

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVYCAZ safely and effectively. See full prescribing information for AVYCAZ.

AVYCAZ (ceftazidime-avibactam) for injection, for intravenous use
Initial U.S. Approval: 2015

-----**INDICATIONS AND USAGE**-----

AVYCAZ (ceftazidime-avibactam) is a combination of a cephalosporin and a beta-lactamase inhibitor indicated for the treatment of patients 18 years or older with the following infections caused by designated susceptible microorganisms:

- Complicated Intra-abdominal Infections (cIAI), used in combination with metronidazole (1.1)
- Complicated Urinary Tract Infections (cUTI), including Pyelonephritis (1.2)

As only limited clinical safety and efficacy data for AVYCAZ are currently available, reserve AVYCAZ for use in patients who have limited or no alternative treatment options. [see *Clinical Studies (14)*].

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AVYCAZ and other antibacterial drugs, AVYCAZ should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

-----**DOSAGE AND ADMINISTRATION**-----

Estimated Creatinine Clearance (mL/min)^a	Recommended Dosage Regimen for AVYCAZ Infuse each dose intravenously over 2 hours
greater than 50	2.5 grams (2 grams/0.5 grams) every 8 hours
31 to 50	1.25 grams (1 gram/0.25 grams) every 8 hours
16 to 30	0.94 grams (0.75 grams/0.19 grams) every 12 hours
6 to 15 ^b	0.94 grams (0.75 grams/0.19 grams) every 24 hours
Less than or equal 5 ^b	0.94 grams (0.75 grams/0.19 grams) every 48 hours

a As calculated using the Cockcroft-Gault formula.
b Both ceftazidime and avibactam are hemodialyzable; thus, administer AVYCAZ after hemodialysis on hemodialysis days.
Recommended duration of treatment: (2.1)
cIAI: 5 to 14 days
cUTI including pyelonephritis: 7 to 14 days

- See Full Prescribing Information for instructions for constituting supplied dry powder and subsequent required dilution. (2.3)
- See Full Prescribing Information for drug compatibilities. (2.4)

-----**DOSAGE FORMS AND STRENGTHS**-----

AVYCAZ (ceftazidime-avibactam) for Injection in single-use vials containing 2 grams ceftazidime and 0.5 grams avibactam. (3)

-----**CONTRAINDICATIONS**-----

Known serious hypersensitivity to ceftazidime, avibactam or other members of the cephalosporin class. (4)

-----**WARNINGS AND PRECAUTIONS**-----

- Decreased efficacy in patients with baseline CrCL of 30 to 50 mL/ min. Monitor CrCL at least daily in patients with changing renal function and adjust the dose of AVYCAZ accordingly. (5.1)
- **Hypersensitivity reactions:** Includes anaphylaxis and serious skin reactions. Cross-hypersensitivity may occur in patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue AVYCAZ. (5.2)
- ***Clostridium difficile*-associated diarrhea:** *Clostridium difficile*-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents, including AVYCAZ. Evaluate if diarrhea occurs. (5.3)
- **Central Nervous System Reactions:** Seizures and other neurologic events may occur, especially in patients with renal impairment. Adjust dose in patients with renal impairment. (5.4)

-----**ADVERSE REACTIONS**-----

Most common adverse reactions (incidence of ≥ 10% in either indication) are vomiting, nausea, constipation, and anxiety. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Forest Laboratories, LLC, at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Complicated Intra-Abdominal Infections (cIAI)

AVYCAZ (ceftazidime-avibactam), in combination with metronidazole, is indicated for the treatment of complicated intra-abdominal infections (cIAI) caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Providencia stuartii*, *Enterobacter cloacae*, *Klebsiella oxytoca*, and *Pseudomonas aeruginosa* in patients 18 years or older.

As only limited clinical safety and efficacy data for AVYCAZ are currently available, reserve AVYCAZ for use in patients who have limited or no alternative treatment options. [see *Clinical Studies (14)*].

1.2 Complicated Urinary Tract Infections (cUTI), including Pyelonephritis

AVYCAZ (ceftazidime-avibactam) is indicated for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Citrobacter freundii*, *Proteus* spp., and *Pseudomonas aeruginosa* in patients 18 years or older.

As only limited clinical safety and efficacy data for AVYCAZ are currently available, reserve AVYCAZ for use in patients who have limited or no alternative treatment options. [see *Clinical Studies (14)*].

1.3 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AVYCAZ and other antibacterial drugs, AVYCAZ should be used to treat only indicated infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy [see *Dosage and Administration (2.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of AVYCAZ is 2.5 grams (2 grams ceftazidime and 0.5 grams avibactam) administered every 8 hours by intravenous (IV) infusion over 2 hours in patients 18 years of age and older. For treatment of cIAI, metronidazole should be given concurrently. The guidelines for dosage of AVYCAZ in patients with normal renal function are listed in Table 1.

