Oritavancin (Orbactiv)

National Drug Monograph

June 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 comprehensive 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 Documents will be placed in the Archive section when the information is deemed to be no longer current.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

Description/Mechanism of Action	Oritavancin is a lipoglycopeptide antibacterial drug that inhibits of the transglycosylation and transpeptidation steps of cell well biosynthesis and disruption of bacterial cell membrane integrity[1]
Indications under review in this document (may include off label)	Oritavancin is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible Gram-positive organisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin–resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group and *Enterococcus faecalis* (vancomycin-susceptible isolates only)[1]
Dosage Form(s) Under Review	Intravenous Powder for Solution, 400mg vial
REMS	☐ REMS ☒ No REMS
Pregnancy Rating	Pregnancy Category C

Executive Summary

Efficacy	• The FDA approval of oritavancin was based on two pivotal Phase 3 non-inferiority trials (SOLO I and SOLO II), which compared a single dose of oritavancin to 7-10 days of vancomycin in adults with ABSSSI caused by Gram-positive bacteria.[2,3] • The primary efficacy endpoint for these trials was early clinical response at 48-72 hours. Results from the SOLO trials demonstrated oritavancin was non-inferior to vancomycin for treatment of ABSSSI.
Safety	• The most common adverse effects (≥2%) include nausea, headache, vomiting, cellulitis, diarrhea, constipation, infusion site extravasation, pyrexia, pruritus, ALT elevation, abscess, dizziness, infusion site phlebitis, tachycardia, insomnia.[1-3] • The use of unfractionated heparin sodium is contraindicated for 48 hours after oritavancin administration due to artificial prolongation of aPTT. PT/INR may be falsely elevated for up to 24 hours. Oritavancin has no effect on the coagulation system.[1] • Additional warnings and precautions state there is a potential increased risk of bleeding with concomitant use of warfarin due to increased warfarin exposure. Also, more cases of osteomyelitis were reported in the oritavancin-treated arm than in the vancomycin-treated arm during Phase 3 trials. If osteomyelitis is suspected or diagnosed, alternative antibacterial therapy should be initiated.
Potential Impact	• Current IDSA guidelines for the treatment of skin and soft tissue infections were updated in June 2014, approximately two months prior to FDA approval of oritavancin. These guidelines recommend vancomycin, daptomycin, linezolid, televancin, or ceftaroline as empiric therapy for treatment of ABSSSI in addition to incision and drainage.[4] • Oritavancin is indicated for the treatment of ABSSSI. The prolonged half-life of oritavancin allows for ABSSSI treatment with a single dose infused over 3 hours.[1]

Background

Purpose for review

The purpose of the review is to evaluate the efficacy and safety of oritavancin.
- ✔ Evidence of need
- ✔ Does oritavancin offer advantages to currently available alternatives?
- ✔ What safety issues need to be considered?

Other IV MRSA options

Formulary Alternatives	Other Considerations in Adults[4-7]
Ceftaroline	• Availability: IV • Limited experience with other MRSA infections besides skin and skin structure infections • Pregnancy category B
Daptomycin	• Availability: IV • Possible cross-resistance with vancomycin • Associated with myopathies and CPK monitoring is recommended • Pregnancy category B
Linezolid	• Availability: IV and PO • Long term use limited by hematologic toxicity, peripheral and optic neuropathy and lactic acidosis. • Reversible inhibitor of monoamine oxidase with possible drug interaction with SSRIs. • Pregnancy category C
Vancomycin	• Availability: IV • Requires monitoring of levels and has been shown to kill *Staphylococcus* more slowly than β-lactams • Associated with nephrotoxicity and Redman syndrome • Pregnancy category C

Please refer to PBM Recommendations for Newer Gram-Positive Agents for more details including information on tedizolid, telavancin, and tigecycline.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to May 2015) using the search terms oritavancin and Orbactiv. The search was limited to randomized, controlled studies performed in humans and published in the English language. From this search, two identically-designed Phase 3 studies evaluating the safety and efficacy of oritavancin for acute bacterial skin and skin structure infections (ABSSSIs) were identified and included in this review.

