CLINICAL UPDATE

Brand Name	Kimyrsa™
Generic Name	oritavancin diphosphate
Drug Manufacturer	Melinta Therapeutics, LLC

Clinical Update

TYPE OF CLINICAL UPDATE

New Brand and Strength (1,200 mg)

FDA APPROVAL DATE

March 12, 2021

LAUNCH DATE

May 21, 2021

REVIEW DESIGNATION

Standard

TYPE OF REVIEW

Type 5 - New Formulation or New Manufacturer, New Drug Application (NDA): 214155

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Kimyrsa™ is a lipoglycopeptide antibacterial drug indicated 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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Kimyrsa™ and other antibacterial drugs, Kimyrsa™ should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

MECHANISMS OF ACTION

Oritavancin has three mechanisms of action: (i) inhibition of the transglycosylation (polymerization) step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors; (ii) inhibition of the transpeptidation (crosslinking) step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall; and (iii) disruption of bacterial membrane integrity, leading to depolarization, permeabilization, and cell death. These multiple mechanisms contribute to the concentration-dependent bactericidal activity of oritavancin.

DOSAGE FORM(S) AND STRENGTH(S)

For injection: 1,200 mg of lyophilized powder in a single-dose vial for reconstitution.

DOSE & ADMINISTRATION

There are two oritavancin products (Kimyrsa™ and Orbactiv™, another oritavancin product) that have differences in dose strength, duration of infusion and preparation instructions, including reconstitution and dilution instructions and compatible diluents.

- Administer 1,200 mg of Kimyrsa™ as a single dose by intravenous infusion over 1 hour.

EFFICACY

A total of 1987 adults with clinically documented ABSSSI suspected or proven to be due to Gram-positive pathogens were randomized into two identically designed, randomized, double-blind, multi-center, multinational, non-inferiority trials (Trial 1 and Trial 2) comparing a single 1,200 mg intravenous dose of oritavancin to intravenous vancomycin (1 g or 15 mg/kg every 12 hours) for 7 to 10 days. The primary analysis population (modified intent to treat, mITT) included all randomized patients who received any study drug. Patients could receive concomitant aztreonam or metronidazole for suspected Gram-negative and anaerobic infection, respectively. Patient demographic and baseline characteristics were balanced between treatment groups. Approximately 64% of patients were Caucasian and 65% were males. The mean age was 45 years and the mean body mass index was 27 kg/m^2. Across both trials, approximately 60% of patients were enrolled from the United States and 27% of patients from Asia. A history of diabetes was present in 14% of patients. The types of ABSSSI across both trials included cellulitis/erysipelas (40%), wound infection (29%), and major cutaneous abscesses (31%). Median infection area at baseline across both trials was 266.6 cm^2.

The primary endpoint in both trials was early clinical response (responder), 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 initiation of therapy.

Table 1: Clinical Response Rates in ABSSSI Trials using Responders at 48-72 Hours after Initiation of Therapy

	Oritavancin n /N (%)	Vancomycin n /N (%)	Difference (95% CI)‡
Trial 1	391/475 (82.3)	378/479 (78.9)	3.4 (-1.6, 8.4)
Trial 2	403/503 (80.1)	416/502 (82.9)	-2.7 (-7.5, 2.0)

* Cessation of spread or reduction in size of baseline lesion, absence of fever (<37.7°C) and no rescue antibacterial drug at 48 to 72 hours.

† Patients who died at 48 to 72 hours, after initiation of therapy or who had increase in lesion size at 48 to 72 hours, after initiation of therapy or who used non-study antibacterial therapy during first 72 hours or who had an additional, unplanned, surgical procedure or who had missing measurements during the first 72 hours from initiation of study drug were classified as non-responders.

‡ 95% CI based on the Normal approximation to Binomial distribution.

A key secondary endpoint in these two ABSSSI trials evaluated the percentage of patients achieving a 20% or greater reduction in lesion area from baseline at 48-72 hours after initiation of therapy. Table 2 summarizes the findings for this endpoint in the two ABSSSI trials.

Table 2: Clinical Response Rates* in ABSSSI Trials using Reduction in Lesion Area of 20% or Greater at 48-72 Hours after Initiation of Therapy

	Oritavancin n /N (%)	Vancomycin n /N (%)	Difference (95% CI)‡
Trial 1	413/475 (86.9)	397/479 (82.9)	4.1 (-0.5, 8.6)
Trial 2	432/503 (85.9)	428/502 (85.3)	0.6 (-3.7, 5.0)

* Patients who died at 48 to 72 hours, after initiation of therapy or who had increase in lesion size at 48 to 72 hours, after initiation of therapy or who used non-study antibacterial therapy during first 72 hours or who had an additional, unplanned, surgical procedure or who had missing measurements during the first 72 hours from initiation of study drug were classified as non-responders.