Infection	Dosage	Frequency	Infusion Time (hours)	Recommended Duration of Total Antimicrobial Treatment
Complicated Intra-abdominal Infections [used in combination with metronidazole]	2.5 grams (2 grams/0.5 grams)	Every 8 hours	2	5 to 14 days
Complicated Urinary Tract Infections including Pyelonephritis	2.5 grams (2 grams/0.5 grams)	Every 8 hours	2	7 to 14 days

2.2 Dosage Adjustments in Patients with Renal Impairment

The recommended AVYCAZ dosage in patients with varying degrees of renal function is presented in Table 2. For patients with changing renal function, monitor creatinine clearance (CrCL) at least daily and adjust the dosage of AVYCAZ accordingly [see *Warnings and Precautions (5.1)*, *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

Estimated Creatinine Clearance (mL/minute)^a	Recommended Dosage Regimen for AVYCAZ
Greater than 50	2.5 grams (2 grams/0.5 grams) intravenously (over 2 hours) every 8 hours
31 to 50	1.25 grams (1 grams/0.25 grams) intravenously (over 2 hours) every 8 hours
16 to 30	0.94 grams (0.75 grams/0.19 grams) intravenously (over 2 hours) every 12 hours
6 to 15 ^b	0.94 grams (0.75 grams/0.19 grams) intravenously (over 2 hours) every 24 hours
Less than or equal to 5 ^b	0.94 grams (0.75 grams/0.19 grams) intravenously (over 2 hours) every 48 hours

a As calculated using the Cockcroft-Gault formula.

b Both ceftazidime and avibactam are hemodialyzable; thus, administer AVYCAZ after hemodialysis on hemodialysis days.

2.3 Preparation of the AVYCAZ Solution for Administration

AVYCAZ is supplied as a dry powder, which must be constituted and subsequently diluted, using aseptic technique prior to intravenous infusion.

- a) Constitute the powder in the AVYCAZ vial with 10 mL of one of the following solutions:
 - sterile water for injection, USP
 - 0.9% of sodium chloride injection, USP (normal saline)
 - 5% of dextrose injection, USP
 - all combinations of dextrose injection and sodium chloride injection, USP, containing up to 2.5% dextrose, USP, and 0.45% sodium chloride, USP, or
 - lactated Ringer's injection, USP.
- b) Mix gently. The constituted AVYCAZ solution will have an approximate ceftazidime concentration of 0.167 grams/mL and an approximate avibactam concentration of 0.042 grams/mL.
- c) With the same diluent used for constitution of the powder (except sterile water for injection), dilute the constituted AVYCAZ solution further to achieve a total volume between 50 mL (40 and 10 mg/mL of ceftazidime and avibactam, respectively) to 250 mL (8 and 2 mg/mL of ceftazidime and avibactam, respectively) before infusion.
- d) Mix gently and ensure that the contents are dissolved completely. Visually inspect the diluted AVYCAZ solution (for administration) for particular matter and discoloration prior to administration (the color of the AVYCAZ infusion solution for administration ranges from clear to light yellow).
- e) Use the diluted AVYCAZ solution in the infusion bags within 12 hours when stored at room temperature. The diluted AVYCAZ solution in the infusion bags may be stored under refrigeration at 2 to 8°C (36 to 46°F) up to 24 hours following dilution and use within 12 hours of subsequent storage at room temperature.

2.4 Drug Compatibility

The AVYCAZ solution for administration at concentrations between 0.008 g/mL ceftazidime + 0.002 g/mL avibactam and 0.04 g/mL ceftazidime + 0.01 g/mL avibactam is compatible with the more commonly used intravenous infusion fluids in infusion bags (including Baxter® Mini-Bag Plus™) such as:

- 0.9% sodium chloride injection, USP
- 5% dextrose injection, USP
- all combinations of dextrose injection and sodium chloride injection, USP, containing up to 2.5% dextrose, USP, and 0.45% sodium chloride, USP
- lactated ringer's injection, USP, and
- in Baxter® Mini-Bag Plus™ containing 0.9% sodium chloride injection or 5% dextrose injection.

Compatibility of AVYCAZ solution for administration with other drugs has not been established.

2.5 Storage of Constituted Solutions

- Constituted solutions of AVYCAZ in the infusion bags should be used within 12 hours when stored at room temperature.
- Constituted solutions of AVYCAZ in the infusion bags may be refrigerated for up to 24 hours following constitution; and then should be used within 12 hours of subsequent storage at room temperature.

3 DOSAGE FORMS AND STRENGTHS

AVYCAZ (ceftazidime-avibactam) for injection is supplied as a white to yellow sterile powder in a single use, sterile, clear glass vial containing 2 grams of ceftazidime (equivalent 2.635 grams of ceftazidime pentahydrate/sodium carbonate powder) and 0.5 grams of avibactam (equivalent to 0.551 grams of avibactam sodium).

