Indications/Uses:
Ceftazidime/Avibactam is indicated for the treatment of the following infections: Complicated Intra-Abdominal Infection (cIAI) (in combination with metronidazole); Complicated Urinary Tract Infection, including Pyelonephritis (cUTI); Hospital-acquired Pneumonia (HAP), including ventilator associated pneumonia (VAP); Infections due to aerobic Gram-negative organisms in patients with limited treatment options. Treatment of adult patients with bacteremia that occurs in association with, or is suspected to be associated with cIAI, cUTI, or HAP/VAP. Consideration should be given to official guidance on the appropriate use of antibacterial agents. For treatment of cIAI use in combination with metronidazole.

Dosage/Direction for Use:
It is recommended that Ceftazidime /Avibactam should be used to treat infections due to aerobic Gram-negative organisms in adults and pediatric patients aged 3 months and older with limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases (see Precautions). Dosage in Adults with Creatinine Clearance (CrCl >50 mL/min): The recommended dosage of Ceftazidime /Avibactam is 1 vial where each vial contains 2 g ceftazidime and 0.5 g avibactam administered by intravenous (IV) over 2 hours. Treatment is repeated every 8 hours.

Indication	Treatment Duration
Complicated Intra-Abdominal Infection (cIAI) [a,b]	5-14 days
Complicated Urinary Tract Infection (cUTI), including Pyelonephritis[c]	5-10 days[d] The total duration of treatment could be increased to 14 day for patients with bacteremia
Hospital-acquired Pneumonia, including ventilator associated pneumonia (HAP / VAP) [b]	7-14 days
Bacteremia associated, or suspected to be associated with the above infections	Duration of treatment should be in accordance with the site of infection.
Infections due to aerobic Gram-negative organisms in patients with limited treatment options [e,f]	Guided by the severity of the infection of the pathogen(s) and the patient's clinical and bacteriological progress

[a] To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.
[b] 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.
[c] Treatment duration includes intravenous plus oral treatment. The time to switch from intravenous Ceftazidime (as pentahydrate) / Avibactam (as sodium) to oral treatment with another antibiotic depends on the clinical situation, but is normally after about 5 days (the minimum duration of treatment with ceftazidime-avibactam in clinical trails was 5 days).

The duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.
Dosage in pediatric patients with creatinine clearance (CrCl) >50 mL/min/1.73 m^2: The recommended dosage of Ceftazidime /Avibactam in pediatric patients (3 months to <18 years) is based on the age and weight of the patient. Ceftazidime/Avibactam is administered every 8 hours as intravenous infusion over 2 hours. The duration of therapy should be guided by the severity, site of infection and the patient's clinical and bacteriological progress.

Dosage in pediatric patients with CrCl>50mL/min/1.73 m^2

Type of Infection	Age group	Dose of ceftazidime/avibatam	Frequency	Infusion Time	Type of Infection
cIAI[a] OR cUTI including pyelonephritis[c] OR HAP / VAP Infections due to aerobic Gram-negative organisms in patients with limited treatment options (LTO)[e,f]	6 months to <18 years	50 mg/kg/12.5 mg/kg to a maximum of 2 g/ 0.5g	Every 8 hours	2 hours	cIAI:5-14days cUTI:5-14 days HAP/VAP: 7-14 days LTO: Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress[f]
	3 months to <6 months	40 mg/kg/ 10 mg/kg	Every 8 hours	2 hours	

[a] To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.
[b] 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.
[c] Treatment duration includes intravenous plus oral treatment.
[e] There is every limited experience with the use of Ceftazidime (as pentahydrate) Avibactam (as sodium) more than 14 days.
[f] Calculated using the Schwartz bedside formula for pediatric patients (mL/min/1.73 m^2).

Special populations:
Elderly patients: No dosage adjustment is considered necessary in elderly patients (≥65 years). The dose regimen should be adjusted if renal impairment is present (see Pharmacology: Pharmacokinetics under Actions).

