Injex PLUS

(Ceftazidime + Avibactam)

2.5 g IV INJECTION

Ceftazidime-avibactam is a combination antimicrobial agent used to treat serious Gram-negative bacterial infections, particularly those resistant to other antibiotics. It consists of the extended-spectrum cephalosporin ceftazidime and the non-β-lactam β-lactamase inhibitor avibactam. Avibactam enhances ceftazidime's activity by inhibiting certain β-lactamases, which are enzymes that can render ceftazidime ineffective.

COMPOSITION:
Each vial contains:
Ceftazidime Pentahydrate Eq. to Ceftazidime……2gm
Avibactam Sodium Eq. to Avibactam..…..…..0.5gm

Directions for Reconstitution:
To be reconstituted with 10ml Sterile Water for Injection.
Product Specs.: Innovator

DESCRIPTION
A white to yellow sterile powder for reconstitution, filled in a glass vial with a rubber stopper and a flip off seal.

CLINICAL PHARMACOLOGY:

Mechanism of Action
Ceftazidime + Avibactam is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2), the Ceftazidime-Avibactam (CAZ-AVI) functions by ceftazidime's direct antibacterial action and avibactam's protection of ceftazidime from degradation by beta-lactamase enzymes. Ceftazidime, a third-generation cephalosporin, inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs), leading to cell lysis and death. Avibactam, a non-beta-lactam beta-lactamase inhibitor, binds to and inactivates certain beta-lactamase enzymes, including those that degrade ceftazidime, thus extending its antimicrobial spectrum.

Distribution:
Less than 10% of ceftazidime was protein bound. The degree of protein binding was independent of concentration. The binding of avibactam to human plasma proteins was low (5.7% to 8.2%) and was similar across the range of concentrations tested in vitro (0.5 to 50 mg/L). The steady-state volumes of distribution of ceftazidime and avibactam were 17 L and 22.2 L, respectively, in healthy adults following multiple doses of 2.5 grams (ceftazidime 2 grams and avibactam 0.5 grams) infused every 8 hours over 2 hours for 11 days. Following administration of 2.5 g (ceftazidime 2 grams and avibactam 0.5 grams) to healthy male subjects every 8 hours as a 2-hour infusion for 3 days, the mean bronchial epithelial lining fluid-to-plasma ratios of avibactam Cmax and AUC0-tau were 35%. The mean bronchial epithelial lining fluid-to-plasma ratios of ceftazidime Cmax and AUC0-tau were 26% and 31%, respectively.

Metabolism
Ceftazidime is mostly (80% to 90% of the dose) eliminated as unchanged drug. 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 after a single intravenous dose of 0.5 grams 14C-labelled avibactam.

Excretion:
Both ceftazidime and avibactam are excreted mainly by the kidneys.

Pharmacokinetics in 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.

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.

Paediatric population
The pharmacokinetics of ceftazidime and avibactam were evaluated in paediatric 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 Injex Plus 2 g/0.5 g (ceftazidime 2 grams and avibactam 0.5 grams) 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 (paediatric patients 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 Injex Plus 2 g/0.5 g. Data from this study and the two Phase 2 paediatric 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.

INDICATIONS AND USAGE
A combination of ceftazidime, a cephalosporin, and avibactam, a beta-lactamase inhibitor, indicated for the treatment of the following infections caused by designated susceptible Gram- negative microorganisms:
• Complicated Intra-abdominal Infections (cIAI), used in combination with metronidazole, in adult and pediatric patients 3 months and older.
• Complicated Urinary Tract Infections (cUTI), including Pyelonephritis, in adult and pediatric patients 3 months and older.
• Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP) in patients 18 years and older.

POSOLOGY AND METHOD OF ADMINISTRATION
Injex Plus 2.5 grams (ceftazidime 2 grams and avibactam 0.5 grams) for injection administered every 8 hours by intravenous (IV) infusion over 2 hours in patients 18 years of age and older with creatinine clearance (CrCl) greater than 50 mL/min. For treatment of cIAI, metronidazole should be given concurrently.
Recommended duration of treatment:
◦ cIAI: 5 to 14 days
◦ cUTI including pyelonephritis: 7 to 14 days

ADVERSE REACTIONS
The most common adverse reactions in cIAI (≥ 5%, when used with metronidazole) are diarrhea, nausea and vomiting. In cUTI, the most common adverse reactions (≥10%) are constipation and anxiety.