4 CONTRAINDICATIONS

AVYCAZ is contraindicated in patients with known serious hypersensitivity to AVYCAZ, avibactam-containing products, ceftazidime, or other members of the cephalosporin class [see *Warnings and Precautions* (5.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Decreased Clinical Response in Patients with Baseline Creatinine Clearance of 30 to 50 mL/min

In a Phase 3 cIAI trial, clinical cure rates were lower in a subgroup of patients with baseline CrCL of 30 to 50 mL/min compared to those with CrCL greater than 50 mL/min (Table 3). The reduction in clinical cure rates was more marked in patients treated with AVYCAZ plus metronidazole compared to meropenem-treated patients. Within this subgroup, patients treated with AVYCAZ received a 33% lower daily dose than is currently recommended for patients with CrCL 30 to 50 mL/min. Monitor CrCL at least daily in patients with changing renal function and adjust the dosage of AVYCAZ accordingly [see *Dosage and Administration* (2.2), and *Adverse Reactions* (6.1)].

	AVYCAZ + Metronidazole % (n/N)	Meropenem % (n/N)
Normal function / mild impairment (CrCL greater than 50 mL/min)	85% (322/379)	86% (321/373)

Moderate impairment (CrCL 30 to 50 mL/min)	45% (14/31)	74% (26/35)
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Microbiological modified intent-to-treat (mMITT) population included patients who had at least one bacterial pathogen at baseline and received at least one dose of study drug.

5.2 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 AVYCAZ 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 AVYCAZ occurs.

5.3 *Clostridium difficile*-associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial drugs, including AVYCAZ, 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.

5.4 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 [see *Dosage and Administration* (2.2)].

5.5 Development of Drug-Resistant Bacteria

Prescribing AVYCAZ 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 [see *Indications and Usage* (1.3)].

6 ADVERSE REACTIONS

The following are discussed in greater detail in the Warnings and Precautions section:

- Decreased Clinical Response in Patients with Baseline CrCL of 30 to 50 mL/min [see *Warnings and Precautions* (5.1)]
- Hypersensitivity Reactions [see *Warnings and Precautions* (5.2)]
- *Clostridium difficile*-Associated Diarrhea [see *Warnings and Precautions* (5.3)]
- Central Nervous System Reactions [see *Warnings and Precautions* (5.4)]
- Development of Drug-Resistant Bacteria [see *Warnings and Precautions* (5.5)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

AVYCAZ was evaluated in two active-controlled Phase 2 clinical trials, one each in cIAI and cUTI, including pyelonephritis. The Phase 2 trials included a total of 169 adult patients treated with AVYCAZ and 169 patients treated with comparators.

Complicated Intra-Abdominal Infections

The Phase 2 cIAI trial included 101 adult patients treated with AVYCAZ (2 grams ceftazidime and 0.5 grams avibactam) administered intravenously over 30 minutes every 8 hours plus 500 mg metronidazole administered intravenously over 60 minutes every 8 hours and 102 patients treated with meropenem. The median age of patients treated with AVYCAZ was 41 years (range 18 to 79 years). Patients were predominantly male (69.3%) and Caucasian (55.4%). Patients with an estimated baseline CrCL 50 mL/min or less were excluded.

Serious adverse reactions occurred in 9/101 (8.9%) of patients receiving AVYCAZ (with metronidazole) and 11/102 (10.8%) of patients receiving meropenem. The most common adverse reactions leading to discontinuation in patients receiving AVYCAZ were skin and subcutaneous tissue disorders (3%).

Adverse reactions occurring in 10% or more of patients receiving AVYCAZ were vomiting and nausea.

Increased Mortality

In a Phase 3 cIAI trial, death occurred in 2.5% (13/529) of patients who received AVYCAZ/ metronidazole and in 1.5% (8/529) of patients who received meropenem. Among a subgroup of patients with baseline CrCL 30 to 50 mL/min, death occurred in 25.8% (8/31) of patients who received AVYCAZ/metronidazole and in 8.6% (3/35) of patients who received meropenem. Within this subgroup, patients treated with AVYCAZ received a 33% lower daily dose than is currently recommended for patients with CrCL 30 to 50 mL/min [*see Dosage and Administration (2.2) and Warnings and Precautions (5.1)*]. In patients with normal renal function or mild renal impairment (baseline CrCL greater than 50 mL/min), death occurred in 1.0% (5/498) of patients who received AVYCAZ/metronidazole and in 1.0% (5/494) of patients who received meropenem. The causes of death varied and contributing factors included progression of underlying infection, baseline pathogens isolated that were unlikely to respond to the study drug, and delayed surgical intervention.

Complicated Urinary Tract Infections, Including Pyelonephritis

The Phase 2 cUTI trial included 68 adult patients treated with AVYCAZ (0.5 grams ceftazidime + 0.125 grams avibactam) administered intravenously over 30 minutes every 8 hours and 67 patients treated with imipenem-cilastatin (0.5 grams intravenously every 6 hours). The dose of AVYCAZ in this trial was lower than the recommended dose [*see Dosage and Administration (2.2)*]. Median age of patients treated with AVYCAZ was 47.5 years (range 18 to 85 years). Patients were predominantly female (75%) and Caucasian (58.8%). Patients with CrCL less than 70 mL/min were excluded.

Serious adverse reactions occurred in 6/68 (8.8%) of patients receiving AVYCAZ and 2/67 (3.0%) of patients receiving imipenem-cilastatin. Two patients prematurely discontinued treatment with AVYCAZ: one due to an accidental overdose and one due to atrial fibrillation.

