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

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Ceftazidime & Avibactam Powder for Concentrate for Solution for Infusion

CEFTAWIN-AV

Composition :
Each vial contains:
Ceftazidime IP
Eq. to Anhydrous Ceftazidime 2.0gm
Avibactam Sodium
Eq. to Avibactam 0.5gm

3. DOSAGE FORM AND STRENGTH
Injection; Ceftazidime for Injection IP (Sterile)Eq. to Ceftazidime 2 g (Sterile Mixture of Ceftazidime & Avibactam Sodium (Sterile)Eq. to Avibactam 0.5 g.
4.CLINICAL PARTICULARS
4.1 Therapeutic indication
Complicated Intra-abdominal infections (cIAI). Complicated Urinary tract infections (cUTI), including pyelonephritis Hospital-acquired pneumonia (HAP) including ventilator associated pneumonia (VAP) with susceptible gram negative microorganisms
4.2 Posology and method of administration
Posology
It is recommended that ceftazidime-avibactam should be used to treat infections due to aerobic Gram-negative organisms in adults and older with limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases.

Type of infection	Dose of ceftazidime/avibactam	Frequency	Infusion time	Duration of treatment
cIAI2,3	2 g/0.5 g	Every 8 hours	2 hours	5-14 days
cUTI, including pyelonephritis3	2 g/0.5 g	Every 8 hours	2 hours	5-10 days4
HAP/VAP3	2 g/0.5 g	Every 8 hours	2 hours	7-14 days.
Bacteraemia associated with, or suspected to be associated with any of the above infections	2 g/0.5 g	Every 8 hours	2 hours	Duration of treatment should be in accordance with the site of infection.
Infections due toaerobic Gram -negative organisms in patients with limited treatment options2,3	2 g/0.5 g	Every 8 hours	2 hours	Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress5

- CrCL estimated using the Cockcroft-Gault formula.
- To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.
- To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process.
- The total duration shown may include intravenous ceftazidime-avibactam followed by appropriate oral therapy.
- There is very limited experience with the use of ceftazidime-avibactam for more than 14 days.

