Ceftazidime/avibactam (Avycaz™, Actavis) **September 2015**
Inpatient – Non-Formulary

Criteria for Formulary Consideration of Ceftazidime/avibactam (Avycaz™)

Efficacy
Ceftazidime/avibactam was approved by the Food and Drug Administration (FDA) on February 25, 2015 for the treatment of complicated intra-abdominal infection (cIAI), in combination with metronidazole, and for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis. Determination of the efficacy of ceftazidime/avibactam was partly supported by previous findings of the efficacy and safety of ceftazidime for the treatment of cIAI and cUTI. The contribution of avibactam was primarily established in *in vitro* and animal models of infection.

Ceftazidime/avibactam was studied in two phase II clinical trials, one each in cIAI and cUTI. In the phase II cIAI trial, ceftazidime/avibactam plus metronidazole was effective and well-tolerated in patients, with a favorable clinical response rate of > 90%, similar to that of meropenem. In the phase II cUTI trial, efficacy and safety of ceftazidime/avibactam was similar to that of imipenem-cilastatin. Ceftazidime/avibactam should be reserved for patients with limited or no alternative treatment options due to limited clinical safety and efficacy data. Additional phase III trials are underway or awaiting publication of results. These include additional cIAI and cUTI trials (including a phase III trial due to ceftazidime-resistant gram-negative bacteria), and a nosocomial pneumonia and ventilator-associated pneumonia trial.

Avibactam has increased potency and an expanded spectrum of inhibition of class A and class C beta-lactamases, relative to available beta-lactamase inhibitors, including extended-spectrum beta-lactamases (ESBLs), AmpC, and *Klebsiella pneumoniae* carbapenemase (KPC) enzymes. Avibactam expands ceftazidime's spectrum of activity to include many ceftazidime- and carbapenem-resistant Enterobacteriaceae.

Safety
Based on phase II data, ceftazdime/avibactam is well tolerated and has a similar safety profile to that of ceftazidime alone. Occurrence of treatment-emergent adverse effects and serious adverse effects was similar among ceftazidime/avibactam and comparators. Serious adverse effects attributed to ceftazidime/avibactam included diarrhea, elevated liver enzymes, and accidental overdose occurring in one patient each. No dose-related adverse effects have been noted.

Uniqueness
Increasing morbidity and mortality associated with antimicrobial-resistant gram-negative bacteria calls for the development of unique antimicrobials that are effective against resistant pathogens. Ceftazidime/avibactam is a newly approved agent combining ceftazidime with a novel beta-lactamase inhibitor, avibactam, which has activity against multidrug-resistant gram-negative bacteria. The current body of evidence suggests that it is a promising addition to the armamentarium with the potential to answer an urgent unmet medical need.

Cost

Product	Cost per Vial	Dosage	Cost per Day
Avycaz™ 2.5g vial NDC 0456-2700-10	$270.93	2.5 g every 8 hours	$812.79

Recommendation
Do not add to inpatient formulary.

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Introduction[1-5]

There are limited treatment options for infections due to multidrug-resistant gram-negative pathogens such as ESBL-producing *Enterobacteriaceae* and *P. aeruginosa*, including cUTIs and cIAIs.

Appropriate management of cIAIs involves source control by way of operative or percutaneous interventions. Antibiotic treatment mainly consists of carbapenems, piperacillin/tazobactam, third or fourth generation cephalosporins plus metronidazole, or aminoglycosides. Patients who receive inadequate empiric antibiotic treatment are at a higher risk of treatment failure, sepsis, increased costs, and death. Inappropriate antibiotic treatment is becoming a pressing issue with increasingly more drug-resistant isolates.

Complicated urinary-tract infections may affect the lower urinary tract or upper urinary tract (pyelonephritis). Urosepsis is associated with mortality of up to 40% among critically ill patients. Fluoroquinolones are among the most commonly used antibiotics for cUTIs. Other agents include cephalosporins, aminoglycosides, and penicillins. Patients with infections caused by resistant organisms are more likely to be treated inappropriately, have longer hospitalizations, and suffer higher costs than patients infected with more susceptible bacteria.

Ceftazidime/avibactam, a cephalosporin combination with a novel beta-lactamase inhibitor, is approved for treatment of cIAIs and cUTIs caused by multidrug-resistant gram-negative bacteria in adults with limited or no alternative treatment options. In addition to published phase II trials, additional phase III trials are underway or awaiting publication of results. These include additional cIAI and cUTI trials (including a phase III trial in cUTI and cIAI infections due to ceftazidime-resistant gram-negative bacteria), and a nosocomial pneumonia and ventilator-associated pneumonia trial.