Adverse reactions occurring in 10% or more of patients receiving AVYCAZ were constipation and anxiety.

Table 4 lists adverse reactions occurring in 5% or more of patients receiving AVYCAZ in the Phase 2 cIAI trial or the Phase 2 cUTI trial.

Table 4. Incidence of Selected Adverse Drug Reactions Occurring in 5% or more of Patients Receiving AVYCAZ in the Phase 2 cIAI Trial or the Phase 2 cUTI Trial				
	Phase 2 cIAI Trial		Phase 2 cUTI Trial	
	AVYCAZ plus Metronidazole^a (N = 101)	Meropenem^b (N = 102)	AVYCAZ^c (N = 68)	Imipenem-Cilastatin^d (N = 67)
Gastrointestinal disorders				
Vomiting	14%	5%	0%	0%
Nausea	10%	6%	2%	5%
Constipation	4%	1%	10%	3%
Abdominal pain	8%	3%	7%	5%
Upper abdominal pain	1%	0%	7%	2%
Investigations				
Increased blood alkaline phosphatase	9%	7%	3%	2%
Increased alanine aminotransferase	8%	13%	3%	6%
Nervous system disorders				
Dizziness	0%	2%	6%	0%
Psychiatric disorders				
Anxiety	5%	1%	10%	8%
a 2.5 grams (2 grams/0.5 grams) intravenously over 30 minutes every 8 hours (with metronidazole 500 mg intravenously every 8 hours) b 1 gram intravenously over 30 minutes every 8 hours c 0.625 grams (0.5 grams/0.125 grams) intravenously over 30 minutes every 8 hours d 0.5 grams intravenously over 30 minutes every 6 hours				

Other Adverse Reactions of AVYCAZ and Ceftazidime

The following selected adverse reactions were reported in AVYCAZ-treated subjects at a rate of less than 5% in the Phase 2 trials and are not described elsewhere in the labeling.

Blood and lymphatic disorders - Eosinophilia, Thrombocytopenia
Investigations - Increased gamma-glutamyltransferase, Prolonged prothrombin time
Metabolism and nutrition disorders - Hypokalemia
Renal and urinary disorders - Acute renal failure, Renal impairment
Skin and subcutaneous tissue disorders - Rash

Additionally, adverse reactions reported with ceftazidime alone that were not reported in AVYCAZ clinical trials are listed below:

Blood and lymphatic disorders - Agranulocytosis, Hemolytic anemia, Leukopenia, Lymphocytosis, Neutropenia, Thrombocytosis
General disorders and administration site conditions - Infusion site inflammation, Injection site hematoma, Injection site phlebitis, Injection site thrombosis
Hepatobiliary disorders – Jaundice
Infections and infestations - Candidiasis
Investigations - Increased blood lactate dehydrogenase
Nervous system disorders - Dysgeusia, Paresthesia
Renal and urinary disorders - Tubulointerstitial nephritis
Reproductive and breast disorders - Vaginal inflammation

Skin and subcutaneous tissue disorders - Angioedema, Erythema multiforme, Pruritis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Urticaria

Laboratory Changes

Seroconversion from a negative to a positive direct Coombs' test result occurred in 6/82 (7.3%) of patients receiving AVYCAZ plus metronidazole and 2/84 (2.4%) of patients receiving meropenem in the cIAI trial. Seroconversion from a negative to a positive direct Coombs' test result occurred in 1/52 (1.9%) of patients receiving AVYCAZ and 5/60 (8.3%) of patients receiving imipenem cilastatin in the cUTI trial. No adverse reactions representing hemolytic anemia were reported in any treatment group.

7 DRUG INTERACTIONS

7.1 Probenecid

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. 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 AVYCAZ or avibactam alone with probenecid has not been conducted, co-administration of AVYCAZ with probenecid is not recommended [*see Clinical Pharmacology (12.3)*].

7.2 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Animal reproductive toxicity studies have been conducted with ceftazidime and with avibactam. However, there are no adequate and well-controlled studies of AVYCAZ, ceftazidime, or avibactam in pregnant women. 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 showed no embryofetal toxicity at doses of 1000 mg/kg/day, approximately 9 times the human dose based on exposure (AUC). In a rat pre- and postnatal 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 weanling pups that was not associated with pathological changes to renal parenchyma or renal function, with renal pelvic dilatation persisting after female weanling pups became adults.

Reproductive studies performed during early pregnancy in rabbits showed no effects on embryofetal development at doses of 100 mg/kg, twice the human exposure (AUC). At higher doses, increased post-

implantation loss, lower mean fetal weights, delayed ossification of several bones and other anomalies were observed.

8.3 Nursing Mothers

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 in a dose dependent manner. Exercise caution if AVYCAZ is to be administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in patients less than 18 years of age have not been established.

8.5 Geriatric Use

Of the 169 patients treated with AVYCAZ in the Phase 2 cIAI and cUTI trials, 18 (10.7%) were 65 years of age and older. Because of limited data, differences in outcomes or specific risks with AVYCAZ cannot be ruled out for patients 65 years of age and older.

