Drug Monograph

Drug Name: **Kimyrsa™ (oritavancin) injection**
Drug Class: **Anti-infective: Lipoglycopeptide**
Prepared For: MO HealthNet
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☒ **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:	Kimyrsa is available as an intravenous injection in single-dose vials that contain 1,200 mg of oritavancin.
Manufacturer:	Melinta Therapeutics, LLC., Lincolnshire, IL 60069.
Summary of Findings:	The efficacy of Kimyrsa for the treatment of adult patients with acute bacterial skin and skin structure infections caused or suspected to be caused by susceptible isolates of designated Gram-positive microorganisms was approved based on a pharmacokinetic study comparing it to Orbactiv®. Orbactiv's efficacy was demonstrated in two clinical trials enrolling 1,987 patients and contains the same active ingredient, has the same route of administration and indication as Kimyrsa. In study 1, 82.3% of the Orbactiv-treated patients vs 78.9% vancomycin-treated patients met the primary outcome measure (difference 3.4 [95% CI: -1.6, 8.4). In study 2, 80.1% of Orbactiv-treated patients vs 82.9% of vancomycin-treated patients met the primary outcome measure (difference -2.7 [95% CI: -7.5, 2.0]). Orbactiv met the criteria for non-inferiority compared to vancomycin in both trials.
Status Recommendation:	☐ Clinical Edit ☐ PA Required ☒ Open Access ☐ PDL
Type of PA Criteria:	☐ Appropriate Indications ☐ Non-Preferred ☒ No PA Required ☐ Preferred

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, payers 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 [1,2]

Acute bacterial skin and skin structure infection (ABSSSI) is defined as a bacterial infection of the skin with a lesion size area of at least 75 cm^2. Symptoms usually include redness and edema, accompanied by lymph node enlargement or fever. Infections include extensive cellulitis/erysipelas, wound infections, burn infections and major cutaneous abscesses. In 2016, it was estimated that ABSSSI accounted for 10% of hospital admissions in the US.

Dosage Form [3]

Kimyrsa is available as an intravenous injection in single-dose vials that contain 1,200 mg of oritavancin.

Manufacturer [3]

Melinta Therapeutics, LLC., Lincolnshire, IL 60069.

Indication(s) [3]

Kimyrsa is indicated for the treatment of adult patients with ABSSSI caused or suspected to be caused by susceptible isolates of designated Gram-positive microorganisms.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Kimyrsa is a lipoglycopeptide with concentration-dependent bactericidal activity. It inhibits cell wall biosynthesis by inhibiting the polymerization step by binding to stem peptides of peptidoglycan precursors, by inhibiting crosslinking by binding to bridging segments, and by disrupting membrane integrity leading to cell death.

Pharmacokinetics:

Volume of Distribution	87.6 L
Metabolism	Not metabolized
Excretion	Feces <1%; Urine <5% as unchanged drug
Half-life	245 hours

Clinical Trials Experience

*** Kimyrsa is made by the same manufacturer as Orbactiv, which was approved in 2014. It contains the same active ingredient and has the same route of administration and indication as Orbactiv. The key difference is that Orbactiv is infused over 3 hours while Kimyrsa is infused over 1 hour. No new clinical trials were conducted with Kimyrsa; FDA approval Kimyrsa was approved based on a pharmacokinetic study comparing it to Orbactiv.*

STUDY 1 DESIGN (SOLO I)	Two identically designed, randomized, double-blind, multi-center, multinational, non-inferiority trial
INCLUSION CRITERIA	• Adult patients with clinically documented ABSSSI suspected or proven to be due to gram-positive pathogens requiring at least 5 days of IV therapy
EXCLUSION CRITERIA	• Prior systemic or topical antibacterial therapy with activity against suspected or proven Gram-positive pathogens within the preceding 14 days • The causative Gram-positive pathogen(s) isolated from the ABSSSI site is resistant in vitro to the antibacterial(s) that was administered with documented clinical progression, or • Patient received a single dose of a short acting antibacterial therapy three or more days before randomization • Infections associated with, or in close proximity to, a prosthetic device • Severe sepsis or refractory shock • Known or suspected bacteremia at time of screening • ABSSSI due to or associated with any of the following: o Infections suspected or documented to be caused by Gram-negative pathogens -- Wound infections (surgical or traumatic) and abscesses with only Gram-negative pathogens o Diabetic foot infections o Concomitant infection at another site not including a secondary ABSSSI lesion o Infected burns o A primary infection secondary to a pre-existing skin disease with associated inflammatory changes o Decubitus or chronic skin ulcer, or ischemic ulcer due to peripheral vascular disease o Any evolving necrotizing process gangrene or infection suspected or proven to be caused by *Clostridium* species o Infections known to be caused by a Gram-positive organism with a vancomycin MIC >2 µg/mL or clinically failing prior therapy with glycopeptides o Catheter site infections • Allergy or intolerance to aztreonam or metronidazole in a patient with suspected or proven polymicrobial wound infection involving Gram-negative and/or anaerobic bacteria • Currently receiving chronic systemic immunosuppressive therapy or AIDS with CD4 count < 200 cells/mm^3 • Neutropenia • Significant or life-threatening condition that would confound or interfere with the assessment of the ABSSSI • Women who are pregnant or nursing • History of immune-related hypersensitivity reaction to glycopeptides • Patients that require anticoagulant monitoring with an activated partial thromboplastin time (aPTT) • Contraindication to vancomycin • Patients unwilling to forego blood and/or blood product donation • Treatment with investigational medicinal product within 30 days before enrollment and for the duration of the study • Investigational device present, or removed <30 days before enrollment, or presence of device-related infection • Patients unlikely to adhere to the protocol, comply with study drug administration, or complete the clinical study • Severe hepatic disease