‡ 95% CI based on the Normal approximation to Binomial distribution.

Another secondary efficacy endpoint in the two trials was investigator-assessed clinical success at post therapy evaluation at Day 14 to 24 (7 to 14 days from end of blinded therapy). A patient was categorized as a clinical success if the patient experienced a complete or nearly complete resolution of baseline signs and symptoms related to primary ABSSSI site (erythema, induration/edema, purulent drainage, fluctuance, pain, tenderness, local increase in heat/warmth) such that no further treatment with antibacterial drugs was needed.

Table 3 summarizes the findings for this endpoint in the mITT and clinically evaluable population in these two ABSSSI trials. Note that there are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at the post therapy visits. Therefore, comparisons of oritavancin to vancomycin based on clinical success rates at these visits cannot be utilized to establish non-inferiority conclusions.

Table 3: Clinical Success Rates* in ABSSSI Trials at the Follow-Up Visit (7-14 days after end of therapy)

	Oritavancin n /N (%)	Vancomycin n /N (%)	Difference (95% CI)‡
Trial 1			
mITT‡	378/475 (79.6)	383/479 (80.0)	-0.4 (-5.5, 4.7)
CE‡	362/394 (91.9)	370/397 (93.2)	-1.3 (-5.0,2.3)
Trial 2			
mITT‡	416/503 (82.7)	404/502 (80.5)	2.2 (-2.6, 7.0)
CE‡	398/427 (93.2)	387/408 (94.9)	-1.6 (-4.9,1.6)

* Clinical success was defined if the patient experienced a complete or nearly complete resolution of baseline signs and symptoms as described above.

‡ 95% CI based on the Normal approximation to Binomial distribution.

‡ mITT population consisted of all randomized patients who received study drug; CE population consisted of all mITT patients who did not have violations of inclusion and exclusion criteria, completed treatment and had investigator assessment at the Follow-Up Visit.

Outcomes by Baseline Pathogen: Table 4 shows outcomes in patients with an identified baseline pathogen in the microbiological Intent-to-Treat (microITT) population in a pooled analysis of Trial 1 and Trial 2. The outcomes shown in the table are clinical response rates at 48 to 72 hours and clinical success rates at follow-up study day 14 to 24.

Table 4: Outcomes by Baseline Pathogen (microITT)

	At 48-72 hours				Study day 14 to 24	
	Early Clinical Responder*		⩾ 20% reduction in lesion size†		Clinical Success‡	
Pathogen§	Oritavancin n/N (%)	Vancomycin n/N (%)	Oritavancin n/N (%)	Vancomycin n/N (%)	Oritavancin n/N (%)	Vancomycin n/N (%)
Staphylococcus aureus	388/472 (82.2)	395/473 (83.5)	421/472 (89.2)	407/473 (86.0)	390/472 (82.6)	398/473 (84.1)
Methicillin-susceptible	222/268 (82.8)	233/272 (85.7)	231/268 (86.2)	232/272 (85.3)	220/268 (82.1)	229/272 (84.2)
Methicillin-resistant	166/204 (81.4)	162/201 (80.6)	190/204 (93.1)	175/201 (87.1)	170/204 (83.3)	169/201 (84.1)
Streptococcus pyogenes	21/31 (67.7)	23/32 (71.9)	24/31 (77.4)	24/32 (75.0)	25/31 (80.6)	23/32 (71.9)
Streptococcus agalactiae	7/8 (87.5)	12/12 (100.0)	8/8 (100.0)	12/12 (100.0)	7/8 (87.5)	11/12 (91.7)
Streptococcus dysgalactiae	7/9 (77.8)	6/6 (100.0)	6/9 (66.7)	5/6 (83.3)	7/9 (77.8)	3/6 (50.0)
Streptococcus anginosus group	28/33 (84.8)	40/45 (88.9)	29/33 (87.9)	42/45 (93.3)	25/33 (75.8)	38/45 (84.4)
Enterococcus faecalis	11/13 (84.6)	10/12 (83.3)	10/13 (76.9)	8/12 (66.7)	8/13 (61.5)	9/12 (75.0)

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* Early clinical response defined as a composite of the cessation of spread or reduction in size of baseline lesion, absence of fever and no rescue antibacterial drug at 48-72 hours.
† Patients achieving a 20% or greater reduction in lesion area from baseline at 48-72 hours after initiation of therapy.
‡ Clinical success was defined if the patient experienced a complete or nearly complete resolution of baseline signs and symptoms as described above.
§ Baseline bacteremia in the oritavancin arm with relevant microorganisms causing ABSSSI included four subjects with MSSA and seven subjects with MRSA. Eight of these eleven subjects were responders at 48 to 72 hours after initiation of therapy.