Ceftazidime and avibactam are excreted primarily by the kidney, and the risk of adverse reactions may be greater in patients with renal impairment. Because elderly patients are more likely to have renal impairment, care should be taken in dose selection in this age group and it may be useful to monitor renal function. Healthy elderly subjects had 17% greater exposure relative to healthy young subjects when administered the same single dose of avibactam, which may have been related to decreased renal function in the elderly subjects. Dosage adjustment for elderly patients should be based on renal function [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

Dosage adjustment is required in patients with moderately or severely impaired renal function (CrCL 50 mL/min or less). For patients with changing renal function, CrCL should be monitored at least daily and dosage of AVYCAZ adjusted accordingly. Both ceftazidime and avibactam are hemodialyzable; thus, AVYCAZ should be administered after hemodialysis on hemodialysis days [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

In the event of overdose, discontinue AVYCAZ 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 AVYCAZ overdose [*see Clinical Pharmacology (12.3)*].

11 DESCRIPTION

AVYCAZ is an antibacterial combination product consisting of the semisynthetic cephalosporin ceftazidime pentahydrate and the beta-lactamase inhibitor avibactam sodium for intravenous administration.

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-

Cardiac Electrophysiology

In a thorough QT study, a suprathreshold dose of ceftazidime (3 grams) was investigated for QT effects in combination with a suprathreshold dose of avibactam (2 grams) given as a 30-minute single infusion. No significant effect on QT_cF interval was detected at peak plasma concentration or at any other time. The largest 90% upper bound for the placebo corrected mean change from baseline was 5.9 ms. There were no QT_cF intervals greater than 450 ms, nor were there any QT_cF interval changes from baseline greater than 30 ms.

12.3 Pharmacokinetics

The mean pharmacokinetic parameters for ceftazidime and avibactam in healthy adult male subjects with normal renal function after single and multiple 2-hour intravenous infusions of AVYCAZ 2.5 grams (2 grams ceftazidime and 0.5 grams avibactam) administered every 8 hours are summarized in Table 5.

Pharmacokinetic parameters of ceftazidime and avibactam were similar for single and multiple dose administration of AVYCAZ and were similar to those determined when ceftazidime or avibactam were administered alone.

Table 5. Pharmacokinetic Parameters (Geometric Mean [%CV]) of Ceftazidime and Avibactam Following Administration of AVYCAZ 2.5 grams (2 grams ceftazidime and 0.5 grams avibactam) in Healthy Adult Male Subjects				
	<i>Ceftazidime</i>		<i>Avibactam</i>	
<i>Parameter</i>	<i>Single AVYCAZ 2.5 grams^a Dose Administered as a 2-hour Infusion (n = 16)</i>	<i>Multiple AVYCAZ 2.5 grams^a Doses Administered every 8 hours as 2-hour Infusions for 11 Days (n = 16)</i>	<i>Single AVYCAZ 2.5 grams^a Dose Administered as a 2-hour Infusion (n = 16)</i>	<i>Multiple AVYCAZ 2.5 grams^a Doses Administered every 8 hours as 2-hour Infusions for 11 Days (n = 16)</i>
C _{max} (mg/L)	88.1 (14)	90.4 (16)	15.2 (14)	14.6 (17)
AUC (mg-h/L) ^b	289 (15) ^c	291 (15)	42.1 (16) ^d	38.2 (19)
T _{1/2} (h)	3.27 (33) ^c	2.76 (7)	2.22 (31) ^d	2.71 (25)
CL (L/h)	6.93 (15) ^c	6.86 (15)	11.9 (16) ^d	13.1 (19)
V _{ss} (L)	18.1 (20) ^c	17 (16)	23.2 (23) ^d	22.2 (18)

CL = plasma clearance; C_{max} = maximum observed concentration; d T_{1/2} = terminal elimination half-life; V_{ss} (L) = volume of distribution at steady state.

a 2 grams ceftazidime + 0.5 grams avibactam.

b AUC_{0-inf} (area under concentration-time curve from time 0 to infinity) reported for single-dose administration; AUC_{0-tau} (area under concentration curve over dosing interval) reported for multiple-dose administration.

c n = 15.

d n = 13.

The C_{max} and AUC of ceftazidime increase in proportion to dose. Avibactam demonstrated approximately linear pharmacokinetics across the dose range studied (50 mg to 2000 mg) for single intravenous administration. No appreciable accumulation of ceftazidime or avibactam was observed following multiple intravenous infusions of AVYCAZ 2.5 grams (2 grams ceftazidime and 0.5 grams avibactam) administered every 8 hours for up to 11 days in healthy adults with normal renal function.

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 AVYCAZ 2.5 grams (2 grams ceftazidime and 0.5 grams avibactam) infused every 8 hours over 2 hours for 11 days.

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.