Patients with renal impairment: The following dose adjustment is recommended in patients with renal impairment. Dose adjustments for Ceftazidime/Avibactam for patients with an estimated creatinine clearance (CrCl) <50 ml/min are outlined as follows. The only irrespective dosing of Ceftazidime pentahydrate/Avibactam sodium for patients requiring dialysis is in the setting of intermittent hemodialysis. For other types of dialysis, it is suggested that the dose/frequency of ceftazidime-avibactam should follow local label/local guidelines for dosing of ceftazidime. For example, for a dose of 500 mg ceftazidime the dose of ceftazidime-avibactam would be 500 mg ceftazidime/125 mg avibactam.

Dosage in adults and pediatric patients with creatinine clearance (CrCl) ≤50 mL/min:

Recommended dose for patients with renal impairment (CrCl≤50 mL/min).				
Age Group	**Estimated CrCl (mL/min)[1]**	**Dose of Ceftazidime / Avibatam[2]**	**Frequency**	**Infusion Time**
Adults	31-50	1 g / 0.25 g	Every 8 hours	2 hours
	16-30	0.75 g / 0.1875 g	Every 12 hours	
	6 to 15		Every 24 hours	
	ESRD including on hemodialysis[3]		Every 48 hours	
Pediatric patients aged 2 years to <18 years	31-50	25 mg/kg/6.25 mg/kg to a maximum of 1 g/ 0.25g	Every 8 hours	2 hours
	16-30	18.75 mg/kg/4.75 mg/kg to a maximum of 0.75 g/0.1875 g	Every 12 hours	
	6 to 15		Every 24 hours	
	ESRD including on hemodialysis[3]		Every 48 hours	

[1] CrCl calculated using the Cockcroft-Gault formula for adult and the Schwartz bedside formula for pediatric patients (mL/min/1.73m.^{2}
[2] Dose recommendations are based on PK modelling.
[3] Both ceftazidime and avibactam are hemodialyzable; thus, Ceftazidime (as pentahydrate) / Avibactam (as sodium) should be administered after hemodialysis on hemodialysis day.

Dosage in pediatric patients <2 years of age with creatinine clearance (CrCl) ≥ 50 mL/min/1.73 m^2: There is insufficient information to recommend a dosage regimen for pediatric patients < 2 years of age that have a CrCL ≥ 50 mL/min/1.73 m^2. In patients with impaired renal function, monitoring of estimated creatinine clearance is advised as in some patients, especially early in the course of their infection, the creatinine clearance estimated from serum creatinine can change quickly.

Hemodialysis: Both ceftazidime and avibactam are hemodialyzable; thus, Ceftazidime /Avibactam should be administered after hemodialysis on hemodialysis day.
Hemofiltration: There is insufficient data to make specific dosage adjustment recommendations for patients undergoing continuous venous hemofiltration.

Peritoneal dialysis: There is insufficient data to make specific dosage adjustment recommendations for patients undergoing peritoneal dialysis.

Patients with hepatic impairment: No dosage adjustment is considered necessary in patients with hepatic impairment. Dose clinical monitoring for safety and efficacy is advised. Pediatric patients: Safety and efficacy in children and adolescents <18 years of age have not yet been established for HAP/HAV and is based on extrapolation (see Precautions). Safety and efficacy in pediatric patients <3 months old have not been established.

Method of administration: Intravenous use.
Ceftazidime/Avibactam is administered to adults by intravenous infusion over 2 hours in an appropriate infusion volume.
Constitution and compatibility: For instructions on reconstitution and dilution of the medicinal product before administration.

Overdosage:
Overdosage of ceftazidime-avibactam is unlikely, although overdosing could potentially occur in patients with moderate to severe renal impairment, and in end stage renal disease including patients undergoing hemodialysis. Overdosing with ceftazidime-avibactam can lead to neurological sequelae including encephalopathy, convulsions, and coma, due to the ceftazidime component. Treatment for overdose should follow local standard medical practice. Both ceftazidime and avibactam can be partially removed by hemodialysis.

Contraindications:
Hypersensitivity to the active substances or to any of the excipients listed in Inactive Ingredients/Excipients under Description. Hypersensitivity to the cephalosporin class of antibacterials. Immediate and severe hypersensitivity (e.g., anaphylactic reaction) to any other type of β-lactam antibacterial agent (e.g., penicillins, monobactams or carbapenems).