CONTRAINDICATIONS
Injex Plus is contraindicated in patients with known serious hypersensitivity to the components of Injex Plus

(ceftazidime and avibactam), avibactam-containing products, or other members of the cephalosporin class.

PRECAUTIONS AND WARNINGS:

Cautions

Decreased Clinical Response in Patients with Baseline Creatinine Clearance of 30 to Less Than or Equal to 50 mL/min.

Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs. Before therapy with Injex Plus is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or carbapenems should be made. Exercise caution if this product is to be given to a penicillin or other beta-lactam-allergic patient because cross sensitivity among beta-lactam antibacterial drugs has been established. Discontinue the drug if an allergic reaction to Injex Plus occurs.

Clostridium difficile-associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial drugs, including Injex Plus, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial drugs alters the normal flora of the colon and may permit overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial drugs. If CDAD is suspected or confirmed, antibacterial drugs not directed against C. difficile may need to be discontinued. Manage fluid and electrolyte levels as appropriate, supplement protein intake, monitor antibacterial treatment of C. difficile, and institute surgical evaluation as clinically indicated.

Central Nervous System Reactions

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. Adjust dosing based on creatinine clearance.

Development of Drug-Resistant Bacteria

Prescribing Injex Plus 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.

DRUG INTERACTIONS

ProbenecidIn vitro, avibactam is a substrate of OAT1 and OAT3 transporters which might contribute to the active uptake from the blood compartment, and thereby its excretion. As a potent OAT inhibitor, probenecid inhibits OAT uptake of avibactam by 56% to 70% in vitro and, therefore, has the potential to decrease the elimination of avibactam when co-administered. Because a clinical interaction study of Injex Plus or avibactam alone with probenecid has not been conducted, co-administration of Injex Plus with probenecid is not recommended.

Drug/Laboratory Test Interactions

The administration of ceftazidime may result in a false-positive reaction for glucose in the urine with certain methods. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

USE IN PREGNANCY AND LACTATION

Pregnancy (Category D):

There are no adequate and well-controlled studies of Injex Plus, ceftazidime, or avibactam in pregnant women. Neither ceftazidime nor avibactam were teratogenic in rats at doses 40 and 9 times the recommended human clinical dose. In the rabbit, at twice the exposure as seen at the human clinical dose, there were no effects on embryofetal development with avibactam.

Lactation:

Ceftazidime is excreted in human milk in low concentrations. It is not known whether avibactam is excreted into human milk, although avibactam was shown to be excreted in the milk of rats. No information is available on the effects of ceftazidime and avibactam on the breast-fed child or on milk production.

OVERDOSE:

In the event of overdose, discontinue Injex Plus and institute general supportive treatment.

Ceftazidime and avibactam can be removed by hemodialysis. In subjects with ESRD administered 1 gram ceftazidime, the mean total recovery in dialysate following a 4-hour hemodialysis session was 55% of the administered dose. In subjects with ESRD administered 100 mg avibactam, the mean total recovery in dialysate following a 4 hour hemodialysis session started 1 hour after dosing was approximately 55% of the dose. No clinical information is available on the use of hemodialysis to treat Injex Plus overdosage.

DOSAGE:

As directed by the physician.

INSTRUCTIONS:

Store below 30°C.
Do not freeze.
Protect from light, heat and moisture.
The reconstituted solution should be administered within 6 hours, if stored at room temperature.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.

PRESENTATION

Injex Plus (Ceftazidime + Avibactam) Injection 2.5g are available in pack of 1x 1's.

Manufactured By:
NovaMed Pharmaceuticals (Pvt.) Ltd.
28-km, Ferozepur Road, Lahore, Pakistan.

Manufactured by :
Indus Pharma (Pvt.) Ltd.
26-27, 63-67, Sector 27, Korangi
Industrial Area, Karachi-74900, Pakistan.