Approximately 80% to 90% of an intravenous dose of ceftazidime is excreted unchanged by the kidneys over a 24-hour period. After the intravenous administration of single 0.5-grams or 1-gram doses, approximately 50% of the dose appeared in the urine in the first 2 hours. An additional 20% was excreted between 2 and 4 hours after dosing, and approximately another 12% of the dose appeared in the urine between 4 and 8 hours later. The elimination of ceftazidime by the kidneys resulted in high therapeutic concentrations in the urine. The mean renal clearance of ceftazidime was approximately 100 mL/min. The calculated plasma clearance of approximately 115 mL/min indicated nearly complete elimination of ceftazidime by the renal route.

Following administration of a single 0.5-grams intravenous dose of radiolabelled avibactam, an average of 97% of administered radioactivity was recovered from the urine, with over 95% recovered within 12 hours of dosing. An average of 0.20% of administered total radioactivity was recovered in feces within 96 hours of dosing. An average of 85% of administered avibactam was recovered from the urine as unchanged drug within 96 hours, with over 50% recovered within 2 hours of the start of the infusion. Renal clearance was 158 mL/min, which is greater than the glomerular filtration, suggesting that active tubular secretion contributes to the excretion of avibactam in addition to glomerular filtration.

Specific Populations

Renal Impairment

Ceftazidime is eliminated almost solely by the kidneys; its serum half-life is significantly prolonged in patients with impaired renal function.

The clearance of avibactam was significantly decreased in subjects with mild (CrCL 50 to 80 mL/min, n = 6), moderate (CrCL 30 to 50 mL/min, n = 6), and severe (CrCL 30 mL/min or less, not requiring hemodialysis; n = 6) renal impairment compared to healthy subjects with normal renal function (CrCL greater than 80 mL/min, n = 6) following administration of a single 100 - mg intravenous dose of avibactam. The slower clearance resulted in increases in systemic exposure (AUC) of avibactam of 2.6-fold, 3.8-fold, and 7-fold in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function.

A single 100-mg dose of avibactam was administered to subjects with ESRD (n = 6) either 1 hour before or after hemodialysis. The avibactam AUC following the post-hemodialysis infusion was 19.5-fold the AUC of healthy subjects with normal renal function. Avibactam was extensively removed by hemodialysis, with an extraction coefficient of 0.77 and a mean hemodialysis clearance of 9.0 L/h. approximately 55% of the avibactam dose was removed during a 4-hour hemodialysis session.

Dosage adjustment of AVYCAZ is recommended in patients with moderate and severe renal impairment and end-stage renal disease. Population PK models for ceftazidime and avibactam were used to conduct simulations for patients with impaired renal function. Simulations demonstrated that the recommended dose adjustments

[see *Dosage and Administration (2.2)*] provide comparable exposures of ceftazidime and avibactam in patients with moderate and severe renal impairment and end-stage renal disease to those in patients with normal renal function or mild renal impairment. Because the exposure of both ceftazidime and avibactam is highly dependent on renal function, monitor CrCL at least daily and adjust the dosage of AVYCAZ accordingly for patients with changing renal function [see *Dosage and Administration (2.2)*].

Hepatic Impairment

The presence of hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 grams intravenously every 8 hours for 5 days.

The pharmacokinetics of avibactam in patients with hepatic impairment have not been established. Avibactam does not appear to undergo significant hepatic metabolism, therefore the systemic clearance of avibactam is not expected to be significantly affected by hepatic impairment.

Dose adjustments are not currently considered necessary for AVYCAZ in patients with impaired hepatic function.

Geriatric Patients

Following single-dose administration of 0.5 grams avibactam as a 30-minute infusion the mean AUC for avibactam was 17% higher in healthy elderly subjects (65 years of age and older, n = 16) than in healthy young adult subjects (18 to 45 years of age, n = 17). There was no statistically significant age effect for avibactam C_{max} .

No dose adjustment is recommended based on age. Dosage adjustment for AVYCAZ in elderly patients should be based on renal function [see *Dosage and Administration (2.2)*].

Gender

Following single-dose administration of 0.5 grams avibactam as a 30-minute infusion, healthy male subjects (n = 17) had 18% lower avibactam C_{max} values than healthy female subjects (n = 16). There was no gender effect for avibactam AUC parameters.

No dose adjustment is recommended based on gender.

Drug Interaction Studies

Avibactam at clinically relevant concentrations does not inhibit the cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 *in vitro* in human liver microsomes. Avibactam showed no potential for *in vitro* induction of CYP1A2, 2B6, 2C9 and 3A4 isoenzymes in human hepatocytes. Against CYP2E1, avibactam showed a slight induction potential at very high concentrations that exceed any clinically relevant exposure. Ceftazidime was evaluated independently in human hepatocytes and showed no induction potential on the activity or mRNA expression of CYP1A1/2, CYP2B6, and CYP3A4/5.

Neither ceftazidime nor avibactam was found to be an inhibitor of the following hepatic and renal transporters *in vitro* at clinically relevant concentrations: MDR1, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, BSEP, MRP4, OCT1 and OCT2. Avibactam was not a substrate of MDR1, BCRP, MRP4, or OCT2, but was a substrate of human OAT1 and OAT3 kidney transporters based on results generated in human embryonic kidney cells expressing these transporters. Probenecid inhibits 56% to 70% of the uptake of avibactam by OAT1 and OAT3 *in vitro*. Ceftazidime does not inhibit avibactam transport mediated by OAT1 and OAT3. The clinical impact of potent OAT inhibitors on the pharmacokinetics of avibactam is not known. Co-administration of AVYCAZ with probenecid is not recommended [see *Drug Interactions (7.1)*].