Special Precautions:
Hypersensitivity reactions: As with all β-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe 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 severe hypersensitivity reactions to ceftazidime, to other cephalosporins or to any other type of β-lactam agent. Caution should be used if ceftazidime-avibactam is given to patients with a history of non-severe hypersensitivity to other β-lactam agents. No clinical studies have been conducted in pediatric patients with nosocomial pneumonia. The efficacy of Ceftazidime/Avibactam for the treatment of pediatric patients ≥3 months of age with HAP/VAP is extrapolated from adults and is based on analyses of the pharmacokinetic-pharmacodynamic relationship for Ceftazidime (as pentahydrate)/Avibactam (as sodium) and on pediatric experience with ceftazidime alone.

Clostridium difficile-associated diarrhea: Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all anti-bacterial agents, including ceftazidime-avibactam, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea during or after the administration of Ceftazidime /Avibactam (see Adverse Reactions). Discontinuation of therapy with Ceftazidime /Avibactam and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Patients with renal impairment: Ceftazidime and avibactam are eliminated via the kidneys; therefore the dose should be reduced according to the degree of renal impairment. Patients with renal impairment should be closely monitored for both safety and efficacy. Neurological sequelae, including tremor, myoclonus, nonconvulsive status epilepticus, convulsion, encephalopathy, and coma, have occasionally been reported with ceftazidime when the dose has not been reduced in patients with renal impairment (see Dosage & Administration). 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.

Non-susceptible organisms: Prolonged use may result in the overgrowth of non-susceptible organisms (e.g., enterococci, fungi), which may require interruption of treatment or other appropriate measures.

Non-drug interference: Ceftazidime does not interfere with enzyme-based tests for glycosuria, but slight interference (false-positive) may occur with copper reduction methods (Benedict's, Fehling's, Clinitest).Ceftazidime does not interfere in the alkaline picrate assay for creatinine.

Direct antiglobulin test (DAGT or Coombs test) seroconversion and potential risk of hemolytic anemia: Cephalosporin use may cause development of a positive direct antiglobulin test (DAGT, or Coombs test), which may interfere with the cross-matching of blood and/or may cause drug induced immune hemolytic anemia. While DAGT seroconversion in patients receiving Ceftazidime/Avibactam was frequent in clinical studies, there was no evidence of hemolysis in patients who developed a positive DAGT on treatment (see Adverse Reactions). However, the possibility that hemolytic anemia could occur in association with Ceftazidime/Avibactam treatment cannot be ruled out. Patients experiencing anemia during or after treatment with Ceftazidime/Avibactam should be investigated for this possibility.

Controlled sodium diet: This medicinal product contains approximately 146 mg sodium per vial, equivalent to 7.3% of the WHO recommended maximum daily intake (RDI) of 2 g sodium for an adult. The maximum daily dose of this product is equivalent to 22.2% of the WHO recommended maximum daily intake for sodium. Ceftazidime/Avibactam is considered high in sodium. This should be considered when administering Ceftazidime /Avibactam to patients who are on a controlled sodium diet. Ceftazidime/Avibactam may be diluted with sodium-containing solutions and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

Use in Children: There is a potential risk of overdosing, particularly for pediatric patients aged from 3 to less than 12 months of age. Care should be taken when calculating the volume of administration of the dose.

Use In Pregnancy & Lactation:
Pregnancy: There is limited clinical data from the use of ceftazidime-avibactam in pregnant women. Animal embryofetal development studies conducted with ceftazidime or avibactam do not indicate harmful effects at exposures equivalent to therapeutic concentrations. Following administration of avibactam throughout pregnancy and lactation in the rat at maternal exposures greater than or equal to approximately 1.5 times human therapeutic exposures, there were minor changes in the morphology of the kidney and ureters in the rat. The effects of ceftazidime-avibactam on fertility in humans have not been studied. Ceftazidime-avibactam should not be used during pregnancy unless clearly necessary and only if the potential benefit outweighs the possible risk.
Lactation: There are no data on human milk excretion of ceftazidime-avibactam. Ceftazidime is excreted in human milk in small quantities. It is unknown whether avibactam is excreted in human milk. Women who are breast-feeding should be treated with ceftazidime-avibactam only if clearly indicated. Interruption of breast-feeding is recommended.

