Drug Monograph

Drug/Drug Class:	**Avycaz™ (ceftazidime and avibactam sodium) powder for injection/ Antibiotic**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Avycaz™ is supplied as an unconstituted powder in a single use, clear glass vial containing 2 grams ceftazidime and 0.5 grams avibactam. Manufactured by: GlaxoSmithKline Manufacturing S.p.A., Verona, Italy 37135 Distributed by: Forest Pharmaceuticals, Inc., Cincinnati, Ohio 45209
Summary of Findings:	The efficacy of Avycaz™ was based on previous efficacy and safety findings for ceftazidime in the treatment of complicated intra-abdominal infections and complicated urinary tract infections. The contribution of avibactam was based on findings from in vitro and animal models. Avycaz™ was evaluated in 2 randomized, phase 2 clinical trials, but the studies were not designed to evaluate efficacy against the active comparators. In the small, phase 2 study of patients with complicated intra-abdominal infections (n=204), Avycaz™ plus metronidazole produced a favorable response in 91.2% of patients.
Status Recommendation:	☐ Prior Authorization (PA) Required ☒ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[3,4]

Intra-abdominal infections are common in clinical practice and comprise a wide variety of clinical presentations and differing sources of infection. Complicated Intra-abdominal infections extend beyond the hollow viscus or origin into the peritoneal space and are associated with either abscess formation or peritonitis.

A complicated urinary tract infection is a urinary infection occurring in a patient with a structural or functional abnormality of the genitourinary tract.

Dosage Form(s) [1]

Avycaz™ is supplied as an unconstituted powder in a single use, clear glass vial containing 2 grams ceftazidime and 0.5 grams avibactam.

Manufacturer [1]

Manufactured by: GlaxoSmithKline Manufacturing S.p.A., Verona, Italy 37135
Distributed by: Forest Pharmaceuticals, Inc., Cincinnati, Ohio 45209

Indication(s) [1]

Avycaz™ is indicated for the treatment of adults with complicated urinary tract infections, including pyelonephritis, caused by susceptible microorganisms (Escherichia coli, Klebsiella pneumoniae, Proteus species, Pseudomonas aeruginosa, Citrobacter freundii, Citrobacter koseri, Enterobacter aerogenes, and Enterobacter cloacae), and for the treatment of adults with complicated intra-abdominal infections, in combination with metronidazole, caused by susceptible microorganisms (Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, and Providencia stuartii).

Clinical Efficacy [1-4] (mechanism of action/pharmacology, comparative efficacy)

Ceftazidime is a semisynthetic, beta-lactam cephalosporin bactericidal agent that inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins. Avibactam is a beta-lactamase inhibitor that protects ceftazidime from enzyme degradation.

Pharmacokinetics

	Ceftazidime	**Avibactam**
Volume of distribution	17 L	22.2 L
Metabolism	Negligible	Negligible
Excretion	Urine, 80% to 90% unchanged	Urine, 97% (85% unchanged)
Half-life	2.76 hours	2.71 hours

Protein binding	< 10%	< 10%

The combination of ceftazidime/avibactam and metronidazole produced a favorable response in 83.2% of patients with complicated intra-abdominal infections.

STUDY DESIGN	Randomized, double-blind, phase 2 clinical trial with no statistical analysis or comparison of efficacy between treatment groups (n=204).
INCLUSION CRITERIA	Adult patients with complicated intra-abdominal infections requiring surgical intervention and antibiotic treatment.
EXCLUSION CRITERIA	Abdominal wall abscess, small bowel obstruction or ischemic bowel without perforation, or any concurrent infection.
TREATMENT REGIMEN	Patients were randomized to receive Avycaz 2000mg/500 mg IV plus metronidazole 500 mg IV every 8 hours (n=101) or meropenem 1 g IV every 8 hours (n=102) for 5 to 14 days.
RESULTS	Among the patients who received Avycaz plus metronidazole (n=101), the median duration of treatment was 6 days and a favorable clinical response was achieved in 91.2% at 2 weeks following the end of treatment.
SAFETY	The most common adverse events in the Avycaz plus metronidazole group consisted of vomiting (13.9%), nausea (9.9%), pyrexia (8.9%), increased AST (8.9%), and increased alkaline phosphatase (8.9%).