Administration of AVYCAZ 2.5 grams (2 grams ceftazidime and 0.5 grams avibactam) to healthy male subjects (n = 28) as a 2-hour infusion following a 1-hour infusion of metronidazole every 8 hours for 3 days, did not affect the C_{max} and AUC values for avibactam or ceftazidime compared to administration of AVYCAZ 2.5 grams (2 grams ceftazidime and 0.5 grams avibactam) alone. Administration of 0.5 grams metronidazole to healthy male subjects as a 1-hour infusion before a 2-hour infusion of AVYCAZ 2.5 grams (2 grams ceftazidime and 0.5 grams avibactam) every 8 hours for 3 days did not affect the C_{max} and AUC of metronidazole compared to administration of 0.5 grams metronidazole alone.

12.4 Microbiology

Mechanism of Action

The ceftazidime component of AVYCAZ is a cephalosporin antibacterial drug with *in vitro* activity against certain gram-negative and gram-positive bacteria. The bactericidal action of ceftazidime is mediated through binding to essential penicillin-binding proteins (PBPs). The avibactam component of AVYCAZ is a non-beta-lactam beta-lactamase inhibitor that inactivates some beta-lactamases and protects ceftazidime from degradation by certain beta-lactamases. Avibactam does not decrease the activity of ceftazidime against ceftazidime-susceptible organisms.

AVYCAZ demonstrated *in vitro* activity against Enterobacteriaceae in the presence of some beta-lactamases and extended-spectrum beta-lactamases (ESBLs) of the following groups: TEM, SHV, CTX-M, *Klebsiella pneumoniae* carbapenemase (KPCs), AmpC, and certain oxacillinases (OXA). AVYCAZ also demonstrated *in vitro* activity against *P. aeruginosa* in the presence of some AmpC beta-lactamases, and certain strains lacking outer membrane porin (OprD). AVYCAZ is not active against bacteria that produce metallo-beta lactamases and may not have activity against gram-negative bacteria that overexpress efflux pumps or have porin mutations.

Cross-Resistance

No cross-resistance with other classes of antimicrobials has been identified. Some isolates resistant to other cephalosporins (including ceftazidime) and to carbapenems may be susceptible to AVYCAZ.

Interaction with Other Antimicrobials

In vitro studies have not demonstrated antagonism between AVYCAZ and colistin, levofloxacin, linezolid, metronidazole, tigecycline, tobramycin, or vancomycin.

Activity against Ceftazidime-Nonsusceptible Bacteria in Animal Infection Models

Avibactam restored activity of ceftazidime in animal models of infection (e.g. thigh infection, pyelonephritis, systemic infection induced by intraperitoneal injection) caused by ceftazidime non-susceptible beta-lactamase-producing (e.g., ESBL, KPC and AmpC) gram-negative bacteria.

AVYCAZ has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections [see *Indications and Usage (1.1) and (1.2)*].

Complicated Intra-abdominal Infections (cIAI)

- Gram-negative bacteria
 - *Escherichia coli*
 - *Enterobacter cloacae*
 - *Klebsiella pneumoniae*
 - *Klebsiella oxytoca*
 - *Proteus mirabilis*

- *Providencia stuartii*
- *Pseudomonas aeruginosa*

Complicated Urinary Tract Infections (cUTI), including Pyelonephritis

- Aerobic Gram-negative bacteria
 - *Citrobacter freundii*
 - *Citrobacter koseri*
 - *Escherichia coli*
 - *Pseudomonas aeruginosa*
 - *Enterobacter aerogenes*
 - *Enterobacter cloacae*
 - *Proteus* spp.
 - *Klebsiella pneumoniae*

The following *in vitro* data are available, but their clinical significance is unknown. AVYCAZ exhibits *in vitro* MIC values of ≤ 8 mcg/mL against most ($\geq 90\%$) isolates of the following bacteria; however, the safety and effectiveness of AVYCAZ in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

- Gram-negative bacteria
 - *Morganella morganii*
 - *Providencia rettgeri*
 - *Serratia marcescens*

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution Techniques

Quantitative methods are used to determine antimicrobial MIC values. These MIC values provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized test method (broth or agar)¹⁻³. MIC values should be determined using serial dilutions of ceftazidime combined with a fixed concentration of 4 mcg/mL of avibactam. Broth dilution MIC values need to be read within 18 hours because of degradation of ceftazidime activity by 24 hours. The MIC values should be interpreted according to the criteria in Table 6.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized method². This procedure uses paper disks impregnated with 30 mcg of ceftazidime and 20 mcg avibactam to test the susceptibility of bacteria to AVYCAZ. The disk interpretive criteria are provided in Table 6.