Special population:
Elderly
No dosage adjustment is required in elderly patients.
Renal impairment
No dosage adjustment is required in patients with mild renal impairment (estimated CrCL > 50 - ≤ 80 mL/min)
Method of administration: For Intravenous use.
ceftazidime-avibactam is administered by intravenous infusion over 120 minutes in an appropriate infusion volume for instructions on reconstitution and dilution of the medicinal product before administration
4.2 Contraindications
Ceftazidime & Avibactam is contraindicated in patients with known serious hypersensitivity avibactam-containing products, ceftazidime, or other members of the cephalosporin class.
4.3 Special warnings and precautions for use
Hypersensitivity reactions
Serious and occasionally fatal hypersensitivity reactions are possible. In case of hypersensitivity reactions, treatment with ceftazidime-avibactam must be discontinued immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be established whether the patient has a history of hypersensitivity reactions to ceftazidime, to other cephalosporins or to any other type of β-lactam antibacterial agent. Caution should be used if ceftazidime/avibactam is given to patients with a history of non-severe hypersensitivity to penicillins, monobactams or carbapenems. Clostridioides difficile -associated diarrhoea Clostridioides difficile associated diarrhoea has been reported with ceftazidime/avibactam, and can range in severity from mild to life-threatening. This diagnosis should be considered in patients who present with diarrhoea during or subsequent to the administration of ceftazidime-avibactam. Discontinuation of therapy with ceftazidime-avibactam and the administration of specific treatment for
Clostridioides difficile
should be considered. Medicinal products that inhibit peristalsis should not be given.
Impairment
Ceftazidime and avibactam are eliminated via the kidneys, therefore, the dose should be reduced according to the degree of renal impairment. Neurological sequelae, including tremor, myoclonus, non-convulsive status epilepticus, convulsion, encephalopathy and coma, have occasionally been reported with ceftazidime when the dose has not been reduced in patients with renal impairment. In patients with renal impairment, close monitoring of estimated creatinine clearance is advised. In some patients, the creatinine clearance estimated from serum creatinine can change quickly, especially early in the course of treatment for the infection.
Nephrotoxicity
Concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect renal function.
4.4 Drugs interactions
In vitro, avibactam is a substrate of OAT1 and OAT3 transporters which might contribute to the active uptake of avibactam from the blood compartment and, therefore, affect its excretion. Probenecid (a potent OAT inhibitor) inhibits this uptake by 56% to 70% in vitro and, therefore, has the potential to alter the elimination of avibactam. Since a clinical interaction study of avibactam and probenecid has not been conducted, co-administration of avibactam with probenecid is not recommended. Avibactam showed no significant inhibition of cytochrome P450 enzymes in vitro.
Avibactam and ceftazidime showed no in vitro cytochrome P450 induction at clinically relevant concentrations. Avibactam and ceftazidime do not inhibit the major renal or hepatic transporters in the clinically relevant exposure range, therefore the interaction potential via these mechanisms is considered to be low.
Clinical data have demonstrated that there is no interaction between ceftazidime and avibactam, and between ceftazidime/avibactam and metronidazole. Other types of interaction Concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect renal function.
Chloramphenicol is antagonistic in vitro with ceftazidime and other cephalosporins. The clinical relevance of this finding is unknown, but due to the possibility of antagonism in vivo this drug combination should be avoided.
4.5 Use in special populations
Pregnancy
Risk Summary There are no adequate and well-controlled studies of 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. The background risk of major birth defects and miscarriage for the indicated population is unknown. The background risk of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies within the general population. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.
Ceftazidime
Reproduction studies have been performed in mice and rats at doses up to 40 times the human dose and showed no evidence of harm to the fetus due to ceftazidime.
Avibactam
Avibactam was not teratogenic in rats or rabbits. In the rat, intravenous studies with 0, 250, 500 and 1000 mg/kg/day avibactam during gestation days 6-17 showed no embryofetal toxicity at doses up to 1000 mg/kg/day, approximately 9 times the human dose based on exposure (AUC). In a rat pre- and post-natal study at up to 825 mg/kg/day intravenously (11 times the human exposure based on AUC), there were no effects on pup growth and viability. A dose-related increase in the incidence of renal pelvic and ureter dilatation was observed in female weaning pups that was not associated with pathological changes to renal parenchyma or renal function, with renal pelvic dilatation persisting after female weaning pups became adults.

Breast-feeding
Ceftazidime is excreted in human milk in small quantities. It is unknown whether avibactam is excreted in human milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast feeding or to discontinue/abstain from ceftazidime/avibactam therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Fertility
The effects of ceftazidime/avibactam on fertility in humans have not been studied. No data are available on animal studies with ceftazidime. Animal studies with avibactam do not indicate harmful effects with respect to fertility.
4.6 Effects on ability to drive and use medicines
Undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines following administration of ceftazidime-avibactam
4.7 Undesirable effects
Fixed Drug Eruption (FDE) has been reported with Cephalosporin Class Drug.
Summary of the safety profile in seven Phase 2 and Phase 3 clinical trials, 2024 adults were treated with ceftazidime avibactam. The most common adverse reactions occurring in ≥5% of patients treated with ceftazidime-avibactam were Coombs direct test positive, nausea, and diarrhea. Nausea and diarrhea were usually mild or moderate in intensity. Tabulated list of adverse reactions The following adverse reactions have been reported with ceftazidime alone and/or identified during the Phase 2 and Phase 3 trials with ceftazidime-avibactam. Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are derived from adverse reactions and/or potentially clinically significant laboratory abnormalities, and are defined according to the following conventions: Very common (≥1/10) Common (≥1/100)

