Ceftazidime/Avibactam (Avycaz®)

National Drug Monograph

December 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1]

Description/Mechanism of Action	Ceftazidime/avibactam is a combination of a third generation cephalosporin and a novel beta-lactamase inhibitor. Ceftazidime binds to penicillin-binding proteins, thereby inhibiting bacterial cell wall synthesis. Avibactam protects ceftazidime from degradation by inhibiting a broader range of beta-lactamases than currently available beta-lactamase inhibitors. It exhibits in vitro activity against many multi-resistant gram negative organisms such as *Enterobacteriaceae* and many strains of *Pseudomonas aeruginosa*, including those expressing certain types of extended spectrum beta-lactamases, serine beta-lactamases and carbapenemases (e.g., KPC, AmpC and certain oxacillinases (OXA)). Ceftazidime/avibactam is not active against metallo-ß-lactamases or gram negative organisms that overexpress efflux pumps or have porin mutations. .
Indication(s) Under Review in this document (may include off label)	Complicated intraabdominal infections (cIAI), used in combination with metronidazole Complicated urinary tract infections (cUTI), including pyelonephritis According to the prescribing information, ceftazidime/avibactam should be reserved for use in patients who have limited or no alternative treatment options since it was approved based upon limited clinical safety and efficacy data.
Dosage Form(s) Under Review	Avycaz® 2.5 g (ceftazidime 2 g + avibactam 0.5 g) sterile powder for constitution
REMS	☐ REMS ☐ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy	Pregnancy Category B

Executive Summary

Efficacy[2, 4, 6]	• Ceftazidime/avibactam) was recently approved by the US Food and Drug Administration (FDA) under the designation of a Qualified Infectious Disease Product (QIDP). This approval was primarily based upon previous safety and efficacy data available for ceftazidime as well as two Phase 2 clinical trials evaluating ceftazidime/avibactam in patients with either complicated intraabdominal infections (cIAI) or complicated urinary tract infections (cUTI), including pyelonephritis. The Phase 2 trials were not designed or powered to test for non-inferiority or superiority. The FDA also reviewed preliminary data from available phase 3 clinical trials (i.e., ceftazidime resistant cIAI and cUTI clinical trial as well as a cIAI trial) during their review process. • The Phase 2 cIAI trial evaluated clinical cure rates in patients receiving ceftazidime/avibactam plus metronidazole compared to meropenem. Clinical cure was achieved in 82% and 89% of patients, respectively. • The Phase 2 cUTI trial evaluated clinical and microbiologic response in patients receiving ceftazidime/avibactam compared to imipenem/cilastatin. Clinical cure and microbiologic eradication rates were similar between groups.
Safety[4,5,6]	• Common adverse events in the two Phase 2 trials included vomiting, nausea,

	constipation, abdominal pain, dizziness, anxiety, increased alkaline phosphatase, and increased alanine aminotransferase. • The FDA reviewed preliminary results of the Phase 3 cIAI at the time of approval which revealed increased mortality and lower clinical outcomes in patients with CrCl 30-50 ml/min. Based on these results, the FDA recommended the original dosing regimen used in the Phase 3 trial be revised and highlighted the importance of frequent monitoring of CrCl. The approved package insert reflects an updated dosing regimen and recommends CrCl be monitored at least daily with doses adjusted accordingly, especially in patients with changing renal function.
Projected Place in Therapy[1,2]	• Ceftazidime/avibactam is approved for the treatment of complicated intraabdominal infections (in combination with metronidazole) and complicated urinary tract infections, including pyelonephritis in patients who have limited or no alternative options. • Ceftazidime/avibactam exhibits in vitro activity against many multi-resistant gram negative organisms such as *Enterobacteriaceae* and *Pseudomonas aeruginosa*, including those expressing certain types of extended spectrum beta-lactamases, serine beta-lactamases and carbapenemases (e.g., KPC, AmpC and certain oxacillinases (OXA)). Of note, avibactam protects ceftazidime from degradation by inhibiting a broader range of beta-lactamases than currently available beta-lactamase inhibitors. • Ceftazidime/avibactam has a role in the treatment of infections caused by multidrug-resistant gram negative organisms in patients with limited therapeutic options. Susceptibility testing is highly recommended in these cases.