Pharmacokinetics[6-8]

Table 1. Pharmacokinetic Properties of Ceftazidime and Avibactam at Steady State

	C_{max} (mg/L)	$AUC_{0\text{-}tau}^{*}$ (mg·h/L)	$fAUC_{0\text{-}tau}^{*}$ (mcg·h/mL)	Protein Binding (%)	V_d (L)	$T_{½}$ (h)	CL (L/h)	Excretion (%)
Ceftazidime 2 g q8h	90.4	291	230	21	17.0	2.76	6.86	82, urine
Avibactam 500 mg q8h	14.6	38.2	35.1	8	22.2	2.71	13.1	97, urine

C_{max}: maximum observed concentration, $AUC_{0\text{-}tau}$: area under concentration curve over dosing interval, $fAUC_{0\text{-}tau}$: free area under concentration curve over dosing interval, V_d: volume of distribution, $T_{½}$: elimination half-life, CL: clearance

Pharmacodynamics[6,7,9-12]

The pharmacodynamics of ceftazidime have been well-described. Efficacy of ceftazidime best correlates with time that unbound plasma concentrations of ceftazidime exceeds the minimum inhibitory concentration based on a neutropenic murine thigh infection model with Enterobacteriaceae and *Pseudomonas aeruginosa*. A free drug concentration above the MIC of about 50% has been shown to predict in vitro bactericidal activity and correlate with successful treatment of gram-negative ventilator-associated pneumonia.

The pharmacodynamic target for avibactam is the percentage of time of the dosing interval that free inhibitor concentration is above the threshold concentration (%fT>C_T). C_T is the concentration of avibactam that must be maintained concomitantly with a beta-lactam to inhibit bacterial growth. Based on *in vitro* hollow-fiber pharmacodynamic studies of ceftazidime/avibactam against Enterobacteriaceae, the C_T for avibactam is 0.5 mg/L or lower. Avibactam concentrations of 0.25-0.5 mg/L should be targeted for ≥ 50% of an 8-hour dosing interval to maintain suppression of bacterial growth.

Similar *in vitro* pharmacodynamic studies in murine models of *P. aeruginosa* infection have been conducted. A murine neutropneic thigh infection model determined that %fT>C_T using a C_T of 1 mg/L was the strongest predictor of reduced bacterial burden. The average %fT>C_T required for inhibition of *P. aeruginosa* growth at 24 hours was ~40% but varied between 15-70% for particular isolates. A neutropenic murine model of P. aeruginosa pneumonia also demonstrated that %fT>C_T using a C_T of 1 mg/L was the strongest predictor of avibactam-associated bacterial growth suppression, but only 20-25% fT>C_T was required.

Data from Monte Carlo simulations support pharmacodynamic target attainment with approved dosing. Using conservative targets for ceftazidime (50% fT>MIC) and avibactam (50% fT> C_T with C_T of 1 mg/L), the proposed dose of ceftazidime 2 g-avibactam 0.5 g infused over 2 hours every 8 hours achieves greater than 98% probability of target attainment ceftazidime/avibactam MICs as high as 8 mg/L. For MICs of 16 mg/L and 32 mg/L, probability of target attainment decreases to 51% and 1%, respectively.

Pharmacology and Microbiology[3-6]

Ceftazidime is a cephalosporin antibiotic that exerts bactericidal activity by binding to essential penicillin binding proteins located in the cell wall of certain gram-negative and gram-positive bacteria. Avibactam is a non-beta-lactam beta-lactamase inhibitor that functions to inactivate some beta-lactamases and protect ceftazidime from degradation by certain beta-lactamases.

Ceftazidime/avibactam has broad gram-negative activity, including Enterobacteriaeceae and *P. aeruginosa*. However, it has minimal activity against gram-positive organisms and anaerobes. Avibactam is active against class A, C, and D beta-lactamases, as well as carbapenemases, but is not active against metallo-beta-lactamases. Susceptibility interpretative criteria, *in vitro* activity against specific bacteria, and *in vitro* activity against specific β-lactamases are highlighted in Tables 2-4, respectively.