Review of Efficacy

The FDA approval of oritavancin was based on two pivotal Phase 3 randomized, double-blind, multicenter, multinational, non-inferiority clinical trials (SOLO I and SOLO II).[2,3] These trials were identically designed to demonstrate non-inferior efficacy of oritavancin compared to vancomycin in adults with ABSSSIs caused by Gram-positive pathogens.

Patients were randomized 1:1 to receive either a single dose of oritavancin IV 1200mg on Day 1 followed by twice daily infusions of placebo or vancomycin IV 1gm or 15mg/kg every 12 hours on day 1.[2,3] After day 1, the vancomycin dose could be adjusted by the unblinded pharmacist/designee based on estimated creatinine clearance, clinical status, and/or vancomycin trough plasma concentrations (target trough 10 to 15 ug/mL or defined by study sites' standard of care). The duration of treatment for each group was 7-10 days. Patients were enrolled into the study based on the following inclusion and exclusion criteria:

Inclusion Criteria[2,3]

- Adults (age >18 years) with traumatic and surgical wounds infections (onset within 7 days prior to randomization and no later than 30 days following trauma or procedure); cellulitis/erysipelas (onset within 7 days prior to randomization); and major cutaneous abscesses, with minimum surface area of 75cm^2
  - Suspected or known to be caused by Gram-positive pathogen
  - Requiring at least 7 days of IV therapy
- At least 2 signs/symptoms of local infection AND ≥ 1 sign of systemic inflammation as follows*:
  - Local: Purulent drainage or discharge, erythema, fluctuance, heat or localized warmth, edema/induration, pain or tenderness to palpation
  - Systemic: Proximal lymph node swelling and tenderness, increased temperature (>38°C), decreased temperature (<36°C), increased WBC (>10,000 cells/μL), bandemia >10%, C-reactive protein (CRP)> upper limit of normal reference range (ULN)

*If patient did not have any of the above systemic signs of inflammation, he/she could be included if any of the following conditions were met:

- Age >70 years, Diabetes Mellitus requiring oral or subcutaneous antidiabetic therapy, treatment with immunosuppressive therapy or chemotherapy in the prior 3 months

Exclusion Criteria[2,3]

- ABSSSI, from or associated with, any of the following:
  - Gram-negative pathogens; diabetic foot infections; decubitus/chronic skin ulcers; infected burns; concomitant infection at another site not including a secondary ABSSSI lesion (e.g., septic arthritis, endocarditis, osteomyelitis); infections caused by a Gram-positive organism with a vancomycin MIC >2 μg/mL or clinically failing prior therapy with glycopeptides
- Prior systemic or topical antimicrobial therapy with activity against suspected or proven Gram-positive pathogens within 14 days of randomization unless:
  - The causative Gram-positive pathogen(s) isolated from the ABSSSI site demonstrated in vitro resistance to the antimicrobial with documented clinical worsening; documented failure to previous ABSSSI antibiotic therapy was available; patient received a single dose of a short-acting antimicrobial within 72 hours of randomization (e.g., surgical prophylaxis)
- Infections associated with, or in close proximity to, a prosthetic device
- Severe sepsis or refractory shock
- Known or suspected bacteremia at time of screening

The primary endpoint in the SOLO studies was early clinical response (ECE) at 48 to 72 hours from initiation of first infusion of study drug.[2,3] Early clinical response was a composite endpoint of cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication. The key secondary endpoints were: 1) lesion size reduction ≥20% at ECE and 2) investigator-assessed sustained clinical response at post-therapy evaluation (PTE) at day 14-24 (7-14 days after the end of therapy). Sustained clinical response was defined as complete or nearly complete resolution of baseline signs or symptoms related to the primary ABSSSI site (erythema, induration/edema, purulent drainage, fluctuance, pain, tenderness, local increase in heat/warmth) such that no further treatment with antibiotics was needed. The primary and secondary endpoints were evaluated in the modified intention-to-treat (mITT) study population, which included all patients who underwent randomization and received study drug. An additional secondary outcome evaluated was clinical response (as defined above) by pathogen at early clinical evaluation and post-therapy evaluation. This endpoint analysis was performed in the microbiologic intention-to-treat (microITT) population, which included all patients in the mITT population with baseline Gram-positive pathogen known to cause ABSSSIs.