Background[1,3]

Purpose for review

Recent FDA approval: February 2015

Issues to be determined:

- ✔ Evidence of need
- ✔ Does ceftazidime/avibactam offer advantages over current VANF agents?
- ✔ What safety issues need to be considered?

Other therapeutic options

Formulary Alternatives	Other Considerations
Complicated Intraabdominal Infections:	
Monotherapy: cefoxitin, ertapenem, moxifloxacin *Combination:* cefazolin, cefuroxime, cefotaxime, ceftriaxone, ciprofloxacin, levofloxacin AND metronidazole	Based on 2010 IDSA Intraabdominal Infection guidelines for **community-acquired infections** with **mild to moderate severity** of disease
Monotherapy: piperacillin/tazobactam, imipenem/cilastatin, meropenem *Combination*: ceftazidime, cefepime, ciprofloxacin, levofloxacin AND metronidazole	Based on 2010 IDSA Intraabdominal Infection guidelines for **community-acquired infections** with **high risk/severity** of disease
Meropenem, imipenem/cilstatin, piperacillin/tazobactam, ceftazidime or cefepime with metronidazole, aminoglycosides, vancomycin	Based on 2010 IDSA Intraabdominal Infection guidelines for **health care-associated infections.** Of note, choice of empiric treatment can be guided by common organisms encountered at local institutions.
Complicated Urinary Tract Infections:	
Ceftriaxone, ceftazidime, cefepime, piperacillin/tazobactam, ertapenem, imipenem/cilastatin, meropenem, ciprofloxacin, levofloxacin	Agents for cUTI broadly represent agents for the treatment of cIAI, as above (with the exception of moxifloxacin). Alternatives for cUTI caused by multidrug resistant (MDR) organisms may include aminoglycosides or polymyxins.

Other alternatives: polymyxin B	Due to side effect profile, often considered as last line alternative for multi-drug resistant organisms
Non-formulary Alternative	**Other Considerations**
Ceftolozane/tazobactam (Zerbaxa®)	• Approved by the FDA in March 2015 for the treatment of Complicated Intraabdominal Infections (in combination with metronidazole) and Complicated Urinary Tract Infections • Combination of an antipseudomonal cephalosporin and a beta-lactamase inhibitor with variable activity against many penicillinases and cephalosporinases • Demonstrates activity against many gram-negative organisms, including certain types of extended-spectrum beta-lactamase producing *Enterobacteriaceae* and multidrug-resistant *P. aeruginosa*
Colistin	Due to side effect profile, often considered as last line alternative for multi-drug resistant organisms

Efficacy (FDA Approved Indications)

Literature Search Summary
A literature search was performed on PubMed/Medline (1966 to October 2015) using the search terms "ceftazidime avibactam" and "Avycaz". The search was limited to studies performed in human and published in the English language. Reference lists of review articles were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included. This search strategy revealed two Phase 2 trials, one for cIAI and one for cUTI. Three phase 3 trials have also been completed. The phase 3 trial in cIAI and the phase 3 trial in resistant pathogens are available in abstract format while the phase 3 trial in cUTI is only available via a press release (not summarized) below.

Review of Efficacy
The FDA approval of ceftazidime/avibactam for the treatment of complicated intraabdominal infections (cIAI) and complicated urinary tract infects (cUTI) was primarily based on two Phase 2 trials, one for each indication, and previous clinical data assessing the safety and efficacy of ceftazidime alone. Approval was granted despite lack of Phase 3 data due to the need for antimicrobial agents for patients with few to none therapeutic options. However, given the limited data available at the time of approval, the prescribing information states that ceftazidime/avibactam should be used in patients with limited or no alternative treatment options. Results of Phase 3 trials evaluating ceftazidime/avibactam for cIAI and resistant pathogens are summarized below (only available as abstracts).

Complicated intraabdominal infection:

Phase 2 Trial[4]: Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intraabdominal infections in hospitalized adults: results of a randomized, double-blind, phase II trial.