Table 3. Susceptibility Interpretive Criteria for Ceftazidime/Avibactam

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

Table 4. *In Vitro* Activity of Ceftazidime/Avibactam Against Specific Bacteria

Organism	Ceftazidime		Ceftazidime/avibactam	
	MIC_{50}/MIC_{90}	MIC Range	MIC_{50}/MIC_{90}	MIC Range
Gram-negative aerobes				
Acinetobacter spp.	>32/>32	NA	32/>32	0.25->32
Imipenem-resistant	>32/>32	NA	32/>32	≤0.03->32
Acinetobacter baumannii	8/>32	NA	8/>16	0.5->16
Carbapenem-resistant	>32/>32	NA	32/>32	0.25->32
OXA-producing	128/>128	4->128	8/>128	4/>128
Burkholderia cepacia	64/>128	8->128	8/>128	≤1->128
Citrobacter spp.	0.25/>32	≤0.25->64	0.25/0.5	≤0.06-2
Ceftazidime non-susceptible	32/>32	NA	0.25/1	≤0.06-4
Citrobacter freundii	0.5->32	≤0.25->32	0.125/0.5	≤0.06-2
Enterobacter spp.	0.25/>32	NA	0.25/1	≤0.03->32
Ceftazidime-resistant	32/>32	NA	0.5/2	0.06->32
AmpC producing + porin loss	256/256	64-256	1/1	0.25-1
Enterobacter aerogenes	0.5->32	≤0.25->32	0.25/0.5	≤0.06-16
Enterobacter cloacae	0.5->32	≤0.25->32	0.25/1	≤0.06-16
Escherichia coli	≤0.25-1	≤0.25->32	0.12/0.25	≤0.06-4
ESBL-producing	16/>32	1->32	0.12/0.25	≤0.06-1
AmpC-hyperproducing	16/>32	1->32	0.12/0.5	≤0.06-2
ESBL-producing + AmpC-hyperproducing	0.12/0.12	0.015-0.12	32/>64	2->64
Haemophilus influenzae	NA	NA	≤0.06-≤0.06	≤0.06-0.1
Klebsiella spp.	0.12/32	NA	0.12/0.5	≤0.03-32
ESBL-producing	>32/>32	NA	0.5/2	≤0.03-32
Carbapenem non-susceptible	>32/>32	NA	0.5/2	≤0.03-32
Klebsiella oxytoca	≤0.25/0.5	≤0.25->32	0.12/2	≤0.06-2
Klebsiella pneumoniae	≤0.25/1	≤0.25->32	0.12/0.5	≤0.06-8
ESBL-producing	32/>32	4-64	0.5/1	≤0.06-2
OXA-48-producing	256/512	≤0.12>512	0.25/0.5	≤0.008-1
KPC-producing	>256/>256	32->256	0.25/1	≤0.06-1
Carbapenem non-susceptible	>32/>32	NA	0.5/2	≤0.03-32
ESBL-producing + porin loss	256/512	126-512	1/1	0.5-2
Morganella morganii	≤0.25-8	≤0.25-16	≤0.06-0.12	≤0.06-0.5
Proteus spp., indole-positive	0.12/8	NA	0.06/0.25	≤0.03-2
Proteus mirabilis	≤0.25-≤0.25	≤0.25-32	≤0.06-0.12	≤0.06-0.25
Proteus vulgaris	0.12/8	NA	0.06/0.25	≤0.03-2
Salmonella spp. (including *S. enterica*)	0.25/0.5	NA	0.25/0.5	≤0.03-0.5
Serratia spp.	0.25/0.5		0.25/0.5	0.06-8
Serratia marcescens	≤0.25-1	≤0.25-16	0.25/0.5	≤0.06-2
Pseudomonas aeruginosa	4/32	≤0.25->32	2/8	≤0.06->16
Multidrug-resistant	>16/>16	4->16	8/>16	4->16
AmpC-derepressed	64->126	8->128	4/8	≤1-64
Intrinsic MexA/OprM	4/8	≤1-16	4/8	≤1-16
Gram-negative anaerobes				
Bacteroides fragilis	0.5/>32	0.5->128	4/32	≤0.06->64
Other *B. fragilis* complex	>128/>128	8->128	32/>128	4->128
Prevotella/Porphyromonas spp.	32/>128	0.5->128	2/4	≤0.125-8
Fusobacterium spp.	NA	0.125-32	NA	≤0.06-2
Gram-positive anaerobes				
Clostridium difficile	128/>128	64->128	32/64	32->128
Clostridium perfringens	64/>128	0.5->128	≤0.06/2	≤0.06-4
Gram-positive anaerobes	1/64	≤0.06-32	0.25/32	≤0.06-16