Adverse Reactions
In Several Phase 2 and Phase 3 clinical trials, 2024 adult patients were treated with Ceftazidime (as pentahydrate)/Avibactam (as sodium). The most common adverse reactions occurring in ≥5% of patients treated with Ceftazidime/Avibactam were Coombs direct test positive, nausea, and diarrhea. These were usually mild or moderate in intensity. No clinically significant differences were observed in the safety profile across indications.

Frequency of adverse reactions by system organ class.					
System Organ Class	**Very common**	**Common**	**Uncommon**	**Very rare**	**Unknown**
Infections and infestations		Candidiasis (including Vulvovaginal candidiasis and Oral candidiasis)	Clostridioides difficile colitis, Pseudomembranous colitis		
Blood and lymphatic system disorders	Coombs direct test positive[a]	Eosinophilia, Thrombocytosis,Thrombocytopenia	Neutropenia, Leukopenia, Lymphocytosis		Agranulocytosis Hemolytic anemia
immune system disorders					Anaphylactic reaction
Nervous system disorders		Headache, Dizziness	Paresthesia		
Gastrointestinal disorders		Diarrhea, Abdominal pain, Nausea, Vomiting	Dysgeusia		
Hepatobiliary disorders		Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased, Blood lactate dehydrogenase increased			Jaundice
Skin and subcutaneous tissue disorders		Rash maculopapular, Urticaria, Pruritus			Toxic epidermal necrolysis, Stevns-Johnson syndrome, Erythema multiforme, Angioedema, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Renal and urinary disorders		Infusion site thrombosis, Infusion site phlebitis, Pyrexia	Blood creatinine increased, Blood urea increased, Acute kidney injury	Tubulointerstitial nephritis	
General disorders and administration site conditions					

[a]see Precautions.

Pediatric population: The safety assessment in children is based on the safety data from 1 trail in which 61 pediatric patients aed from 3 years to less than 18 years with cIAI received Cefazidime (as pentahydrate) / Avibactam (as sodium) and 67 patients with cUTI (aged from 3 months to less than 18 years) received Ceftazidime (as pentahydrate)/Avibactam (as sodium). Overall, the safety profile in these 128 pediatric patients was similar to that observed in the adult population with cIAI and cUTI.

Drug Interactions:
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 (see Precautions). Chloramphenicol is antagonistic *in vitro* with ceftazidime and other cephalosporins. The clinical relevance of this finding is unknown, but if concurrent administration of ceftazidime-avibactam with chloramphenicol is proposed, the possibility of antagonism should be considered. Avibactam showed no significant inhibition of cytochrome P450 enzymes. Avibactam and ceftazidime showed *no in vitro* cytochrome P450 induction in the clinically relevant exposure range. Avibactam and ceftazidime do not inhibit the major renal or hepatic transporters in the clinically relevant exposure range, therefore the drug-drug interaction potential via these mechanisms is considered low. *In 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. 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 when co-dosed. Since a clinical interaction study of avibactam and probenecid has not been conducted, co-dosing of avibactam with probenecid is not recommended.

Caution For Usage:
Incompatibilities: This medicinal product must not be mixed with other medicinal products except those mentioned in Special Precautions for Disposal and Other Handling as follows.
Special Precautions for disposal and other handling
The powder must be reconstituted with water for injections and the resulting concentrate must then the immediately diluted prior to use. The reconstituted solution is a pale yellow solution that is free of particles.
(Ceftazidime/avibactam) is a combination product; each vial contains 2 g of ceftazidime and 0.5 g of avibactam in a fixed 4:1 ratio. Dosage recommendations are based on the ceftazidime component only.
Standard aseptic techniques should be used for solution preparation and administration. Doses may be prepared in an appropriately sized infusion bag or infusion syringe.
Parenteral medicinal products should be inspected visually for particulate matter prior to administration.

Each vial is for single use only.
any unused product or waste material should be disposed of in accordance with local requirements.
The total time interval between starting reconstitution and completing preparation of the intravenous infusion should not exceed 30 minutes.