The Phase 2 trial for cIAI utilized a prospective, randomized, double-blind, active control design. Patients were enrolled in the study based on inclusion and exclusion criteria defined in Table 1. Randomization occurred in a 1:1 ratio, stratified by investigation site/country and baseline severity of disease (APACHE II score < 10 and 10-25), to either ceftazidime/avibactam 2000 mg/500mg IV every 8 hours plus metronidazole 500 mg IV every 8 hours or meropenem 1000 mg IV every 8 hours plus matching saline placebo IV every 8 hours for 5 to 14 days. Per the FDA review, the primary efficacy endpoint was clinical response in the microbiological modified intention treatment (mMITT) population at the test-of-cure (TOC) visit. This population was defined as all subjects who received at least 1 dose of study drug and had at least one pathogen identified at study entry. Of note, the investigators also evaluated the primary efficacy endpoint in the microbiologically evaluable (ME) population (data not summarized below). Clinical response was classified as clinical cure, failure or indeterminate. Cure was defined as complete or significant resolution of signs and symptoms of infection and no requirement of additional antibiotics or surgical interventions per investigator assessments. Failure was defined as death related to cIAI, persistent/recurrent infection, post-surgical wound infections, treatment with additional antibiotics for on-going symptoms. Indeterminate was defined as study data not available for evaluation of efficacy (ex: death occurred where

index infection was noncontributory or extenuating circumstances). Assessment of TOC was performed 2 weeks after the last dose of study antibiotic. A key secondary endpoint was microbiological response defined as the eradication of the baseline pathogen.

Table 1: Key Inclusion and Exclusion Criteria for Phase 2 cIAI Trial

Inclusions
Age 18 – 90
Complicated intraabdominal infection (requiring surgical intervention and antibiotics) defined as one of the following: • Cholecystitis (with rupture or perforation) or progression beyond the gall bladder • Diverticular disease with perforation or abscess • Appendiceal perforation or periappendiceal abscess • Acute gastric or duodenal perforation (if operated on >24 hours after perforation) • Traumatic perforation of the intestine (if operated on >12 hours after perforation) • Secondary peritonitis or intraabdominal abscess with evidence of intraperitoneal involvement
Pre-study cultures positive for microorganisms susceptible to study interventions
Confirmation of cIAI • Intra/post operatively via visual inspection and specimen culture • Pre-operatively via clinical examination and confirmed during surgical intervention within 24 hours
Exclusions
Any of the following intraabdominal infections or processes • Abdominal wall abscess • Small bowel obstruction or ischemic bowel without perforation • Perinephric infections or infection of the female genital tract
Receipt of systemic antibiotic within 72 hours of study therapy or need for systemic antibiotics concurrently with study antibiotics
Concurrent infection or infections caused by pathogens known to be resistant to study antibiotics
Sepsis with shock unresponsive to intravenous fluid
APACHE II score > 25
Anticipated survival less than the study period
Severe renal impairment (CrCl < 50 ml/min) or hepatic disease
Immunocompromised or severe anemia, neutropenia, or thrombocytopenia

Table 2: Baseline Characteristics of the Safety Population for Phase 2 cIAI Trial

Characteristic	**Ceftazidime/avibactam + Metronidazole (n=101)**	**Meropenem (n=102)**
Age		
<65	92 (91.1%)	87 (85.3%)
65-75	7 (6.9%)	12 (11.8%)
75-90	2 (2.0%)	3 (2.9%)
Gender		
Female	31 (30.7%)	21 (20.6%)
Male	70 (69.3%)	81 (79.4%)
APACHE II		
≤ 10	84 (83.2%)	85 (83.3%)
>10 but ≤ 25	17 (16.8%)	17 (16.7%)
Site of Infection		
Appendix	49 (48.5%)	47 (46.1%)
Stomach/duodenum	29 (28.7%)	23 (22.5%)
Colon	12 (11.9%)	6 (5.9%)
Small bowel	4 (4.0%)	12 (12.7%)
Gall Bladder	5 (5.0%)	9 (8.8%)
Parenchymal (liver)	2 (2.0%)	3 (2.9%)

