Interactions1:*

No drug-drug interactions were observed between ceftazidime and avibactam in clinical study. *In vitro* and *in vivo* do not indicate any likely causes of clinically relevant interactions related to CYPs and transporters at therapeutic concentrations. In vitro, probenecid inhibits OAT uptake of avibactam by 56-70% and has the potential to decrease the elimination of avibactam.

### *Dosing and Administration1:*

## Dosage

Available as fixed combination containing 4:1 ratio of ceftazidime to avibactam.

Ceftazidime component provided as mixture of ceftazidime pentahydrate and sodium carbonate (dosage of this component expressed in terms of anhydrous ceftazidime); avibactam component provided as avibactam sodium (dosage of this component expressed in terms of avibactam).

Dosage of ceftazidime and avibactam fixed combination expressed in terms of the total of the ceftazidime and avibactam content.

Each single-dose vial contains a total of 2.5 g (i.e., 2 g of ceftazidime and 0.5 g of avibactam).

### Adults

#### Intra-abdominal Infections

#### IV

2.5 g (ceftazidime 2 g and avibactam 0.5 g) every 8 hours given in conjunction with metronidazole.

Treatment duration is 5–14 days.

#### Urinary Tract Infections

#### IV

2.5 g (ceftazidime 2 g and avibactam 0.5 g) every 8 hours.

Treatment duration is 7–14 days.

# Special Populations

## Hepatic Impairment

Dosage adjustments not needed in adults with hepatic impairment.

## Renal Impairment

Adjust dosage in adults with $Cl_{cr}$ ≤50 mL/minute, including those undergoing hemodialysis. (See Table 2.)

Monitor $Cl_{cr}$ at least once daily in patients with changing renal function; adjust dosage accordingly.

On hemodialysis days, give the dose after dialysis.

## Geriatric Patients

Dosage adjustments based solely on age not needed. Select dosage with caution and monitor renal function since geriatric patients more likely to have decreased renal function than younger adults.

## PAEDIATRIC (3 MONTHS TO 18 YEARS)

**3-6 Months - 50mg/Kg of body weight**
**6- Months- 2 years - 62.50 mg/Kg of body weight**
**2- 18 years - 62.50 mg/KG of body weight**
**(Not to exceed 2.50 gm/Dose)**
**(Duration 5-14 days depending up on the infection)**

All combinations of dextrose injection and sodium chloride injection (containing up to 2.5% dextrose and 0.45% sodium chloride), or lactated Ringer's injection, USP. Final volume is approximately 11.4 mL. The reconstituted solution is not for direct injection and should be added to an infusion bag containing 50-250mL of the same diluent used for constitution of the powder except for SWFI.

## PREPARATION OF DOSES

| CEFTAZIDIME/AVIBACTAM DOSE | VOL.TO WITHDRAW FROM RECONS.VIAL |
|---|---|
| 2.5 G(2+0.5 GM) | 11.40 ML(ENT. CONTENT) |
| 1.25 GM(1+0.250 GM) | 5.70 ML |
| 940 MG(750 MG+190 MG) | 4.30 ML |

Ceftazidime/avibactam is supplied in a powder form containing 2 g ceftazidime (equivalent to 2.635 g of ceftazidime pentahydrate/sodium carbonate) and 0.5 g avibactam (equivalent to 0.551 g avibactam sodium) in each single-use vial. Vials are in cartons of 10 vials. Vials should be stored at room temperature, at 25°C (77°F) and protected from light.

After reconstitution, the solution is stable for 12 hours when stored at room temperature or 24 hours when stored under refrigeration at 2 to 8°C (36 to 46°F). Use solution within 12 hours of removal from the refrigerator. Do not freeze solution.

### ***Recommended Monitoring[1]:***

The following parameters are recommended for therapy monitoring:

- Culture and Sensitivity
- Serum creatinine
- BUN

## Summary and Recommendations:

Ceftazidime/avibactam is a newly FDA-approved intravenous antibacterial agent in the treatment of cIAIs in combination with metronidazole and in cUTIs including pyelonephritis in patients who have limited or no alternative treatment options. Its spectrum of activity in treating cIAIs is relatively narrow, encompassing minimal Gram-positive and extensive Gram-negative organisms. It has comparable efficacy to meropenem when combined with metronidazole. In the treatment of cUTIs including pyelonephritis, its spectrum of activity is limited to Gram-negative organisms including those that produce extended-spectrum beta-lactamases (ESBLs) and some carbapenemases. In both treatment of cIAIs and cUTIs including pyelonephritis, very few microbiological cures were seen with these pathogens owing to the small sample sizes. It's also important to note that reduced efficacy was observed in patients with a CrCl of 30-50 ml/min versus comparators in these trials.

This agent was approved on the basis of two-Phase II studies encompassing 232 patients for the treatment of cIAIs and cUTIs including pyelonephritis. From an *in vitro* standpoint, ceftazidime/avibactam has excellent activity against Gram-negative bacteria that produce ESBLs, and some that produce carbapenemases, though not against metallo-beta-lactamases such as New Delhi metalloprotease (NDM). In addition, it remains to be seen in larger populations if it will have activity against Gram-negative bacteria that overexpress efflux pumps or have porin mutations. Larger studies are required to determine if ceftazidime/avibactam will perform reliably against these pathogens *in vivo*.

That being said, there are few agents available to treat such resistant pathogens and early studies indicate that ceftazidime/avibactam will likely be a significant contribution to the Gram-negative treatment armamentarium. The Phase II studies cited herein indicate that it is well tolerated in patients and appears to be effective in treating both cIAIs and cUTIs including pyelonephritis. A Phase III study is underway evaluating the use of ceftazidime/avibactam versus meropenem in the treatment of nosocomial pneumonia and if positive will significantly increase the usefulness of this agent. At this time however, its use seems to be limited to documented infections with resistant Gram-negative pathogens where there are few options other than colistin. Our recommendation is to make this agent

formulary, but restrict its use only for when it is absolutely necessary, including treatment of carbapenemse-producing pathogens or other Gram-negative pathogens resistant to other treatment options. Additionally, it is recommended that, when possible, the use of this agent be restricted to an Infectious Diseases service.

## References:


1) Cincinnati, OH: Forest Pharmaceuticals. Inc. Pharmaceuticals. Avycaz (ceftazidime/avibactam) [prescribing information]. March 2015.

2) Zhanel GG, Lawson CD, Adam H, et al. Ceftazidime/Avibactam: a novel cephalosporin/beta-lactamase inhibitor combination. *Drugs*. 2013; 73:159-77

3) Lexicomp Online®, Ceftazidime/avibactam Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Accessed April 2, 2015.

4) Lucasti C, Popescu I, Ramesh MK, et al. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind Phase II trial. *J Antimicrob Chemother.* 2013; 68(5):1183-92.

5) Vasquez JA, Patzán LD, Stricklin D, et al. Efficacy and safety of ceftazidime–avibactam versus imipenem–cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. *Curr Med Res Opin*. 2012; 28(12):1921-31.