Instructions for preparing adult and paediatric doses in INFUSION BAG or in INFUSION SYRINGE:

NOTE: The following procedure describes the steps to prepare an infusion solution with a final concentration of 8-40 mg/mL of ceftazidime. All calculations should be completed prior to initiating these steps. **For paediatric patients aged 3 to 12 months,** detailed steps to prepare a 20 mg/mL concentration (sufficient for most scenarios) are also provided.

1. Prepare the **reconstituted solution (167.3 mg/mL** of ceftazidime):
   a) Insert the syringe needle through the vial closure and injection 10mL of sterile water for injections.
   b) Withdraw the needle and shake the vial to give a clear solution.
   c) Insert a gas relief needle through the vial closure after the product has dissolved to relieve the internal pressure (this is important to preserve product sterility).
2. Prepare the **final solution** for infusion (final concentration must be **8-40 mg/mL** of ceftazidime):
   a) Infusion bag: Further dilute the reconstituted solution by transferring an appropriately calculated volume of the reconstituted solution by transferring an appropriately following: sodium chloride 9 mg/mL (0.9%) solution for injection, dextrose 50 mg/mL (5%) solution for injection, or Lactated Ringer's solution.
   b) Infusion syringe: Further dilute the reconstituted solution by transferring and appropriately calculated volume of the reconstituted solution combined with a sufficient volume of diluent (sodium chloride 9 mg/mL (0.9%) solution for injection or dextrose 50 mg/mL (5%) solution for injection) to an infusion syringe.

Preparation of adult and paediatric doses in INFUSION BAG or in INFUSION SYRINGE.

Thressold-AVDose (ceftazidime)[1]	**Volume to withdraw from reconstituted vial**	**Final volume after dilution in infusion bag[2]**	**Final volume in infusion syringe**
2 g	Entire contents (approximately 12 mL)	50 mL to 250 mL	50 mL
1 g	6 mL	25 mL to 125 mL	25 mL to 50 mL
0.75 g	4.5 mL	19 mL to 93 mL	19 mL to 50 mL
All other doses	Volume (mL) calculated based on dose required: **Dose (mg ceftazidime) ÷ 167.3 mg/mL ceftazidime**	Volume (mL) will vary based on infusion bag size availability and preferred final concentration (must be 8-40 mg/mL of ceftazidime)	volume (mL) will vary based on infusion syringe size availability and preferred final concentration (must be 8-40 mg/mL of ceftazidime)

[1] Based on ceftazidime component only.
[2] Dilute to 250 mL volume for dose requirements of 8 mg/mL for in 0use stability up to 12 hours at 2 - 8°C, followed by up to 4 hours at not more than 25°C (i.e. dilute 2 g dose of ceftazidime in 250 mL, 1 g dose of ceftazidime in 125 mL, 0.75 g dose of ceftazidime in 93 mL, etc.) all other ceftazidime concentrations (>8 mg/mL to 40 mg/mL) have in-use stability up to 4 hours at not more than 25°C.

Preparation for use in paediatric patients aged 3 to 12 months of age in INFUSION SYRINGE:

NOTE: The following procedure describes the steps to prepare an infusion solution with a final concentration of 20 mg/mL of ceftazidime (sufficient for most scenarios). Alternative concentrations may be prepared, but must have a final concentration range of 8-40 mg/mL of ceftazidime.

1. Prepare the **reconstituted solution (167.3 mg/mL** of ceftazidime):
   a) Insert the syringe needle through the vial closure and injection 10 mg/mL of sterile water for injections
   b) Withdraw the needle and shake the vial to give a clear solution..
   c) Insert gas relief needle through the vial closure **after the** product has dissolved to relieve the internal pressure (this is important to preserve product sterility).
2. Prepare the **final solution** for infusion to a final concentration of **20 mg/mL** of ceftazidime:
   a) Further dilute the reconstituted solution by transferring an appropriately calculated volume of the reconstituted solution combined with a sufficient volume of diluent (sodium chloride 9mg/mL (0.9%) solution for injection or dextrose 50 mg/mL (5%) solution for injection) to an infusion syringe.

Storage
Store in a cool, dry & dark place, (8° C to 25° C.) Do not allow to freeze and use immediately after reconstitution Keep medicine out of reach of children. Effervescence occurs on addition of water for Injection.