Table 5. *In Vitro* Activity of Ceftazidime and Ceftazidime/Avibactam Against Specific Beta-Lactamases			
Organism	**β-Lactamase**	**Ceftazidime MIC**	**Ceftazidime/avibactam MIC**
Escherichia coli			
Extended-spectrum β-lactamases	CTX-M-9	2	0.25
	CTX-M-14	2	0.06
	CTX-M-15	32	0.12
	PER-1	256	1
	SHV-3	32	0.06
	SHV-4	128	0.25
	SHV-5, TEM-3	64	0.25
	TEM-3	64	0.25
	TEM-5	32	0.06
	TEM-6	>128	0.5
	TEM-7	16	1
	TEM-8	256	0.25
	TEM-9	>128	0.5
	TEM-10	128	0.5
	TEM-12	16	0.25
	TEM-16	256	0.5
	TEM-24	>64	4
	TEM-43	4	0.25
	OXA-2	0.25	0.12
	OXA-48	4	≤0.008
	CTX-M-2, TEM-1	32	0.5
	CTX-M-15, TEM-1	32	0.12
	CTX-M-15, OXA-1	16	0.25
	CTX-M-16, TEM-1	>128	1
	SHV-12, TEM-1	16	0.06
	CTX-M-15, TEM-1, OXA-1	128	0.25
Carbapenemases	KPC-2	64	0.25
	KPC-2, TEM-1	128	0.5
	KPC-3	64	2
	GES-3	128	0.25
	GES-4	128	1
Metallo-β-lactamases	NMC-A	0.25	≤0.015
	PER-1	>64	4
	VEB-1	2	0.5
	IMP-1	256	64
	NDM	>256	>256
	VIM-1	>512	512
Ambler Class C β-lactamases	AmpC	16	1
	AmpC, CTX-M-15	>32	0.12
	AmpC, CTX-M-15, OXA-1, TEM-1	>32	0.25
	ACC-1	>64	4
	CMY-2, VEB-2	256	128
	CMY-2, CTX-M-14, TEM-1	128	1
	CMY-2, CTX-M-15, OXA-1	32	0.06
	FOX-1	32	4
Klebsiella pneumoniae			
Extended-spectrum β-lactamases	CTX-M-3	16	0.5
	CTX-M-14	16	1
	CTX-M-15	>128	1
	SHV-2	>64	0.5
	SHV-3	>64	0.5
	SHV-4	>256	4
	SHV-5	64	0.5
	SHV-6	4	1
	SHV-18	64	2
	SHV-38	8	2
	TEM-4	32	0.5
	CTX-M-2, TEM-1B	128	2
	CTX-M-16, OXA-1	256	1
	SHV-5, TEM-10	>128	2
	CTX-M-2, SHV-5, TEM-12	>128	2
	CTX-M-2, SHV-2, TEM-12	>128	4
	CTX-M-3, SHV-1, TEM-1B	256	2
	CTX-M-15, TEM-1, OXA-1	256	2
	SHV-1, TEM-2, PER	256	4
Carbapenemases	KPC-2	>128	1
	KPC-3	256	0.5
	KPC-2, SHV-11, SHV-12, TEM-1	512	≤0.06
Metallo-β-lactamases	VIM-1, SHV-5	256	256
Ambler Class C β-lactamases	AmpC + SHV-11	64	2
	DHA-2	256	2
	ACC-1, TEM-1	128	1
	LAT-4, SHV-11 variant	32	1
	CMY-4, TEM-1	256	0.5
	DHA-1, SHV-2a, TEM-1	>128	1
	MOX-2, SHV-5, TEM-1	256	1

FDA Approved Indications[6,13]

The FDA approved ceftazidime/avibactam on February 25, 2015 for the treatment of patients 18 years or older with the following infections caused by designated susceptible microorganisms:

- Complicated intra-abdominal infections, in combination with metronidazole, caused by Escherichia coli, Klebsiella pneumonia, Proteus mirabilis, Providencia stuartii, Enterobacter cloacae, Klebsiella oxytoca, and Pseudomonas aeruginosa.
- Complicated urinary tract infections, including pyelonephritis, caused by Escherichia coli, Klebsiella pneumoniae, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Citrobacter freundii, Proteus spp., and Pseudomonas aeruginosa.

Only limited clinical safety and efficacy data are currently available for ceftazidime/avibactam and it should be reserved for use in patients with limited or no alternative treatment options.

Clinical Trials[14,15]

Table 6. Clinical Trials

Study Design

Vazquez JA et al, 2012

Trial Design:

- Prospective, multicenter, randomized (1:1), double-blind, phase II comparative study
- Compared ceftazidime/avibactam versus imipenem/cilastatin for treatment of cUTI, including pyelonephritis
- November 2008-June 2010

Interventions:

- Ceftazidime/avibactam 625 mg IV every 8 hours
- Imipenem/cilastatin 1000 mg IV every 6 hours
- Patients were to receive minimum 4 days of IV study therapy before switching to oral ciprofloxacin with a minimum and maximum of 7 and 14 total days of antibiotics respectively based on investigator discretion

Primary Outcome:

- Microbiologic response at test-of-cure (TOC) visit 5-9 days following last dose of study medication in the microbiologically evaluable (ME) population

Secondary Outcomes:

- Microbiologic response at end of IV therapy and late follow-up (LFU) in the ME population
- Clinical response at TOC and LFU within the clinically evaluable (CE) population

Methods

Inclusion Criteria:

- Age 18-90 with acute pyelonephritis or other cUTI due to gram-negative pathogens requiring IV therapy

Exclusion Criteria:

- Infection with pathogen resistant to either study drug at baseline
- Received > 1 dose of potentially effective antibiotic within 48 hours prior to the admission urine culture
- Presence of ileal loops, vesicoureteral reflux, complete obstruction of urinary tract, perinephric or intrarenal abscess, or fungal UTI
- Permanent indwelling catheter unless removed within 48 hours of study entry
- Pregnancy, breastfeeding
- Unlikely to survive study period
- Hypersensitivity to study medication

Statistical Analysis:

- Formal sample size calculation not performed
- Not statistically powered to demonstrate non-inferiority
- Population of 150 patients considered sufficient to provide estimate of efficacy and safety
- Outcomes summarized using descriptive statistics and two-sided 95% CIs

Results

Primary and Secondary Outcomes:

