Ceftazidime-Avibactam (Avycaz)

For the Treatment of Complicated Intra-Abdominal and Urinary Tract Infections

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INTRODUCTION

Infectious diseases have become a growing problem in the health care field, and more than $120 billion is spent on their treatment every year.[1] Due to the rising issue of drug-resistant organisms, infections that are typically cleared with common oral antibiotics could result in an extended hospital stay or even death.[2] In response to this crisis, Congress and the Food and Drug Administration (FDA) passed and implemented the Generating Antibiotic Incentives Now Act of 2011 to encourage the development of qualified infectious disease products (QIDPs) to treat these serious or life-threatening conditions.[3] In 2014, Dalvance (dalbavancin, Allergan), Sivextro (tedizolid phosphate, Merck), Orbactiv (oritavancin, The Medicines Company), and Zerbaxa (ceftolozane-tazobactam, Merck) became the first antibiotics to be granted QIDP status by the FDA.[4] Avycaz (ceftazidime-avibactam, Forest Pharmaceuticals, Inc.) joined the ranks in 2015.[5]

Complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) are increasingly caused by multidrug-resistant bacteria, which decrease the efficacy of traditional therapies, such as second- or third-generation cephalosporins in combination with metronidazole.[6,7] There was a need for treatments more effective than the existing antibiotics and, through the QIDP program, Avycaz and Zerbaxa were developed to address that need. Both are indicated for the treatment of potentially deadly cUTI and cIAI.[8,9] This article will focus on the newer of the two agents, Avycaz.

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INDICATIONS

Avycaz is indicated for treatment of cIAI in combination with metronidazole and for the treatment of cUTI, including pyelonephritis, in patients 18 years of age and older with creatinine clearance (CrCl) greater than 50 mL/min.[8]

DOSAGE AND ADMINISTRATION

The recommended dosage and frequency of administration of Avycaz range from 0.94 g to 2.5 g and are based on the patient's estimated CrCl (Table 1). Each dose is infused intravenously over two hours. For treatment of cIAI, metronidazole should be given concurrently. The recommended duration of treatment is five to 14 days for patients with cIAI and seven to 14 days for those with cUTI, including pyelonephritis.[8]

Avycaz is supplied as a dry powder, which must be constituted and subsequently diluted, before intravenous (IV) infusion.[8]

Table 1 Recommended Avycaz Dosage Regimen[8]

Estimated CrCl (mL/min)[a]	Recommended Dosage Regimen[b]
> 50	2.5 g every eight hours
31–50	1.25 g every eight hours
16–30	0.94 g every 12 hours
6–15[c]	0.94 g every 24 hours
≤ 5[c]	0.94 g every 48 hours

CrCl = creatinine clearance.

[a] As calculated using the Cockcroft-Gault formula

[b] All doses of Avycaz are administered by intravenous infusion over two hours.

[c] Both ceftazidime and avibactam are hemodialyzable; thus, administer Avycaz after hemodialysis on hemodialysis days.

CLINICAL PHARMACOLOGY

The first component of Avycaz is ceftazidime, a third-generation cephalosporin with a great advantage over common antibiotics in that it has the broadest extended-spectrum beta-lactamase (ESBL) profile in its class. Whereas some third- and fourth-generation cephalosporins are extensively hydrolyzed by ESBL, ceftazidime is not, which makes it a better treatment option against multidrug-resistant bacteria.[8]

The second component, avibactam, is a new beta-lactamase inhibitor that adds a protective factor to ceftazidime. Avibactam inactivates the beta-lactamases that would eventually lead to the degradation of ceftazidime, which gives ceftazidime a broader ESBL profile.[8]

Avycaz sets itself apart by being the first cephalosporin–beta-lactam combination with activity against carbapenemases.[8]