Other	0	2 (2.0%)
Infection process		
Peritonitis	84 (83.2%)	89 (87.3%)
Visceral perforation	44 (43.6%)	40 (39.2%)
Abscess	26 (25.7%)	28 (27.5%)
Surgical procedure		
Laparotomy	91 (90.1%)	91 (89.2%)
Laparoscope	9 (8.9%)	9 (8.8%)
Percutaneous drainage	1 (1.0%)	2 (2.0%)
Prior antibiotic therapy	53 (52.5%)	54 (52/9%)

Safety population: all subjects who received at least one dose of study drug

Table 3: Efficacy Endpoint in Phase 2 cIAI Trial

Primary efficacy endpoint in mMITT population at TOC visit	**Ceftazidime/avibactam plus metronidazole** (n=85)	**Meropenem** (n=89)	**Difference (95% CI)**
Cure	70 (82.4%)	79 (88.8%)	-6.4 (-18.0, 5.2)
Failure	7 (8.2%)	5 (5.6%)	NA
Indeterminate	8 (9.4%)	5 (5.6%)	NA

Overall Quality of Evidence: Moderate (Refer to Appendix A; pivotal clinical trial sponsored by Actavis)

Table 4: Clinical Response in Subjects with Ceftazidime-Non-susceptible Pathogens

Clinical response	**Ceftazidime/avibactam plus metronidazole** (n=30)	**Meropenem** (n=23)	**Difference (95% CI)**
Cure	27 (90.0%)	19 (82.6%)	7.4 (-15.3, 30.0)
Failure/indeterminate	3 (10.0%)	4 (17.4%)	NA

Phase 3 Trial[5]: Efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem for the treatment of complicated intraabdominal infection - results from a phase 3 program

Two phase 3 trials have been conducted, RECLAIM 1 and RECLAIM 2; however, results have only been published in abstract form to date. Data from both trials were combined and analyzed as a single dataset. The Phase 3 trials utilized a prospective, randomized, multicenter, double-blind design. Randomization occurred in a 1:1 ratio to either ceftazidime/avibactam 2000mg/500mg every 8 hours and metronidazole 500mg every 8 hours or meropenem 1000mg every 8 hours. Ceftazidime/avibactam infusion was prolonged to 2 hours in the Phase 3 trial compared to 30 mins in the Phase 2 trial. The primary efficacy endpoint was clinical response, as defined in the Phase 2 study, at the TOC visit. TOC was assessed 28-35 days after randomization (a longer time period compared to the Phase 2 trial) in the mMITT population (patients meeting disease criteria with at least 1 pathogen identified). Baseline characteristics between study groups were similar. A total of 1066 patients were randomized (532 to ceftazidime/avibactam and 534 to meropenem) over a 2 year time period. Clinical cure was achieved in 81.6% of patients receiving ceftazidime/avibactam and 85.1% of patients receiving meropenem with a 95% CI of -2.4 (-6.90, 2.10). Non-inferiority of ceftazidime/avibactam compared to meropenem was demonstrated.

Of note, the Phase 3 trial revealed increased mortality in patients with moderate renal impairment (CrCl 30-50 ml/min) in those patients who received ceftazidime/avibactam compared to meropenem, 25.8% and 8.6% respectively. These differences may be due to insufficient dosing. In patients, with normal or mild renal impairment, these differences in mortality were not seen. Of note, the Phase 2 trials excluded patients with CrCl less than 50 ml/min. Dose adjustments have since been revised and are reflected in the current package insert. Additionally, to ensure proper dosing in renal impairment, approved labeling recommends CrCl be monitored daily and doses adjusted as needed.

Complicated urinary tract infection

Phase 2 Trial[6]: Efficacy and safety of ceftazidime/avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator blinded, randomized study.