	Ceftazidime/avibactam n (%)	Imipenem/cilastatin n (%)
ME population	n=27	n=35
MR at TOC	19 (70.4)	25 (71.4)
MR at end of IV therapy	25/26 (96.2)	34/34 (100)
MR at LFU	15/26 (57.7)	18/30 (60)
CE population	n=28	n=36
CR at end of IV therapy	28/28 (100.0)	36/36 (100.0)
CR at TOC	24/28 (85.7)	29/36 (80.6)
CR at LFU	20/27 (74.1)	24/36 (66.7)

Microbiological Response Rate Per Diagnosis and Pathogen:

	Ceftazidime/avibactam n (%)	Imipenem/cilastatin n (%)
ME population	n=27	n=35
Primary diagnosis		
Acute pyelonephritis	13/18 (72.2)	14/19 (73.7)
Other cUTI	6/9 (66.7)	11/16 (68.8)
Baseline pathogen		
E. coli	19/25 (76.0)	23/33 (69.7)
P. aeruginosa	0/2 (0.0)	0/0
C. koseri	1/1 (100.0)	0/0
E. cloacae	0/0	1/1 (100.0)
P. mirabilis	0/0	1/1 (100.0)
Ceftazidime-resistant pathogens		
E. coli	6/7 (85.7)	8/10 (80.0)
E. cloacae	0/0	1/1 (100.0)

Adverse Events Occurring in ≥ 5% of Patients in Either Treatment Group:

	Ceftazidime/avibactam (n=68)	Imipenem/cilastatin (n=67)
# patients with ≥ 1 AE	46 (67.6)	51 (76.1)
Constipation	7 (10.3)	2 (3.0)
Diarrhea	6 (8.0)	7 (10.4)
Abdominal pain	10 (14.7)	4 (6.0)
Abdominal distention	0	5 (7.5)
Headache	13 (19.1)	21 (31.3)
Dizziness	4 (5.9)	0
Chest pain	4 (5.9)	3 (4.5)
Injection site reaction	5 (7.4)	16 (23.9)
Anxiety	7 (10.3)	5 (7.5)
Insomnia	4 (5.9)	4 (6.0)
ALT increase	2 (2.9)	4 (6.0)
Back pain	2 (2.9)	4 (6.0)
Hypertension	4 (5.9)	2 (3.0)

Serious Adverse Events:

	Ceftazidime/avibactam (n=68)	Imipenem/cilastatin (n=67)
Acute renal failure	1 (1.5)	0
Renal impairment	1 (1.5)	0
Atrial fibrillation	1 (1.5)	0
Diarrhea	1 (1.5)	0
Accidental overdose	1 (1.5)	0
Vertebral disc protrusion	1 (1.5)	0
Urosepsis	0	1 (1.5)
Creatinine increased	0	1 (1.5)

Conclusions/Comments

Author's Conclusion:

- Efficacy and safety of ceftazidime/avibactam may be similar to that of imipenem/cilastain for cUTI, including pyelonephritis

Comments:

- Excluded patients if cUTI was known to be resistant to either study drug, effectively excluding infections caused by carbapenemase-producing bacteria
- Mostly female cohort
- Predominant pathogen = *E. coli*
- No isolates were resistant to imipenem/cilastatin
- 20 isolates were nonsusceptible to ceftazidime, with 8 occurring in the ceftazidime-avibactam group
- 30% of patients in both treatment arms had a baseline pathogen possessing the *bla*CTX-M-15 gene (ability to produce ESBLs)
- Limitations include small number of patients in the ME population

		Drug-Related Adverse Events Leading to Discontinuation: • Ceftazidime/avibactam: n=1 (accidental overdose) **Deaths:** • None reported	

Study Design	Methods	Results	Conclusions/Comments

Lucasti C et al, 2013

Trial Design:
- Prospective, multicenter, randomized (1:1), double-blind, phase II controlled trial
- Compared ceftazidime/avibactam plus metronidazole versus meropenem for treatment of cIAI

Interventions:
- Ceftazidime/avibactam 2.5 g IV every 8 hours plus metronidazole 500 mg IV every 8 hours
- Meropenem 1 g IV every 8 hours
- Patients were to receive 5-14 days of study therapy and were allowed concomitant vancomycin, linezolid, or daptomycin for suspected or confirmed gram-positive co-infection

Primary Outcome:
- Clinical response at TOC visit in the ME population

Secondary Outcomes:
- Clinical response at end of IV therapy, TOC, and LFU visit in the CE population

Inclusion Criteria:
- Age 18-90 years with cIAI requiring surgical intervention and antibiotics

Exclusion Criteria:
- Abdominal wall abscess
- Small bowel obstruction or ischemic bowel without perforation
- Received other systemic antibiotics within 72 hours of study therapy
- APACHE II > 25
- Significant liver disease
- CrCl < 50 mL/min
- Immunocompromised status
- Infection with pathogen resistant to either study drug at baseline

Statistical Analysis:
- No formal sample size calculation was performed; sample size of 200 planned for inclusion based on currently accepted standards for this type of study
- Not statistically powered to demonstrate non-inferiority to the comparator
- Response rates were calculated for each treatment group for primary and secondary efficacy variables

Primary and Secondary Outcomes:

	Ceftazidime/avibactam + metronidazole n (%)	Meropenem n (%)
ME population	n=68	n=76
CR at TOC visit	62/68 (91.2)	71/76 (93.4)
CE population	n=87	n=90
CR at end of IV therapy	84/87 (96.6)	87/89 (97.8)
CR at TOC visit	80/87 (92.0)	85/90 (94.4)
CR at LFU visit	79/86 (91.9)	84/89 (94.4)

Microbiological Response by Pathogen at TOC Visit (ME Population):

	Ceftazidime/avibactam + metronidazole (n=68)	Meropenem (n=76)
Gram-positives		
E. faecium	3/4 (75.0)	4/4 (100.0)
Other	13/13 (100.0)	15/15 (100.0)
Gram-negatives		
E. coli	47/52 (90.4)	49/53 (92.5)
K. pneumoniae	6/6 (100.0)	11/11 (100.0)
P. aeruginosa	5/5 (100.0)	5/5 (100.0)
K. oxytoca	2/2 (100.0)	2/2 (100.0)
A. baumannii	1/1 (100.0)	1/1 (100.0)
E. aerogenes	0/0	0/1 (0.0)
E. cloacae	1/1 (100.0)	4/4 (100.0)
Other	2/2 (100.0)	7/7 (100.0)
Anaerobes		
B. fragilis	3/6 (50.0)	3/3 (100.0)
Other	16/16 (100.0)	11/11 (100.0)

Microbiological Response in Patients with Ceftazidime-Intermediate or –Resistant Gram-Negative Isolates (ME Population):

	Ceftazidime/avibactam + metronidazole (n=26)	Meropenem (n=76)
A. baumannii	1/1 (100.0)	0 (0.0)
E. coli	19/20 (95.0)	13/14 (92.9)
K. pneumoniae	3/3 (100.0)	3/3 (100.0)
P. mirabilis	1/1 (100.0)	0 (0.0)
P. aeruginosa	1/1 (100.0)	1/1 (100.0)
Overall response rate	25/26 (96.2)	16/17 (94.1)

Adverse Events Occurring in ≥ 5% of Patients in Either Treatment Group:

	Ceftazidime/avibactam + metronidazole (n=101)	Meropenem (n=102)
# patients with ≥ 1 AE	65 (64.4)	59 (57.8)
Nausea	10 (9.9)	6 (5.9)
Vomiting	14 (13.9)	5 (4.9)
Abdominal pain	8 (7.9)	3 (2.9)
Pyrexia	9 (8.9)	11 (10.8)
Wound secretion	3 (3.0)	6 (5.9)
Cough	6 (5.9)	4 (3.9)
ALT increased	8 (7.9)	13 (12.7)
AST increased	9 (8.9)	15 (14.7)
Alk phos increased	9 (8.9)	7 (6.9)
Platelets increased	4 (4.0)	7 (6.9)
WBC count increased	5 (5.0)	6 (5.9)
Hematuria	4 (4.0)	6 (5.9)

Author's Conclusion:
- Ceftazidime/avibactam plus metronidazole was effective and generally well tolerated in patients with cIAI, with a favorable clinical response rate in the ME population similar to that of meropenem

Comments:
- Dosing of meropenem is different from the dosing strategy at our institution
- Mostly male cohort with APACHE II score of 10 or lower
- Most common sites of infection were appendix and stomach or duodenum
- Predominant diagnosis was peritonitis (> 80%)
- More than1/3 of patients had polymicrobial infection with *E. coli* as the most common organism isolated from both the cIAI site and bloodstream
- Median duration of treatment was 6 days for ceftazidime/avibactam and 6.5 days for meropenem

		Serious Adverse Events: • Ceftazidime/avibactam: n=9 (8.9%) • Meropenem: n=11 (10.8%) **Drug-Related Adverse Events Leading to Discontinuation:** • None reported **Deaths:** • Ceftazidime/avibactam: n=3 • Meropenem: n=1 • None of the deaths were considered to be related to the study drug	

Warnings, Precautions, and Adverse Effects[6,14,15]

Table 7. Warnings and Precautions	
Warning/Precaution	*Description*
Decreased clinical response in patients with baseline creatinine clearance of 30-50 mL/min	Monitor creatinine clearance at least daily in patients with changing renal function and adjust the dose accordingly.
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 ceftazidime/avibactam.
Clostridium difficile-associated diarrhea (CDAD)	CDAD has been reported with nearly all systemic antibacterial agents, including ceftazidime/avibactam. Evaluate if diarrhea occurs.
Central nervous system reactions	Seizures and other neurologic events may occur, especially in patients with renal impairment. Adjust dose in patients with renal impairment.
Development of drug-resistant bacteria	Prescribing ceftazidime/avibactam in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit and increases the risk for development of drug-resistant bacteria.
Pregnancy category B	No adequate and well-controlled studies in pregnant women.