	• Presence of hyperuricemia
TREATMENT REGIMEN	Patients were randomized to receive Orbactiv (n=475) 1,200 mg IV or Vancomycin (n=479) 1 g or 15 mg/kg IV every 12 hours for 7 to 10 days.
RESULTS	The primary outcome measure was early clinical response, defined as cessation of spread or reduction in size of baseline lesion, absence of fever, and no rescue antibacterial drug at 48 to 72 hours after initial of therapy. Results show that 82.3% of patients in the Orbactiv group and 78.9% of patients in the vancomycin group met the primary outcome measure (difference 3.4 [95% CI: -1.6, 8.4)
SAFETY	Discussed in the Adverse Effects section below.

STUDY 2 DESIGN (SOLO II)	Two identically designed, randomized, double-blind, multi-center, multinational, non-inferiority trial
INCLUSION CRITERIA	• Adult patients with clinically documented ABSSSI suspected or proven to be due to gram-positive pathogens requiring at least 5 days of IV therapy
EXCLUSION CRITERIA	• See above (same exclusion criteria)
TREATMENT REGIMEN	Patients were randomized to receive Orbactiv (n=503) 1,200 mg IV or Vancomycin (n=502) 1 g or 15 mg/kg IV every 12 hours for 7 to 10 days.

RESULTS	• The primary outcome measure was early clinical response, defined as:
	  ○ Cessation of spread or reduction in size of baseline lesion,
	  ○ Absence of fever, and
	  ○ No rescue antibacterial drug at 48 to 72 hours after initial of therapy.
	• Results: 80.1% of patients in the Orbactiv group and 82.9% of patients in the vancomycin group met the primary outcome measure (difference -2.7 [95% CI: -7.5, 2.0]). The non-inferiority hypothesis was concluded if the lower limit of the two-sided 95% CI for the difference in response rates in the modified intent-to-treat (mITT) population is greater than -10%.

SAFETY	Discussed in the Adverse Effects section below.

Contraindications [3,4]

- Use of intravenous unfractionated heparin sodium is contraindicated for 120 hours (5 days) after Kimyrsa administration
- Known hypersensitivity to oritavancin products

Warnings and Precautions [3,4]

- Coagulation test interference: Kimyrsa has been shown to artificially prolong aPTT for up to 120 hours, and may prolong prothrombin time (PT) and international normalized ratio (INR) for up to 12 hours and activated clotting time (ACT) for up to 24 hours. For patients who require aPTT monitoring within 120 hours of Kimyrsa dosing, consider a non-phospholipid dependent coagulation test such as Factor X_a assay or an alternative anticoagulant not requiring aPTT.
- Serious hypersensitivity reactions, including anaphylaxis, have been reported with the use of oritavancin products. Discontinue infusion if signs of acute hypersensitivity occur.
- Infusion related reactions: Infusion related reactions have been reported with glycopeptide class of antimicrobial agents. Stopping or slowing the infusion may result in cessation of these reactions.

- *Clostridioides difficile*-associated diarrhea: Evaluate patients if diarrhea occurs.
- Concomitant warfarin use: Oritavancin has been shown to artificially prolong PT/INR for up to 12 hours. Patients should be monitored for bleeding if concomitantly receiving Kimyrsa and warfarin.
- Osteomyelitis: Institute appropriate alternate antibacterial therapy in patients with confirmed or suspected osteomyelitis.
- Development of drug resistant bacteria: Use of Kimyrsa in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the development of drug-resistant bacteria.