Mechanism of Action

The ceftazidime component of Avycaz is a third-generation cephalosporin 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.[8] The avibactam component of Avycaz is a non–beta-lactam beta-lactamase inhibitor that inactivates some beta-lactamases and protects ceftazidime from degradation.[10] Avibactam gives ceftazidime a longer half-life and more time to work in the body. Avycaz is active against a variety of bacteria (Table 2), both *in vitro* and in clinical infections.[8]

Table 2 Aerobic, Gram-Negative Bacteria Effectively Targeted By Avycaz[8]

Complicated Intra-Abdominal Infections
• *Escherichia coli*
• *Enterobacter cloacae*
• *Klebsiella pneumoniae*
• *K. oxytoca*
• *Proteus mirabilis*
• *Pseudomonas aeruginosa*
• *Citrobacter freundii* complex
Complicated Urinary Tract Infections, including Pyelonephritis
• *C. freundii*
• *C. koseri*
• *E. coli*
• *P. aeruginosa*
• *Enterobacter aerogenes*
• *E. cloacae*
• *Proteus* spp.
• *K. pneumoniae*

Pharmacodynamics

The time that unbound plasma concentrations of ceftazidime exceed the Avycaz minimum inhibitory concentration (MIC) against the infecting organism best correlates with efficacy in a neutropenic murine thigh infection model with Enterobacteriaceae and *Pseudomonas aeruginosa*. The time above the threshold concentration best predicts the efficacy of avibactam in *in vitro* and *in vivo* nonclinical models.[8]

Cardiac Electrophysiology

In a thorough QT study, a supratherapeutic dose of ceftazidime (3 g) was investigated for QT effects in combination with a supratherapeutic dose of avibactam (2 g) 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.[8]

Pharmacokinetics

The 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.[8]

The peak concentration and area under the curve of ceftazidime increase in proportion to the dose. Avibactam demonstrated approximately linear pharmacokinetics across the dose range studied (50 mg to 2,000 mg) for single IV administration. No appreciable accumulation of ceftazidime or avibactam was observed following multiple Avycaz 2.5-g IV infusions administered every eight hours for up to 11 days in healthy adults with normal renal function.[8]

Distribution

Less than 10% of ceftazidime is protein bound. The degree of protein binding is independent of concentration. The binding of avibactam to human plasma proteins is low (5.7% to 8.2%) and similar across the range of concentrations tested *in vitro* (0.5–50 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 g infused every eight hours over two hours for 11 days.[8]

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 IV dose of 0.5 g ^{14}C-labelled avibactam.[8]

Excretion

Both ceftazidime and avibactam are excreted mainly by the kidneys. Approximately 80% to 90% of an IV dose of ceftazidime is excreted unchanged by the kidneys over a 24-hour period. After the IV administration of single 0.5-g or 1-g doses, approximately 50% of the dose appeared in the urine in the first two hours. An additional 20% was excreted between two and four hours after dosing, and approximately another 12% of the dose appeared in the urine between four and eight 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.[8]

Following administration of a single 0.5-g IV dose of radiolabeled avibactam, an average of 97% of administered radioactivity was recovered from the urine, with more than 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 more than 50% recovered within two 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.[8]

DRUG INTERACTIONS

Coadministration of Avycaz with probenecid is not recommended. *In vitro*, avibactam is a substrate of organic anion transporters (OAT) 1 and 3, 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 coadministered. A clinical interaction study of Avycaz or avibactam alone with probenecid has not been conducted.[8]

CLINICAL TRIALS

Avycaz was evaluated in four active-controlled clinical trials in patients with cIAI or cUTI, including pyelonephritis. These trials included two phase 2 trials, one in cIAI and one in cUTI, as well as two phase 3 trials, one in cIAI and one in cIAI or cUTI due to ceftazidime-resistant pathogens. The four clinical trials included a total of 862 adult patients treated with Avycaz and 866 patients treated with comparators.[8] Data from the two most recent trials (phase 3 for cIAI and phase 2 for cUTI) follow.