Contraindications [(1)]

- Serious hypersensitivity to ceftazidime, avibactam, or other cephalosporin drugs

Warnings and Precautions [(1)]

- Clostridium difficile-associated diarrhea has been reported, including cases occurring more than 2 months after administration; discontinue use and institute appropriate medical management if suspected or confirmed.
- Serious and fatal hypersensitivity reactions have been reported; discontinue if allergic reaction occurs.
- Cross sensitivity may occur in patients with previous hypersensitivity reactions to cephalosporins, penicillins, or beta-lactams.
- Decreased efficacy has been reported in patients with baseline creatinine clearance of 30 to 50 mL/min; monitoring recommended.
- CNS reactions including seizures, nonconvulsive status epilepticus, encephalopathy, and coma have been reported, especially in patients with renal impairment; dosage adjustment based on creatinine clearance may be necessary.

- Concomitant use with probenecid is not recommended.

Adverse Effects [1]

Complicated Intra-Abdominal Infections:

Most Common, ≥ 5%	Avycaz™ plus Metronidazole (n=101)	Meropenem (n=102)
Vomiting	14%	5%
Nausea	10%	6%
Increased alkaline phosphatase	9%	7%
Increased ALT	8%	13%
Anxiety	5%	1%

Complicated Urinary Tract Infections:

Most Common, ≥ 5%	Avycaz™ (n=68)	Imipenem/Cilastatin (n=67)
Anxiety	10%	8%
Constipation	10%	3%
Abdominal pain	7%	5%
Upper abdominal pain	7%	2%
Dizziness	6%	0%

Drug Interactions [1]

- Probenecid

Dosage and Administration [1]

Complicated urinary tract infections: Avycaz 2.0 g/0.5 g IV over 2 hours every 8 hours for 7 to 14 days. Complicated intra-abdominal infections: same dose for 5 to 14 days in combination with metronidazole. A dose reduction is recommended for renal impairment.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST*/ DAY
Ceftazidime/ Avibactam	Avycaz	Forest	2 g/0.5 g vial	2 g/0.5 g every 8 hours	$855.00

Ceftolozane/ Tazobactam	Zerbaxa	Cubist	1 g/0.5 g vial	1 g every 8 hours	$249.00
Imipenem/ Cilastatin	Primaxin	Merck	500 mg/ 500 mg vial	500 mg every 6 hours	$125.67
Meropenem	Merrem	AstraZeneca	1 g vial	1 g every 8 hours	$193.73

* Wholesale Acquisition Cost

Conclusion

Avycaz™ is a combination of a beta-lactam cephalosporin and a beta-lactamase inhibitor that is indicated for the treatment of adults with complicated urinary tract infections, including pyelonephritis, and for the treatment of complicated intra-abdominal infections, in combination with metronidazole, when caused by susceptible microorganisms. It is designated as a Qualified Infectious Disease Product (QIDP) and is intended to treat serious or life-threatening infections, which granted it priority review by the US Food and Drug Administration. The efficacy of Avycaz was based on previous efficacy and safety findings for ceftazidime. The contribution of avibactam was based on findings from in vitro and animal models. Avycaz was evaluated in 2 randomized, phase 2 clinical trials, but the studies were not designed to evaluate efficacy against the active comparators. In the small, phase 2 study of patients with complicated intra-abdominal infections (n=101), Avycaz plus metronidazole produced a favorable response in 91.2% of patients. Because of a lack of safety and efficacy data, Avycaz should only be used in patients with limited or no alternative treatment options, and must be reserved for infections that are caused by or are strongly suspected to be caused by susceptible bacteria. The most common adverse events included vomiting, nausea, constipation, and anxiety.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

1. Product Information: Avycaz™, ceftazidime/avibactam injection. Forest Pharmaceuticals, Inc, Cincinnati, OH, 2/2015.
2. Lucasti C, Popescu I, Ramesh MK et al: 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 Chemother 2013; 68(5):1183-1192.
3. Solomkin, JS, JE Mazuski, JS Bradley et al., 2010, Diagnosis and Management of Complicated Intra-Abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Disease Society of America, Clinical Infectious Diseases, 50:133-164.
4. “Complicated urinary tract infection in adults”. Retrieved 8/31/15 from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2094997/

Prepared by: Luke Boehmer, PharmD

Date: August 31, 2015