The Phase 2 trial for cUTI utilized a prospective, randomized, double-blind, active control design. Patients were enrolled in the study based on inclusion and exclusion criteria defined in Table 5. Randomization occurred in a 1:1 ratio, stratified by infection type, to either ceftazidime/avibactam 500 mg/125mg IV every 8 hours or imipenem/cilastatin 500 mg IV every 6 hours for 7 to 14 days. Switch to oral antibiotics (ciprofloxacin 500mg PO Q12h) was permitted after at least 4 days of study therapy based on pre-specified criteria. Per the FDA review, the primary efficacy endpoint was favorable microbiological response in the microbiological modified intention treatment (mMITT) population at the test-of-cure visit (5-9 days after last dose of study antibiotic). This population was defined as all subjects who received at least 1 dose of study drug and had positive pre-treatment urine cultures (>10^5 CFU/mL). Of note, the investigators also evaluated the primary efficacy endpoint in the microbiologically evaluable population (results not summarized below). A favorable microbiological response was defined as eradication of the pathogen from the urine (<10^4 CFU/mL) and absence of the pathogen in the blood.

Table 5: Key Inclusion and Exclusion Criteria for Phase 2 cUTI Trial

Inclusions
Age 18 - 90
Acute pyelonephritis (AP) or complicated urinary tract infection due to gram negative pathogens • AP – fever, flank pain pyuria, and positive urine culture • Sign and symptoms of UTI and positive urine culture
Required 7-14 days of parenteral therapy, per discretion of investigator
If female, evidence of one or more urological abnormalities or function/anatomical abnormalities of the urinary tract
Exclusions
Receipt of systemic antibiotic within the 48 hours prior to admission urine culture (or 1 or more doses after urine culture)
Infections caused by pathogens known to be resistant to study antibiotics
Presence of ileal loops, vesicoureteral reflux, complete obstruction or the urinary tract, perinephric or intrearenal abscess, fungal UTI
Permanent indwelling catheter or instrumentation (unless removed within 48 hours of study entry)
Pregnant or breastfeeding women
Anticipated survival less than the study period
History of hypersensitivity to the study medication
Estimated creatinine clearance less than 70 ml/min, hemodialysis, peritoneal dialysis, or renal transplant

Table 6: **Baseline Characteristics of the Safety Population for Phase 2 cUTI Trial**

Characteristic	**Ceftazidime/avibactam (n=68)**	**Imipenem/cilastatin (n=67)**
Age		
<65	57 (83.8%)	55(82.1%)
65-75	5 (7.4%)	2 (3.0%)
75-90	6 (8.8%)	10 (14.9%)
Gender		
Female	51 (75.0%)	49 (73.1%)
Male	17 (25.0%)	18 (26.9%)
Type of infections		
Acute pyelonephritis	44 (64.7%)	41 (61.2%)
Other cUTI	24 (35.3%)	26 (38/8%)

Table 7: Efficacy Endpoints in Phase 2 cUTI Trial at TOC Visit

Microbiological response rates in mMITT	**Ceftazidime/avibactam** (n = 46)	**Imipenem/cilastatin** (n = 49)	**Difference (95% CI)**

population (primary endpoint)			
Eradication[1]	31 (67.4%)	31 (63.3%)	4.1 (-16.1, 23.8)
Persistence[2]	10 (21.7%)	14 (28.6%)	NA
Indeterminate[3]	5 (10.9%)	4 (8.2%)	NA
Clinical response in mMITT population	**Ceftazidime/avibactam** (n=46)	**Imipenem/cilastatin** (n=49)	**Difference (95% CI)**
Cure[4]	37 (80.4%)	36 (73.5%)	7.0 (-10.4, 23.9)
Failure[5]	5 (10.9%)	9 (18.4%)	NA
Indeterminate[3]	4 (8.7%)	4 (8.2%)	NA

Overall Quality of Evidence: Moderate (Refer to Appendix A; pivotal clinical trial sponsored by Actavis)

[1]Eradication – eradication of uropathogen
[2]Persistance – persistence of uropathogen
[3]Indeterminate – loss to follow-up; unable to determine clinical/microbiologic response
[4]Cure – resolution of all or most signs and symptoms; no additional study drug required
[5]Failure – persistence of signs and symptoms, need for additional study drug

Table 8: Clinical Response in Subjects with Ceftazidime Non-susceptible Pathogens