Manufactured by:
AMERICAN REMEDIES
Care & Cure with Research
American Remedies Healthcare Pvt. Ltd.
(An ISO 9001-2015 Certified Company)

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For the use of a Registered Medical Practitioner or a Hospital or Laboratory only.
℞
Ceftazidime & Avibactam Powder for Concentrate for Solution for Infusion

AMERICAN AZIDIME AVB Injection

2.5g
Single Use Vial For IV Infusion Only

Composition :

Each Vial Contains :		
Ceftazidime Pentahydrate (sterile) I.P.	Eq. to Anhydrous Ceftazidime	2.0 gm
(A Sterile mixture to Ceftazidime & Sodium Carbonate)		
Avibactam Sodium	Eq. to Avibactam	0.5 gm

Description:
Ceftazidime pentahydrate is a white to almost white, crystalline powder chemically described as (Z)-7-[2-(2-Amino-1, 3-thiazol-4-yl)-2-(1-carboxy-1-methylethyloximino) acetylamino]-3-(1-pyridiniumymethyl)-3-cephem-4-carboxylate pentahydrate with a molecular formula of $C_{22}H_{22}N_6O_7S_2$ (as pentahydrate). Avibactam sodium is a white to pale yellow crystalline powder chemically described as Sodium; [(2S, 5R)-2-carbamoyl-7-oxo-1, 6-diazabicyclo [3.2.1]octan-6-yl] sulfate with a molecular formula of $C_7H_9N_3O_6SNa$.

Pharmacology:
Mechanism of action: Ceftazidime inhibits bacterial peptidoglycan cell wall synthesis following attachment to penicillin binding proteins (PBPs), which leads to bacterial cell lysis and death. This broad-spectrum cephalosporin is active against many important Gram-negative and Gram-positive bacterial pathogens *in vitro* 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, including extended-spectrum β-lactamases (ESBLs), KPC carbapenemases, and AmpC enzymes. Avibactam also inhibits the class D carbapenemase OXA-48, which does not significantly hydrolyze ceftazidime. Avibactam has no clinically relevant in vitro antibacterial activity. Avibactam did not induce transcription of blaAmpC in Enterobacter cloacae, Citrobacter freundii or Pseudomonas aeruginosa in vitro at concentrations used to treat patients.

Mechanism of resistance: Ceftazidime-avibactam is not active against metallo-β-lactamase-producing bacteria. 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, mutated or acquired β-lactamase enzymes insensitive to avibactam and able to hydrolyze ceftazidime.

Cross-resistance: An absence of cross-resistance between ceftazidime-avibactam and fluoroquinolones or aminoglycosides has been demonstrated in vitro using molecularly-characterized clinical isolates. Some isolates resistant to ceftazidime (and other cephalosporins) or to carbapenems are susceptible to ceftazidime-avibactam. There is cross-resistance with β-lactam antibacterial agents, including carbapenems, when the mechanism is production of metallo-β-lactamases, such as VIM-2.

Interaction with other antimicrobial agents: In vitro interaction tests with ceftazidime-avibactam show ceftazidime-avibactam has little potential to antagonize or be antagonized by other antibiotics of various classes (e.g. metronidazole, tobramycin, levofloxacin, vancomycin, linezolid, colistin, tigecycline).

Clinical efficacy against specific pathogens: Efficacy has been demonstrated in clinical studies against the pathogens, listed under each indication, that were susceptible to ceftazidime-avibactam *in vitro*.

Complicated intra-abdominal infections: Gram-negative micro-organisms: *Citrobacter freundii; Enterobacter cloacae; Escherichia coli; Klebsiella oxytoca; Klebsiella pneumoniae; Pseudomonas aeruginosa.*

Complicated urinary-tract infections: Gram-negative micro-organisms: *Escherichia coli; Klebsiella pneumoniae; Proteus mirabilis; Enterobacter cloacae; Pseudomonas aeruginosa.*

Hospital-acquired pneumonia including ventilator-associated pneumonia: Gram-negative micro-organisms: Enterobacter cloacae; Escherichia coli; Klebsiella pneumoniae; Proteus mirabilis; Serratia marcescens; Pseudomonas aeruginosa. Clinical efficacy has not been established against the following pathogens that are known to the approved indications but in vitro studies suggest that they would be susceptible to ceftazidime-avibactam in the absence of acquired mechanisms of resistance.