Complicated Intra-Abdominal Infections: Phase 3 Trial[8]

A total of 1,058 adults hospitalized with cIAI were randomized and received trial medications in a multinational, multicenter, double-blind trial comparing Avycaz 2.5 g administered intravenously over 120 minutes every eight hours plus metronidazole (0.5 g intravenously over

60 minutes every eight hours) to meropenem (1 g intravenously every eight hours) for five to 14 days of therapy. Five hundred twenty-nine patients were assigned to each group. The cIAI cases included appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, perforation of the intestine, and other causes of intra-abdominal abscesses and peritonitis.

The median age of patients treated with Avycaz was 50 years (range, 18–90 years), and 22.5% of patients were 65 years of age or older. Patients were predominantly male (62%) and Caucasian (76.6%).

The microbiologically modified intent-to-treat (mMITT) population, which included all patients who had at least one baseline intra-abdominal pathogen regardless of the susceptibility to study drug, consisted of 823 patients; the median age was 51 years and 62.8% were male. The majority of patients (64.9%) were from Eastern Europe; 7.5% were from the United States. Less than 1% of patients were of Pacific Island or African descent. The most common primary cIAI diagnosis was appendiceal perforation or periappendiceal abscess, occurring in 44.7% of patients. Bacteremia at baseline was present in 4.3% of patients.

Clinical cure was defined as complete resolution or significant improvement in signs and symptoms of the index infection at the test-of-cure (TOC) visit, which occurred 28 to 35 days after randomization. Table 3 presents the clinical cure rates in the mMITT population and in the microbiologically evaluable (ME) population, which included all protocol-adherent mMITT patients. Avycaz plus metronidazole was noninferior to meropenem with regard to the primary endpoint (clinical cure rate at the TOC visit in the mMITT population).

Of the 823 patients in the mMITT population, 14 (1.7%) had baseline *Escherichia coli* bacteremia; seven of 10 patients (70.0%) in the Avycaz arm and three of four patients (75.0%) in the meropenem arm had a clinical cure.

At baseline, 111 patients in the mMITT population had gram-negative isolates that were not susceptible to ceftazidime, including 61 patients with *E. coli* and 26 patients with *Klebsiella pneumoniae*. Cure rates were 39 of 47 patients (83.0%) who received Avycaz and 55 of 64 patients (85.9%) who received meropenem.

In a subset of gram-negative pathogens from both arms of the phase 3 cIAI trial that met phenotypic screening criteria for the presence of a beta-lactamase, genotypic testing identified certain ESBL groups (e.g., TEM-1, SHV-12, CTX-M-15, OXA-48) and AmpC that were expected to be inhibited by avibactam in 105 (12.8%) of the 823 patients in the mMITT population. Clinical cure rates in this subset were similar to the overall results.

Treatment discontinuation due to an adverse reaction occurred in 2.6% of patients (14 of 529) receiving Avycaz plus metronidazole and 1.3% of patients (seven of 529) receiving meropenem. There was no specific adverse reaction leading to discontinuation.

Adverse reactions occurring in 1% or more of patients receiving Avycaz plus metronidazole and with incidences greater than the comparator in the phase 3 cIAI clinical trial were headache, dizziness, diarrhea, nausea, vomiting, and abdominal pain. Adverse reactions occurring in 5% or more of patients were diarrhea, nausea, and vomiting.

Increased Mortality[8]

In the phase 3 cIAI trial, death occurred in 2.5% of patients (13 of 529) who received Avycaz plus metronidazole and in 1.5% of patients (eight of 529) who received meropenem. Among a subgroup of patients with a baseline CrCl of 30–50 mL/min, death occurred in 19.5% of patients (eight of 41) who received Avycaz plus metronidazole and in 7.0% of patients (three of 43) who received meropenem. Within this subgroup, patients treated with Avycaz received a 33% lower daily dose than is currently recommended for patients with CrCl of 30–50 mL/min. In patients with normal renal function or mild renal impairment (baseline CrCl greater than 50 mL/min), death occurred in 1.0% of patients (five of 485) who received Avycaz plus metronidazole and in 1.0% of patients (five of 484) 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.