Clinical response	**Ceftazidime/avibactam** (n=14)	**Imipenem/cilastatin** (n =18)	**Difference (95% CI)**
Clinical Cure	11 (78.6%)	10 (55.6%)	23.0 (-27.4, 41.3)
Clinical Failure	2 (14.3%)	5 (27.8%)	NA
Indeterminate	1 (7.1%)	3 (16.7%)	NA

Ceftazidime-Resistant Infections[7]

Efficacy and safety of ceftazidime-avibactam and best available therapy in the treatment of ceftazidime-resistant infections – results from a phase 3 study

A phase 3 trial, the REPRISE trial, was conducted to examine the safety and efficacy of ceftazidime/avibactam in patients with serious ceftazidime-resistance gram negative infections. The phase 3 trial utilized a prospective, international, randomized, open-label design. Patients with a cIAI or cUTI caused by ceftazidime-resistant pathogens were randomized in a 1:1 ratio to receive either ceftazidime/avibactam 2000mg/500mg every 8 hours (plus metronidazole for cIAIs) or best available therapy determined by the study investigator. The primary efficacy endpoint was clinical cure at the TOC visit, 7 to 10 days after the end of treatment. Results indicated that clinical cure rates were similar between both treatment groups. Detailed results are only available in abstract form, and have not been published.

Table 8: Clinical response rates at TOC for ceftazidime resistant infections

	Ceftazidime/avibactam		**Best Available Therapy**	
	N(%)	*95% CI*	*N(%)*	*95% CI*
Overall clinical cure	140/154 (90.9)	85.6,94.7	135/148 (91.2)	85.9, 95.0
Clinical cure for cUTI	132/144 (91.7)	86.3, 95.4	129/137 (94.2)	89.3, 97.2
Clinical cure for cIAI	8/10 (80)	47.9, 95.6	6/11 (54.5)	27.0, 80.0

Summary*:*

In the Phase 2 trial evaluating ceftazidime/avibactam for cIAI, 85 patients receiving ceftazidime/avibactam plus metronidazole and 89 patients receiving meropenem were analyzed for the primary efficacy endpoint. The majority of patients in both groups were males, <65 years of age, and had an APACHE II score of ≤ 10. Clinical cure rates in both groups were similar. Of note, this trial was not designed or powered to demonstrate non-inferiority. Non-inferiority was demonstrated in a Phase 3 trial, through results are only available in poster form. The Phase 3 trial also revealed increased mortality in patients with renal impairment (CrCl 30-50 ml/min), prompting recommendations for close monitoring of renal function and an increase in the dose in the approved package label.

In the Phase 2 trial evaluating ceftazidime/avibactam for cUTI, 46 patients receiving ceftazidime/avibactam and 49 patients receiving imipenem/cilastatin were analyzed for the primary efficacy endpoint. The majority of patients in both groups were females, <65 years of age. Clinical cure and microbiological eradication rates in both groups were similar. Of note, this trial

was not was not designed or powered to demonstrate non-inferiority. A Phase 3 trial was completed comparing ceftazidime/avibactam to doripenem; however, results are not yet available, except through press releases.

Potential Off-Label Use[8]

- Infections caused by multi-drug resistant gram-negative organisms at other sites (other than cUTI and cIAI)
    - Per clinicaltrials.gov, the pharmaceutical company has a registered Phase 3 clinical trial for ventilator-associated pneumonia and nosocomial pneumonia
- Infections caused by gram-negative bacteria for which there are other effective and tolerable treatment options.

Safety[1,2]

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• None
Contraindications	• Known serious hypersensitivity to the components of ceftazidime/avibactam, avibactam-containing products, or other members of the cephalosporin class.
Warnings/Precautions	• Decreased efficacy in patients with baseline CrCl between 30-50 ml/min. Monitor CrCl at least daily and adjust dose accordingly. • Hypersensitivity reactions. Cross reactivity may occur in patients with a history of penicillin allergy. • *Clostridium difficile*-associated diarrhea. • Seizures or neurologic events may occur in patients with renal impairment. Appropriate dose adjustment is required. • Development of drug-resistant bacteria.