Table 8. Adverse Effects Occurring in ≥ 5% of Patients Receiving Ceftazidime/avibactam in Phase II Clinical Trials		
	Phase II cIAI Trial	*Phase II cUTI Trial*
Gastrointestinal		
Vomiting	14%	0%
Nausea	10%	2%
Constipation	4%	10%
Abdominal pain	8%	7%
Upper abdominal pain	1%	7%
Central Nervous System		
Dizziness	0%	6%
Psychiatric		
Anxiety	5%	10%
Laboratory		
Increased alkaline phosphatase	9%	3%
Increased alanine aminotransferase	8%	3%

Interactions[6,16]

Ceftazidime and avibactam do not inhibit or show potential for induction of the cytochrome P450 enzyme system and there is limited potential for significant drug-drug interactions. Probenicid is a potent OAT inhibitor and may inhibit up to 70% of avibactam uptake by OAT transporters *in vitro* resulting in the potential for decreased elimination of avibactam. Co-administration of ceftazidime/avibactam and probenicid is not recommended.

A series of checkerboard experiments noted no microgioloic interaction between ceftazidime/avibactam and a variety of other antibiotics, including colistin, tobramycin, tigecycline, levofloxacin, vancomycin, and linezolid.

Dosage and Administration[6]

Table 9. Dosage by Indication					
Indication	*Dose*[a]	*Route*	*Infusion Time*	*Frequency*	*Duration*
cUTI	2.5 g	Intravenous	2 hours	Every 8 hours	7-14 days
cIAI[b]	2.5 g	Intravenous	2 hours	Every 8 hours	5-14 days

[a]Ceftazidime/avibactam 2.5 g contains ceftolozane 2 g and tazobactam 500 mg
[b]Used in conjunction with metronidazole 500 mg intravenously every 8 hours

Table 10. Dosage Adjustments in Patients with Renal Impairment		
Estimated Creatinine Clearance (mL/min)	*Recommended Dose*	
Renal impairment	CrCl > 50 mL/min	2.5 g (2 g/0.5 g) IV every 8 hours
	CrCl 31-50 mL/min	1.25 g (1 g/0.25 g) IV every 8 hours
	CrCl 16-30 mL/min	0.94 g (0.75 g/0.19 g) IV every 12 hours
	CrCl 6-15 mL/min	0.94 g (0.75 g/0.19 g) IV every 24 hours
	CrCl ≤ 5 mL/min	0.94 g (0.75 g/0.19 g) IV every 48 hours
	Intermittent hemodialysis	Dose based on estimated CrCl , administer after dialysis
Hepatic impairment	No dosage adjustment necessary	
Geriatric patients	Dosage adjustments should be based on renal function	
Pediatric patients	Safety and effectiveness has not been established in patients less than 18 years of age	
Gender	No dosage adjustment is recommended based on gender	
Race	No dose adjustment is recommended based on race	

Monitoring Parameters[6]

Serum creatinine and creatinine clearance should be monitored at baseline and at least daily in patients with moderately or severely impaired renal function or changing renal function.

How Supplied/Cost/Preparation[6]

Table 11. Product Supply			
Product	*Cost per Vial*	*Dosage*	*Cost per Day*
Avycaz™ 2.5g vial NDC 0456-2700-10	$270.93	2.5 g every 8 hours	$812.79

Ceftazidime/avibactam is supplied as a dry powder, which must be reconstituted and subsequently diluted using aseptic technique prior to administration. The powder in the vial may be reconstituted with 10 mL of sterile water for injection, 0.9% sodium chloride injection, 5% dextrose injection, all combinations of dextrose and sodium chloride injections containing up to 2.5% dextrose and 0.45% sodium chloride, or lactated ringer's injection. The same diluent used for reconstitution of the powder (except sterile water for injection) should be used to further dilute the reconstituted solution to achieve a total volume between 50-250 mL before infusion. Diluted solution should be used within 12 hours when stored at room temperature or may be stored under refrigeration at 2-8^{o}C for up to 24 hours following dilution and used within 12 hours of subsequent storage at room temperature.

Utilization
There has been no non-formulary utilization of ceftazidime/avibactam to date.

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Appendix: Summary of Safety Issues and Implications for Pharmacy Operations