System Organ Class	Very common	Common	Uncommon	Very rare	Unknown
Infections and infestations		Candidiasis (including Vulvovaginal candidiasis and Oral candidiasis)	Clostridioides difficile colitis Pseudomembran ous colitis		
Blood and lymphatic system disorders	Coombs direct test positive	Eosinophilia Thrombocytosis Thrombocytopenia	Neutropenia Leukopenia Lymphocytosis		Agranulocytosis Haemolytic anaemia
Immune system disorders					Anaphylactic reaction
Nervous system disorders		Headache Dizziness	Paraesthesia		
Gastrointestinal disorders		Diarrhoea Abdominal pain	Dysgeusia		
		Nausea Vomiting			
Hepatobiliary disorders		Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphatase increased Gammaglutamyltransferase increased Blood lactate dehydrogenase Increased			Jaundice
Skin and subcutaneous tissue disorders		Rash maculopapular Urticarial Pruritus			Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Angioedema Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Renal and urinary disorders			Blood creatinine increased Blood urea increased Acute kidney injury	Tubulointerstitial nephritis	
General disorders and administration site conditions		Infusion site thrombosis Infusion site phlebitis Pyrexia			

Paediatric population The safety assessment in paediatric patients is based on the safety data from two trials in which 61 patients (aged from 3 years to less than 18 years) with cIAI and 67 patients with cUTI (aged from 3 months to less than 18 years) received Overall, the safety profile in these 128 paediatric patients was similar to that observed in the adult population with cIAI and cUTI.
Reporting of side effects or suspected adverse reactions: If you experience any side effects, talk to your doctor or If you experience any side effects, talk to your doctor or pharmacist or report to indiapvgsafety@aiums.in or report side effects directly by calling on the toll-free number 829 700 0060 or directly via the National Pharmacovigilance Program of India. By reporting side effects, you can help provide more information on the safety of this product.
4.9 Overdose
Overdose with ceftazidime/avibactam can lead to neurological sequelae including encephalopathy, convulsions and coma, due to the ceftazidime component. Serum levels of ceftazidime can be reduced by haemodialysis or peritoneal dialysis. During a 4-hour haemodialysis period, 55% of the avibactam dose was removed.
5.PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, other beta-lactam antibacterials, third-generation cephalosporins
Mechanism of action
Ceftazidime inhibits bacterial peptidoglycan cell wall synthesis following binding to penicillin binding proteins (PBPs), which leads to bacterial cell lysis and death. 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 and some class D enzymes, including extended-spectrum β-lactamases (ESBLs), KPC and OXA-48 carbapenemases, and AmpC enzymes. Avibactam does not inhibit class B enzymes (metallo-β-lactamases) and is not able to inhibit many class D enzymes.
Resistance 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, and β-lactamase enzymes refractory to inhibition by avibactam and able to hydrolyse ceftazidime. Antibacterial activity in combination with other antibacterial agents No synergy or antagonism was demonstrated in in vitro drug combination studies with ceftazidime/avibactam and metronidazole, tobramycin, levofloxacin, vancomycin, linezolid, colistin and tigecycline.
5.2 Pharmacokinetic properties
Distribution
The human protein binding of both ceftazidime and avibactam is approximately 10% and 8%, respectively. The steady-state volumes of distribution of ceftazidime and avibactam were about 17 L and 22 L, respectively in healthy adults following multiple doses of 2 g/0.5 g ceftazidime/avibactam infused over 2 hours every 8 hours. Both ceftazidime and avibactam penetrate into human bronchial epithelial lining fluid (ELF) to the same extent with concentrations around 30% of those in plasma. The concentration time profiles are similar for ELF and plasma. Penetration of ceftazidime into the intact blood-brain barrier is poor. Ceftazidime 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. Ceftazidime crosses the placenta readily, and is excreted in the breast milk.
Biotransformation
Ceftazidime is not metabolised. 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 intravenous 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 avibactam 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 faeces.
6. NON CLINICAL PROPERTIES
Ceftazidime Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproduction toxicity or genotoxicity. Carcinogenicity studies have not been conducted with ceftazidime.
Avibactam
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity. Carcinogenicity studies have not been conducted with avibactam. *Reproduction toxicity*
In pregnant rabbits administered avibactam at 300 and 1000 mg/kg/day, there was a dose-related lower mean foetal weight and delayed ossification, potentially related to maternal toxicity. Plasma exposure levels at maternal and foetal NOAEL (100 mg/kg/day) indicate moderate to low margins of safety. In the rat, no adverse effects were observed on embryo foetal development or fertility. Following administration of avibactam throughout pregnancy and lactation in the rat, there was no effect on pup survival, growth or development, however there was an increase in incidence of dilation of the renal pelvis and ureters in less than 10% of the rat pups at maternal exposures greater than or equal to approximately 1.5 times human therapeutic exposures.
7. DESCRIPTION
Ceftazidime & Avibactam is an antibacterial combination product consisting of the semisynthetic cephalosporin ceftazidime pentahydrate and the beta-lactamase inhibitor avibactam sodium for intravenous administration.