Safety Considerations

The safety assessment is based upon data from two Phase 2 trials, one for cIAI and one for cUTI. Combined, these trials evaluated 169 patients treated with ceftazidime/avibactam and 169 patients treated with a comparator agent (meropenem or imipenem/cilastatin). FDA approval relied in part on the Agency's finding of safety and effectiveness for the ceftazidime component of ceftazidime/avibactam.

Adverse Reactions

Common adverse reactions	Incidence ≥5%: vomiting, nausea, constipation, abdominal pain, dizziness, anxiety, increased alkaline phosphatase, increased alanine aminotransferase
Death/Serious adverse reactions	Data from cIAI Phase 3 trial: *Mortality*: Death occurred in 2.5% (13/529) of patients who received ceftazidime/avibactam and metronidazole compared to 1.5% (8/529) of patients who received meropenem. In patients with moderate renal impairment (CrCl 30-50ml/min), death occurred in 25.8% (8/31) of patients receiving ceftazidime/avibactam and metronidazole compared to 8.6% (3/35) of patients receiving meropenem. It was noted that patients in this subpopulation received a lower than recommended dose. Cause of death varied and contributing factors included progression of underlying infection, delayed surgical intervention, and pathogens unlikely to respond to study therapy. Data from cIAI Phase 2 trial: *Serious adverse events*: Serious adverse events occurred in 8.9% of patients receiving ceftazidime/avibactam and metronidazole compared to 10.8% patients receiving meropenem Data from cUTI Phase 2 trial: *Serious adverse events*: Serious adverse events occurred in 8.8% of patients receiving ceftazidime/avibactam compared to 3.0% of patients receiving imipenem/cilastatin
Discontinuations due to adverse reactions	cIAI Phase 2 Trial: 5.9% vs. 3.9% in the comparator group. The most common adverse reaction leading to discontinuation of ceftazidime/avibactam was skin

	and subcutaneous tissue disorders. cUTI Phase 2 Trial: 2.9% vs. 0% in comparator group. Reasons for discontinuation of ceftazidime/avibactam included accidental overdose and atrial fibrillation

Drug Interactions

Drug-Drug Interactions

- No significant drug-drug interactions have been observed or are anticipated between ceftazidime/avibactam and the substrates, inhibitors, or inducers of cytochrome P450 enzymes.
- Avibactam is a known substrate of OAT1 and OAT3 transporters. Co-administration with the OAT inhibitor probenecid has been shown decrease the elimination of avibactam by 56-70% in vitro. The clinical implication of this drug interaction is unknown at this time; however, co-administration with probenecid is not recommended.

Drug-Lab Interactions

- Ceftazidime may cause a false positive reaction for glucose in the urine.

Risk Evaluation

As of 11/09/2015

Comments

Sentinel event advisories

- None

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First Databank	ISMP	Clinical Judgement
Ceftazidime/avibactam	None	TBD	None	Ceftazidime Ceftolozane/tazobactam Cefazolin Ceftaroline
Avycaz	None	TBD	None	Avandia Avinza

Other Considerations

Postmarketing requirements for adults[2]:

- Conduct a five-year, prospective study after the introduction of ceftazidime/avibactam to determine if decreased susceptibility is occurring in the target population of bacteria that are in the approved labeling.
- Conduct or submit data from the Phase 3 trial in cIAI to evaluate the pharmacokinetics, safety, and clinical outcomes of ceftazidime/avibactam (dose adjusted for renal function) in patients with baseline CrCl < 50ml/min.

Microbiology[9]:

Ceftazidime/avibactam is a combination of a third generation cephalosporin, ceftazidime, and a novel beta-lactamase inhibitor, avibactam. Avibactam differs from other beta-lactamases such as clavulanic acid and tazobactam due to its ability to inhibit Ambler Class A, C and some D beta-lactamases. These include beta-lactamases such as ESBLs (e.g., CTX-M), KPCs, and AmpCs. However, avibactam lacks inhibitory activity against metallo-beta-lactamases (Ambler Class B). Ceftazidime/avibactam has activity against *Enterobacteriaceae* and *P. aeruginosa*, including those isolates expressing the types of beta-lactamases listed above. Therefore, ceftazidime/avibactam possesses in vitro activity against certain carbapenem-resistant gram negatives such as *Klebsiella pneumonia* producing KPCs. Ceftazidime/avibactam does not exhibit activity against most clinically-relevant anaerobic bacteria.