Characteristic	Summary
Drug generic name (brand name)	Ceftazidime-avibactam (Avycaz™)
Drug manufacturer	Actavis
Schedule of medication	None
Anticipated use per month, anticipated patient population	<5 patients with infections due to MDR organisms with no other treatment options
Route of administration	Intravenous
Does the product package insert currently have any black box warning?	No
Contraindications or significant warnings against medication use?	Known hypersensitivity to ceftazidime, avibactam or other members of the cephalosporin class
Is there a Risk Evaluation and Management Strategy (REMS) program for the medication? If so, where may healthcare providers find these criteria?	No
Does the manufacturer require patients to meet specific criteria for treatment with this medication? If so, where may healthcare providers find these criteria?	No
Does the manufacturer have a restricted or special distribution program? If so, how may healthcare providers contact the program?	No
Is the medication (brand name, generic name, product packaging) similar to any other medications on the Institute for Safe Medication Practices (ISMP) Sound-Alike-Look-Alike (SALA) list? If not, is the medication expected to be added to the list?	No, not expected to be added to the list.
Recommended storage conditions for medication, and how to manage excursions outside these conditions	Store unconstituted vials at 25ºC (77ºF); excursions permitted between 15ºC and 30ºC (59ºF and 86ºF). Protect from light.
Preparation	Constitute the powder in the vial with 10 mL of one of the following solutions and mix gently – sterile water for injection, 0.9% sodium chloride injection, 5% dextrose injection, all combinations of dextrose injection and sodium chloride injection, containing up to 2.5% dextrose and 0.45% sodium chloride, or lactated Ringer's injection. With the same diluent used for constitution of the powder (except sterile water for injection), dilute the constituted solution further to achieve a total volume between 50 mL to 250 mL before infusion. Mix gently and ensure that the contents are dissolved completely. Visually inspect the diluted solution (for administration) for particulate matter and discoloration prior to administration.
Stability	Diluted solution in the infusion bags may be stored under refrigeration at 2-8ºC (36-46ºF) up to 24 hours following dilution and use within 12 hours of subsequent storage at room temperature.
Are Safe Handling precautions required?	No
Does the medication require disposal in a Resource Conservation and Recovery Act (RCRA) black box?	No
Can medication doses be sent to patient care units via pneumatic tube system?	Yes
Is filtration required during preparation or administration of the IV medication?	No
Is the IV medication a vesicant or irritant?	No
Is special monitoring recommended when starting therapy with this medication (eg. Telemetry)?	No
Is there a significant risk of a hypersensitivity risk with this medication?	No

References:

1. Golan Y. Empiric therapy for hospital-acquired, gram-negative complicated intra-abdominal infection and complicated urinary tract infections: a systematic literature review of current and emerging treatment options. *BMC Infect Dis*. 2015;15:313.
2. Nicolau DP. Focus on ceftazidime-avibactam for optimizing outcomes in complicated intra-abdominal and urinary tract infections. *Expert Opin Investig Drugs*. 2015;24(9):1261-73.
3. Zasowski EJ, Rybak JM, Rybak MJ. The β-lactams strike back: ceftazidime-avibactam. *Pharmacotherapy*. 2015;35(8):755-70.
4. Lagace-Wiens P, Walkty A, Karlowsky JA. Ceftazidime-avibactam: an evidence-based review of its pharmacology and potential use in the treatment of gram-negative bacterial infections. *Core Evidence*. 2014;9:13-25.
5. Zhanel GG, Lawson CD, Adam H, et al. Ceftazidime-avibactam: a novel cephalosporin/β-lactamase inhibitor combination. *Drugs*. 2013;73:159-77.
6. AVYCAZ™ (ceftazidime-avibactam) for injection [package insert]. Actavis, Inc. February 2015.
7. Cerexa I, a subsidiary of Actavis plc. Ceftazidime-avibactam for injection anti-infective drugs advisory committee. In: Administration USFaD, ed. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM425459.pdf2014.
8. Boselli E, Breihl D, Rimmele T, et al. Plasma and lung concentrations of ceftazidime administered in continuous infusion to critically ill patients with severe nosocomial pneumonia. *Intensive Care Med*. 2004;30(5):989-91.
9. MacVane SH, Kuti JL, Nicolau DP. Clinical pharmacodynamics of antipseudomonal cephalosporins in patients with ventilator-associated pneumonia. *Antimicrob Agents Chemother.* 2014;58(3):1359-64.
10. Coleman K, Levasseur P, Girard AM, et al. Activities of ceftazidime and avibactam against beta-lactamase-producing Enterobacteriaecea in a hollow-fiber pharmacodynamics model. *Antimicrob Agents Chemother*. 2014;58(6):3366-72.
11. Berkhout J, Melchers MJ, Van Mill CH, et al. Exposure response relationships of ceftazidime and avibactam in a neutropenic thigh model. Paper presented at 53rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Denver, CO, 2013.
12. Berkhout J, Melchers MJ, Van Mill CH, et al. Pharmacodynamics of ceftazidime and avibactam in a neutropenic mouse lung model. Paper presented at 53rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Denver, CO, 2013.
13. FDA. FDA approves new antibacterial drug Avycaz. February 26, 2015. Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435629.htm. Accessed June 2015.
14. Vazquez JA, Gonzalez Patzan LD, Stricklin D, et al. 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. *Curr Med Res Opin*. 2012;28(12):1921-31.
15. Lucasti C, Popescu I, Ramesh MK, Lipka J, Sable C. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, phase II trial. *J Antimicrob Agents Chemother*. 2013;68(5):1183-92.
16. Dallow J, Otterson LG, Huband MD, Krause KM, Nichols WW. Microbiologic interaction studies between ceftazidime-avibactam and pulmonary surfactant and between ceftazidime-avibactam and antibacterial agents of other classes. *Int J Antimicrob Agents*. 2014;44(6):552-6.