Table 3 Clinical Cure Rates at TOC From the Phase 3 Complicated Intra-Abdominal Infection Trial[8]

Analysis Population	Avycaz Plus Metronidazole[a] n/N (%)	Meropenem[b] n/N (%)	Treatment Difference (95% CI)[c]
mMITT	337/413 (81.6)	349/410 (85.1)	–3.5 (–8.6 to 1.6)
ME	244/265 (92.1)	272/287 (94.8)	–2.7 (–7.1 to 1.5)

CI = confidence interval; IV = intravenously; ME = microbiologically evaluable; mMITT = microbiologically modified intent-to treat; TOC = test-of-cure.

[a] Avycaz 2.5 g IV every eight hours plus metronidazole 0.5 g IV every eight hours

[b] 1 g IV every eight hours

[c] The 95% CI was calculated as an unstratified Miettinen and Nurminen method.

Complicated Urinary Tract Infections, Including Pyelonephritis: Phase 2 Trial[8]

The phase 2 cUTI trial included 68 adult patients treated with Avycaz administered intravenously over 30 minutes every eight hours and 67 patients treated with imipenem-cilastatin (0.5 g intravenously every six hours). The dose of Avycaz in this trial was 0.625 g, which is lower than the recommended dose. The median age of patients treated with Avycaz was 47.5 years (range, 18–85 years). Patients were predominantly female (75%) and Caucasian (58.8%). Patients with CrCl less than 70 mL/min were excluded.

Adverse reactions occurring in 10% or more of patients receiving Avycaz were constipation and anxiety. Adverse reactions occurring in 5% or more of patients receiving Avycaz and with incidences greater than the comparator were constipation, abdominal pain, dizziness, and anxiety.

The determination of efficacy of Avycaz in cUTI is supported in part by the previous findings of the efficacy and safety of ceftazidime for the treatment of cUTI. In cUTI, the contribution of avibactam to Avycaz has been established *in vitro* and in animal models of infection. Avycaz was studied in the phase 2 randomized, blinded, active-controlled, multicenter trial above; however, the trial was not

designed with any formal hypotheses for inferential testing against the active comparators.

ADVERSE DRUG REACTIONS

The following selected adverse reactions were reported in Avycaz-treated subjects at a rate of less than 1% in the phase 3 cIAI trial or less than 5% in the phase 2 cUTI trial: eosinophilia; thrombocytopenia; injection site phlebitis; candidiasis; increased aspartate aminotransferase, increased alanine aminotransferase, increased gamma-glutamyltransferase, and prolonged prothrombin time; hypokalemia; dysgeusia; acute renal failure and renal impairment; rash, maculopapular rash, urticaria, and pruritus.[8]

SPECIAL POPULATIONS

Pregnancy and Lactation

Due to lack of human data on the teratogenicity of Avycaz, the drug should be used in pregnant women only if clearly needed. Similarly, there is little data regarding the effects of ceftazidime and avibactam on the breast-fed child or on milk production.[8]

Pediatric Use

The efficacy and safety of Avycaz in patients younger than 18 years of age have not been established.[8]

Geriatric Use

In the pooled phase 2 and phase 3 cIAI trials, the incidence of adverse reactions was higher in patients 65 years of age and older. In the phase 3 cIAI trial, clinical cure rates for patients 65 years of age or older were 73.0% (73 of 100) in the Avycaz plus metronidazole arm and 78.6% (77 of 98) in the meropenem arm. Because of limited clinical data in cUTI patients, differences in outcomes or specific risks cannot be ruled out for cUTI patients 65 years of age and older.[8]