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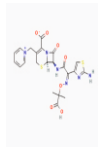
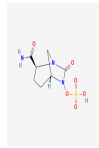
Ceftazidime
Ceftazidime is a semisynthetic, beta-lactam antibacterial drug. It is the pentahydrate of (6R,7R, Z)-7-[2-(2 aminothiazol-4-yl)-2-[2-carboxypropan-2-yloxyimino) acetamido)-8-oxo-3-[pyridinium-1-ylmethyl)-5-thia-1
azabicyclic [4.2.0] oct-2-ene-2-carboxylate.
Molecular Formula - $C_{22}H_{32}N_6O_{12}S_2$
Molecular weight-636.6
Chemical Structure



Avibactam
Avibactam sodium chemical name is sodium [(2S,5R)-2-carbamoyl-7-oxo-1,6-diazabicyclo [3.2.1] octan-6-yl] sulfate.
Molecular Formula - C7H10 N3O6SNa.
Molecular weight-287.23
Chemical Structure



8. PHARMACEUTICAL PARTICULARS
8.1 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
8.2 Shelf life
As on Carton.
8.3 Packaging information
CEFTAWIN-AV Injection is available in 30 ml vial.
8.4 Storage and handling instruction
Store in a cool, dry & dark place, (8º C to 25º C.)
Once the pack has been opened, the product should be used immediately.
Keep medicine out of reach of children.
9. PATIENT COUNSELLING INFORMATION
Read this entire leaflet carefully before you start taking this medicine because it contains important information for you.
Keep this leaflet. You may need to read it again
If you have any further questions, ask your doctor or pharmacist.
This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.
What Ceftazidime & Avibactam Sodium is and what it is used for?
Ceftazidime & Avibactam is an antibiotic medicine that contains two active substances ceftazidime and avibactam.
Ceftazidime belongs to the group of antibiotics called "cephalosporins". It can kill many types of bacteria.
Avibactam is a "beta-lactamase inhibitor" that helps ceftazidime kill some bacteria that it cannot kill on its own.
Ceftazidime & Avibactam is used in adults and paediatric patients aged 3 months and over to treat:
infections of the stomach and gut (abdomen)
infections of the bladder or kidneys called "urinary tract infections"
an infection of the lungs called "pneumonia"
infections caused by bacteria that other antibiotics may not be able to kill Ceftazidime & Avibactam is used in adults to treat infection of the blood associated with infections of the abdomen, urinary tract, or pneumonia. **What you need to know before you use Ceftazidime & Avibactam**
Do not use Ceftazidime & Avibactam if:
you are allergic to other cephalosporin antibiotics
you have ever had a severe allergic reaction to other antibiotics belonging to the penicillin or carbapenem
What you need to know before you are treated with Ceftazidime & Avibactam Injection?
Before using ceftazidime and avibactam injection, be sure to mention any of the following: Probenecid (Probalan, in Col-Probenecid) Your doctor may need to change the doses of your medications or monitor you carefully for side effects. tell your doctor if you have or have ever had kidney disease.
Doctors need to take special care when using
- If you get migraines.
- If you have asthma.
- If you have problems with your heart or your circulation (such as high blood pressure).
- If you have any other medical condition
- If any of these apply to you, tell your doctor
- If you are allergic to Ceftazidime & Avibactam or any of the ingredients Ceftazidime & Avibactam Injection If you have any disease of the liver or kidneys.
- If you have pre-eclampsia (high blood pressure in pregnancy) or eclampsia (toxaemia of pregnancy).
- If you have any serious heart disease.
- If you have epilepsy.
- If you ever have had an allergic reaction to oxytocin (sometimes given as a drip or injection during or after labour) If any of these apply to you, tell your doctor.