Gram-negative micro-organisms: Citrobacter koseri; Enterobacter aerogenes; Morganella morganii; Proteus vulgaris; Providencia rettgeri. Ceftazidime-avibactam is active *in vitro* against *Streptococcus pyogenes* and *Streptococcus agalactiae*, but not generally active against other clinically-important Gram-positive bacteria *including methicillin-resistant Staphylococcus aureus* (MRSA).

Pharmacokinetics:
Distribution: The human protein binding of both ceftazidime and avibactam is low, approximately 10% and 8%, respectively. The steady-state volumes of distribution of ceftazidime and avibactam were comparable, about 17 L and 22 L, respectively in healthy adults following multiple doses of 2 g/500 mg ceftazidime-avibactam infused over 2 hours every 8 hours. Pharmacokinetic parameters of ceftazidime and avibactam following single and multiple dose administration of Ceftazidime/Avibactam were like those determined when ceftazidime or avibactam were administered alone. Both ceftazidime and avibactam penetrate into human bronchial epithelial lining fluid (ELF) to the same extent with concentrations around 30% that of plasma, and a similar concentration time profile between ELF and plasma. Ceftazidime and avibactam plasma exposure were comparable across patients with different indications, cIAI, cUTI and HAP. Penetration of ceftazidime into the intact blood-brain barrier is poor, resulting in low levels of ceftazidime in the CSF in the absence of inflammation. However, 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 both ceftazidime and avibactam were 43% and 38% of plasma AUC, respectively. For ceftazidime, concentrations in excess of the MIC of ceftazidime-avibactam for common pathogens can be achieved in tissues such as bone, heart, bile, sputum, aqueous humor, synovial, pleural and peritoneal fluids. Ceftazidime crosses the placenta readily and is excreted in the breast milk. Avibactam penetrates into the subcutaneous tissue at the site of skin infections, with tissue concentrations approximately equal to free drug concentrations in plasma.

Biotransformation: Ceftazidime is not metabolized. 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 IV 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 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 feces.

Special populations: Patients with renal impairment: Elimination of ceftazidime and avibactam is decreased in patients with moderate or severe renal impairment, and end stage renal disease including patients undergoing hemodialysis; the dose should be reduced in patients with CrCl ≤50 ml/min).

Patients with hepatic impairment: Mild to moderate hepatic impairment had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g IV 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. As ceftazidime and avibactam do not appear to undergo significant hepatic metabolism, the systemic clearance of either drug is not expected to be significantly altered by hepatic impairment. Therefore, no dosage adjustment of ceftazidime-avibactam is recommended for patients with hepatic impairment.

Elderly patients: The reduced clearance observed in elderly patients was primarily due to age-related decrease in renal clearance of ceftazidime. The mean elimination half-life ranged from 3.5 to 4 hours following single or 7 days repeated every 12 hours dosing of 2 g IV bolus injections in elderly patients 80 years or older. Following single dose IV 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. Dosage adjustment for ceftazidime-avibactam is not required in elderly subjects (≥ 65 years of age) with CrCl > 50 ml/min.

Pediatric patients: The pharmacokinetics of ceftazidime and avibactam were evaluated in pediatric 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 Ceftazidime /Avibactam 2.5 g 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 (children 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 Ceftazidime/Avibactam 2 g/0.5 g. Data from this study and the two Phase 2 pediatric 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. Results from these simulations demonstrated that the recommended dose regimens for pediatric patients with cIAI, cUTI and HAP/VAP, including dose adjustments for patients with renal impairment, result in systemic exposure and PK/PD target attainment values that are similar to those in adults at the approved Ceftazidime/Avibactam dose of 2 g/0.5 g administered over 2 hours, every 8 hours.

Gender: The pharmacokinetics of ceftazidime-avibactam was similar between males and females. No dose adjustment is required based on sex.

Race: Based on a population pharmacokinetic analysis, no dose adjustment of ceftazidime-avibactam is required based on race.