Ceftazidime and avibactam are known to be substantially excreted by the kidney; therefore, the risk of adverse reactions to ceftazidime and avibactam may be greater in patients with decreased renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection 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.[8]

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, particularly early in treatment, and the dosage of Avycaz adjusted accordingly. Both ceftazidime and avibactam are hemodialyzable; thus, Avycaz should be administered after hemodialysis on hemodialysis days.[8]

CONTRAINDICATIONS

Avycaz is contraindicated in patients with known serious hypersensitivity to Avycaz, avibactam-containing products, ceftazidime, or other members of the cephalosporin class.[8]

WARNINGS AND PRECAUTIONS

Decreased Clinical Response in Patients with Baseline CrCL of 30–50 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. 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 of 30 to 50 mL/min. Monitor CrCL at least daily in patients with changing renal function and adjust the dosage of Avycaz accordingly.[8]

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.[8]

Clostridium difficile-Associated Diarrhea

C. 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. 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 two 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.[8]

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. Dosing should be adjusted according to creatinine clearance.[8]

COST

The average wholesale price for a 2.5-g vial of Avycaz is $359.[11] The total cost of Avycaz treatment is dependent on the infection type and severity and on the patient's estimated CrCl.[5] As an example, a patient with a cUTI and CrCl greater than 50 mL/min requires a 2.5-g Avycaz IV infusion every eight hours for seven to 14 days, resulting in a cost ranging from $7,539 to $15,078.[8,11] Patients with cIAI require concurrent treatment with 0.5 g of IV metronidazole, which contributes an additional $49 to $98 to the cost.[12]

P&T COMMITTEE CONSIDERATIONS

Avycaz is the first cephalosporin/beta-lactamase combination to be active against carbapenemases.[8] The drug has the same broad gram-negative activity as ceftazidime, which includes efficacy against Enterobacteriaceae and *P. aeruginosa*, and with the addition of avibactam, ceftazidime can maintain activity longer in the presence of certain resistance mechanisms of bacteria.[6] Because ceftazidime is a time-dependent drug, maintaining concentrations above the

MIC for a longer period of time is beneficial to the bactericidal effects.[8] Avibactam also inhibits a broader class of extended-spectrum beta-lactamases, which makes the combination of ceftazidime and avibactam active against Class A, some Class C, and some Class D beta-lactamases.[10]

Avycaz and QIDP-designated Zerbaxa—the "superheroes of gram-negative bacteria"—carry the same indications.[8,9,13] Cure rates for each of the drugs are similar, as are the preparation and administration; adverse effects; and warnings and precautions. While the drugs work against some of the same pathogens, they are also active against different micro-organisms when compared. Avycaz is active only against gram-negative bacteria, but is unique in its ability to target carbapenemases.[8] In addition to acting on gram-negative bacteria, Zerbaxa also attacks some anaerobes and some gram-positive bacteria.[9] The cost of Zerbaxa is considerably lower than Avycaz. Using the example from the "Cost" section, the patient described would require a seven-day regimen of Zerbaxa at a total cost of $2,310.[9,14]

Because studies have shown that the mortality rate of Avycaz is slightly higher than that of meropenem (2.5% and 1.5%, respectively), Avycaz should be used as a last-line treatment option for those patients who have either had negative or no response to first-line treatment options.[8]

CONCLUSION

Avycaz, a combination of ceftazidime and avibactam, is the fifth antibacterial drug to be designated as a QIDP. It is FDA approved for the treatment of complicated intra-abdominal infections and urinary tract infections, including pyelonephritis. The combination of the cephalosporin and non–beta-lactam beta-lactamase inhibitor increases the half-life of ceftazidime, which equates to a longer duration of action in the body. With its effectiveness against many drug-resistant, gram-negative bacteria and its unique action against carbapenemases, Avycaz is seemingly an appropriate choice for the last-line treatment of life-threatening infections.

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