Pathogen	Minimum Inhibitory Concentration (mg/L)		Disk Diffusion Zone Diameter (mm)	
	S	R	S	R
Enterobacteriaceae	≤ 8/4	≥ 16/4	≥ 21	≤ 20
<i>Pseudomonas aeruginosa</i>	≤ 8/4	≥ 16/4	≥ 18	≤ 17

A report of “Susceptible” indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration at the site of infection. A report of “Resistant” indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the site of infection; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test¹⁻³. Standard AVYCAZ powder should provide the following range of MIC values provided in Table 7. For the diffusion technique using the 30 mcg ceftazidime/20-mcg avibactam disk, the criteria provided in Table 7 should be achieved.

Quality Control Organism	Minimum Inhibitory Concentration ^a (mg/L)	Disk Diffusion Zone Diameter (mm)
<i>Staphylococcus aureus</i> ATCC 29213	4 - 16	-
<i>Staphylococcus aureus</i> ATCC 25923	-	16 - 22
<i>Escherichia coli</i> ATCC 25922	0.06 - 0.5	27 - 35
<i>Escherichia coli</i> ATCC 35218	0.03 - 0.12	28 - 35
<i>Pseudomonas aeruginosa</i> ATCC 27853	0.5 - 4	25 - 31
<i>Klebsiella pneumoniae</i> ATCC 700603 ^b	0.25 - 2	-
<i>Haemophilus influenzae</i> ATCC 49247	0.06 - 0.5	28 - 34
<i>Haemophilus influenzae</i> ATCC 49766	0.015 - 0.06	-
<i>Streptococcus pneumoniae</i> ATCC 49619	0.25 - 2	-

a MIC for ceftazidime in the presence of a fixed concentration of 4 mg/L of avibactam.

b *K. pneumoniae* ATCC 700603 should be tested against ceftazidime-avibactam and ceftazidime alone to confirm the activity of avibactam in the combination and to ensure that the plasmid encoding the beta-lactamase has not been lost in this strain. The acceptable range for ceftazidime alone is greater than 16 mg/L.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ceftazidime and avibactam were each evaluated for mutagenic potential in several *in vitro* and *in vivo* assays. Ceftazidime was negative for mutagenicity in a mouse micronucleus test and an Ames test. Avibactam was negative for genotoxicity in the Ames assay, unscheduled DNA synthesis, chromosomal aberration assay, and a rat micronucleus study.

Avibactam had no adverse effects on fertility of male and female rats given up to 1 g/kg/day (approximately 20 fold higher than the recommended clinical dose on a body surface area basis). There was a dose-related increase in the percentage of pre- and post-implantation loss relative to controls, resulting in a lower mean litter size at doses 0.5 g/kg and greater with intravenous administration to female rats beginning 2 weeks prior to mating.

14 CLINICAL STUDIES

The determination of efficacy of AVYCAZ was supported in part by the previous findings of the efficacy and safety of ceftazidime for the treatment of cIAI and cUTI. The contribution of avibactam to AVYCAZ was primarily established *in vitro* and in animal models of infection [see *Clinical Pharmacology (12.4)*]. AVYCAZ was studied in two Phase 2 randomized, blinded, active-controlled, multicenter trials, one each in cIAI and cUTI, including pyelonephritis. These trials were not designed with any formal hypotheses for inferential testing against the active comparators.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Tenth Edition*. CLSI document M07-A10, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Twelfth Edition*. CLSI document M02-A12, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fifth Informational Supplement*, CLSI document M100-S25, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

16 HOW SUPPLIED/STORAGE AND HANDLING

AVYCAZ for injection is supplied in single use, clear glass vial.

2 grams ceftazidime (equivalent to 2.635 grams of ceftazidime pentahydrate/sodium carbonate) and 0.5 grams avibactam (equivalent to 0.551 grams of avibactam sodium) - individual vial (NDC# 0456-2700-01) and carton containing 10 vials (NDC# 0456-2700-10)

Store unconstituted AVYCAZ vials at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]. Protect from light.

17 PATIENT COUNSELING INFORMATION

Serious Allergic Reactions

Advise patients, their families, or caregivers that allergic reactions, including serious allergic reactions, could occur that require immediate treatment. Ask them about any previous hypersensitivity reactions to AVYCAZ, other beta-lactams (including cephalosporins), or other allergens [see *Warnings and Precautions* (5.2)].

Potentially Serious Diarrhea

Advise patients, their families, or caregivers that diarrhea is a common problem caused by antibacterial drugs. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, tell them to contact his or her healthcare provider [see *Warnings and Precautions* (5.3)].

Nervous System Reactions

Advise patients, their families, or caregivers that neurological adverse reactions can occur with AVYCAZ use. Instruct patients their families, or caregivers to inform a healthcare provider at once of any neurological signs and symptoms, including encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures, for immediate treatment, dosage adjustment, or discontinuation of AVYCAZ [see *Warnings and Precautions* (5.4)].

Antibacterial Resistance

Counsel patients, their families, or caregivers that antibacterial drugs including AVYCAZ should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When AVYCAZ is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by AVYCAZ or other antibacterial drugs in the future [see *Warnings and Precautions* (5.5)].

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