Adverse Effects [3,4]

Most common, ≥ 1.5%	Orbactiv (N=976) n (%)	Vancomycin (N=983) n (%)
Nausea	97 (9.9)	103 (10.5)
Headache	69 (7.1)	66 (6.7)
Vomiting	45 (4.6)	46 (4.7)
Abscess	37 (3.8)	23 (2.3)
Diarrhea	36 (3.7)	32 (3.4)
Alanine aminotransferase increased	27 (2.8)	15 (1.5)
Dizziness	26 (2.7)	26 (2.6)
Tachycardia	24 (2.5)	11 (11.1)
Infusion site phlebitis	24 (2.5)	15 (1.5)
Infusion site reaction	19 (1.9)	34 (3.5)
Aspartate aminotransferase increased	18 (1.8)	15 (1.5)

Drug Interactions [3,4]

- CYP substrates: Oritavancin is a nonspecific, weak inhibitor (CYP2C9 and CYP2C19) or inducer (CYP3A4 and CYP2D6) of several CYP isoforms. Avoid administering Kimyrsa concomitantly with drugs that are predominantly metabolized by one of the affected CYP450 enzymes, as co-administration may increase or decrease concentration of those drugs.
- Drug-laboratory test interactions:
  - Prolongation of certain laboratory coagulation tests:
    - Kimyrsa may artificially prolong certain laboratory coagulation tests (PT, INR, aPTT, ACT, SCT, DRVVT and D-dimer) by binding and preventing the action of the phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests. For patients who require aPTT monitoring within the indicated time frame of Kimyrsa dosing, consider a non-phospholipid dependent coagulation test such as Factor X_a assay or an alternative anticoagulant not requiring aPTT.
    - Oritavancin does not interfere with coagulation in vivo. Oritavancin does not affect tests that are used for diagnosis of Heparin Induced Thrombocytopenia.
  - Positive indirect and direct antiglobulin tests (IAT/DAT):
    - Positive IAT/DAT were noted with administration of oritavancin products in studies with healthy volunteers and patients with ABSSI. Positive IAT may interfere with cross-matching before blood transfusion.

Dosage and Administration [3,4]

- Administer 1,200 mg of Kimyrsa as a single dose by intravenous infusion over 1 hour
- Product must be reconstituted

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**
Oritavancin	Kimyrsa™ Orbactiv®	Melinta Therapeutics, LLC	1.2 g as a single dose	$4,900 $3,000
Dalbavancin	Dalvance®	AbbVie	1.5 g as a single dose	$4,800

** Wholesale Acquisition Cost

Conclusion

Kimyrsa, a lipoglycopeptide antibiotic, is indicated for the treatment of adult patients with ABSSSI caused or suspected to be caused by susceptible isolates of designated Gram-positive microorganisms. The safety and efficacy of Kimyrsa was based on two clinical trials of Orbactiv, as both products contain the same active ingredient, same route of administration, and indication. Both studies of Orbactiv met FDA-specified primary endpoints of statistical non-inferiority in the mITT population compared to the active comparator population. The most common adverse reactions (>3%) with Kimyrsa were nausea, headache, vomiting, abscess and diarrhea.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

1) U.S. Department of Health and Human Services Food and Drug Administration. Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. www.fda.gov. Accessed June 2021.
2) Jensen IS, Wu E, Fan W, Lodise TP, Nicolau DP, Dufour S, Cyr PL, Sulham KA. Use of Oritavancin in Moderate-to-Severe ABSSSI Patients Requiring IV Antibiotics: A U.S. Payer Budget Impact Analysis. J Manag Care Spec Pharm. 2016 Jun;22(6):752-64. doi: 10.18553/jmcp.2016.22.6.752. PMID: 27231802.
3) Kimyrsa [package insert]. Lincolnshire, IL: Melinta Therapeutics, LLC.; March 2021.
4) A Multicenter, Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of Single-Dose IV Oritavancin Versus IV Vancomycin for the Treatment of Patients With Acute Bacterial Skin and Skin Structure Infection (SOLO I). NCT012552719. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01252719?term=oritavancin&draw=3&rank=14. Accessed June 2021.
5) A Multicenter, Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of Single-Dose IV Oritavancin Versus IV Vancomycin for the Treatment of Patients With Acute Bacterial Skin and Skin Structure Infection (SOLO II). NCT01252732. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/study/NCT01252732?term=oritavancin&draw=3&rank=13. Accessed June 2021.

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