ISMP Safety Alert[10]:

In September 2015, the FDA issued a safety alert regarding confusion about the dosing strength displayed on the labeling of the ceftazidime/avibactam vial. Ceftazidime/avibactam is dosed based on the sum of its active ingredients. However, original labeling for the product displayed the individual strengths of the active ingredients rather than the sum, resulting in a

potential for dosing errors. Labeling has since been revised to indicate that ceftazidime/avibactam 2.5 grams includes ceftazidime 2 grams and avibactam 0.5 grams.

Dosing and Administration[1]

Ceftazidime/avibactam is 2.5 gram (ceftazidime 2 grams and avibactam 0.5 grams) administered every 8 hours by intravenous infusion over 2 hours in adults with normal renal function (CrCl greater than 50 mL/min). For the treatment of cIAI, metronidazole should be given concurrently. The indicated duration of therapy is 5 to 14 days for cIAI and 7 to 14 days for cUTI.

Dose adjustments in patients with renal impairment

Estimated Creatinine Clearance (mL/min)	Recommended Dose
31 to 50	1.25grams (ceftazidime 1 gram and avibactam 0.25 grams) every 8 hours
16 to 30	0.94grams (ceftazidime 0.75 grams and avibactam 0.19 grams) every 12 hours
6 to 15	0.94grams (ceftazidime 0.75 gram and avibactam 0.19 grams) every 24 hours
Less than or equal to 5	0.94grams (ceftazidime 0.75 gram and avibactam 0.19 grams) every 48 hours

Special Populations (Adults)[1]

	Comments
Elderly	• No dose adjustment based on age is recommended • Elderly patients are more likely to have baseline renal impairment, increasing the risk of adverse reactions. Monitoring renal function may be useful in the elderly population and dose adjustments should be based on renal function. See "**Renal Impairment**"
Pregnancy	• Pregnancy category B. Adequate studies in pregnant humans have not been conducted. Ceftazidime/avibactam should only be used in pregnancy if clearly needed.
Lactation	• Ceftazidime is excreted in human breast milk in low concentrations. While avibactam was shown to be excreted in the milk of rats, excretion in human breast milk is unknown. Exercise caution when administering to a nursing woman.
Females and Males of Reproductive Potential	• No data identified
Renal Impairment	• Clearance is significantly decreased and serum half-life is significantly prolonged in patients with impaired renal function. • Avibactam AUC increase 2.6-fold, 3.8-fold, and 7-fold in patients with mild, moderate, and severe renal impairment respectively. • Dose adjustment is required for patients with moderately or severely impaired renal function (CrCl 50 mL/min or less). • CrCl should be monitored at least daily in patients with changing renal function with dose adjustments made accordingly. • Ceftazidime/avibactam should be administered after hemodialysis on dialysis days
Hepatic Impairment	• No dose adjustments based on hepatic function are recommended • Ceftazidime pharmacokinetics is not affected by hepatic dysfunction • Avibactam does not undergo hepatic metabolism, thus changes in clearance due to hepatic impairment is not expected
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy[1,2]

Ceftazidime/avibactam is approved for use in the treatment of complicated intraabdominal infections (in combination with metronidazole) and complicated urinary tract infections, including pyelonephritis. Approval was primarily based on results of Phase 2 trials. Because of limited clinical and safety data available at the time of FDA review, ceftazidime/avibactam is approved only for patients who have limited or no alternative treatment options. Ceftazidime/avibactam has a role in the treatment of infections caused by certain multidrug-resistant gram negative organisms with limited treatment options (e.g. carbapenem-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa,* without metallo-beta-lactamases). Susceptibility testing is highly recommended in these cases.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.