How to use Ceftazidime & Avibactam
Posology
Ceftazidime & Avibactam will be given to you by a doctor or a nurse.
The recommended dose for adults is one vial (2 g of ceftazidime and 0.5 g of avibactam), every 8 hours.
Method of administration: For Intravenous use.
Other medicines and Ceftazidime & Avibactam Injection
Tell your doctor or nurse if you are using, have recently used or might use any other medicines. Talk to your doctor before using Ceftazidime & Avibactam Injection if you are taking any of the following medicines:
an antibiotic called chloramphenicol
a type of antibiotic called an aminoglycoside – such as gentamicin, tobramycin
a water tablet called furosemide
a medicine for gout called probenecid

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.
Driving and using machines
Ceftazidime & Avibactam may make you feel dizzy. This may affect you being able to drive, use tools or machines.
Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:
Serious side effects
Tell your doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:
severe allergic reactions – signs include sudden swelling of your lips, face, throat or tongue, a severe rash or other severe skin reactions, difficulty swallowing or breathing. This reaction may be life-threatening
diarrhoea that keeps getting worse or does not go away, or stools that contains blood or mucus – this may happen during or after treatment is stopped with Ceftazidime & Avibactam Injection. If this happens do not take medicines that stop or slow bowel movement.
Other side effects
Tell your doctor or nurse if you notice any of the following side effects:
Very common: (may affect more than 1 in 10 people)
abnormal result with a test called "DAGT" or "Coombs". This test looks for antibodies that fight against your red blood cells. It is possible that this could cause anaemia (which may make you feel tired) and jaundice (yellowing of the skin and eyes)
Common: (may affect up to 1 in 10 people)
fungal infections, including those of the mouth and vagina
change in the number of some types of blood cells (called "eosinophils" and "thrombocytes") – shown in blood tests
headache
feeling dizzy
feeling sick (nausea) or being sick (vomiting)
stomach pain
diarrhoea
increase in the amount of some enzymes produced by your liver - shown in blood tests
raised itchy skin rash ("hives")
itchiness
redness, pain or swelling where Zavicefta was given into a vein
fever
Uncommon: (may affect up to 1 in 100 people)
decrease in the number of some types of blood cells (called "leucocytes") - shown in blood tests
tingling or numbness
bad taste in your mouth
an increase in the level of some types of substances in your blood (called "creatinine" and "urea"). These show how well your kidneys are working.
Very rare: (may affect up to 1 in 10,000 people)
decrease in the number of red blood cells (haemolytic anaemia) – shown in blood tests
severe allergic reaction (see Serious side effects, above)
yellowing of the whites of the eyes or skin sudden onset of a severe rash or blistering or peeling skin, possibly accompanied by a high fever or joint pain (these may be signs of more serious medical conditions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme or a condition known as DRESS, Drug Reaction with Eosinophilia and Systemic Symptoms)
swelling under the skin, particularly lips and around the eyes
How should I store Ceftazidime & Avibactam Sodium Injection?
Store in a cool, dry & dark place, (8º C to 25º C.)
Keep medicine out of reach of children.
Do not use this medicine after the expiry date which is stated on the carton after expiry. The expiry date refers to the last day of that month.
What are the ingredients of Ceftazidime & Avibactam Sodium Injection?
Ceftazidime & Avibactam Sodium Injection Contains Ceftazidime 2g & Avibactam 0.5g

Storage: Store in a cool, dry & dark place, (8º C to 25º C.)

Keep medicine out of reach of children.

Mfd. by: Protech Telelinks
(A WHO-GMP Certified Company)
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Dehradun-248110, Uttarakhand