Patient demographics and baseline characteristics were balanced between the treatment groups (See Table A).[2,3,8] The mean age was 45 years. Approximately 64% of patients were Caucasians and 65% were males. Across both trials, roughly 60% of patients were enrolled from the United States and 27% of patients were from Asia. The types of ABSSSIs across both trials included cellulitis/erysipelas (40%), major cutaneous abscess (31%), and wound infection (29%). The medium infection area across both trials was 266.6cm^2. Incision and drainage was performed in roughly 34.5% of patients across both trials. Approximately 17.4% of patients met systemic inflammatory response syndrome (SIRS) criteria and 2.4% of patients were bacteremic.

Table A. Baseline Characteristics in SOLO I and SOLO II (mITT population)[2,3,8]		
	SOLO I	**SOLO II**

	Oritavancin (n=475)	Vancomycin (n=479)	Oritavancin (n=503)	Vancomycin (n=502)
Mean age (years)	46.2	44.3	45	44.4
Male, n (%)	301 (63.4)	301 (62.8)	338 (67.2)	343 (68.3)
Race, n (%) • White • Black • Asian • Other	 274 (57.7) 43 (9.1) 153 (32.2) 5 (1.1)	 275 (57.4) 40 (8.4) 154 (32.2) 10 (2.1)	 356 (70.8) 14 (2.8) 122 (24.3) 11 (2.2)	 356 (70.9) 17 (3.4) 122 (24.3) 7 (1.4)
ABSSSI Category, n (%) • Cellulitis/erysipelas • Major cutaneous abscess • Wound infection	 241 (51) 140 (29.6) 92 (19.5)	 235 (48.9) 141 (29.3) 105 (21.8)	 144 (29) 168 (33) 191 (38)	 167 (33) 159 (32) 176 (35)
Incision and drainage, n (%)	171 (36.2)	168 (34.9)	173 (34.4)	163 (32.5)
Median lesion size (cm^2)	248	225.6	287.8	308.8
SIRS, n (%)	73 (15.4)	73 (15.2)	95 (18.9)	101 (20.1)
Temperature ≥38°C, n (%)	67 (14.2)	80 (16.6)	118 (23.5)	106 (21.2)
WBC > 12,000 cells/μL, n (%)	104 (24)	85 (19.8)	112 (24.7)	125 (27.8)
Bacteremia	18 (3.8)	9 (1.9)	10 (2)	10 (2)

SIRS: Systemic Inflammatory Response Syndrome

Table B. Primary and Key Secondary Efficacy Endpoints[2,3,8]

	Oritavancin	Vancomycin	Absolute Difference (95% CI)
Primary Efficacy Endpoint: Early clinical response at 48-72 hours (performed in mITT population)			
SOLO I	391/475 (82.3%)	378/479 (78.9%)	3.4 (-1.6, 8.4)
SOLO II	403/503 (80.1%)	416/502 (82.9%)	-2.8 (-7.5, 2)
Key Secondary Efficacy Endpoint: ≥ 20% reduction in lesion area from baseline at 48-72 hours (performed in mITT population)			
SOLO I	413/475 (86.9%)	397/479 (82.9%)	4.1 (-0.5, 8.6)
SOLO II	432/503 (85.9%)	428/502 (85.3%)	0.6 (-3.7, 5)
Key Secondary Efficacy Endpoint: Sustained clinical response at post-therapy evaluation (performed in mITT population)			
SOLO I	379/475 (79.6%)	383/479 (80%)	0.4 (-5.5, 4.7)
SOLO II	416/503 (82.7%)	404/502 (80.5%)	2.2 (-2.6, 7)

Overall quality of evidence: High (Refer to Appendix A); please note that all trials were funded by the manufacturer.

Table C. Efficacy Endpoints by Baseline Pathogen (microITT)[1]

	At 48-72 hours				Study Day 14-24	
	Early Clinical Responder		≥20% reduction in lesion size		Clinical Success	
Pathogen	oritavancin	vancomycin	oritavancin	vancomycin	oritavancin	vancomycin
Staph aureus	388/472 (82.2%)	395/473 (83.5%)	421/472 (89.2%)	407/473 (86%)	390/472 (82.6%)	398/473 (84.1%)
MRSA	166/204 (81.4%)	162/201 (80.6%)	190/204 (93.1%)	175/201 (87.1%)	170/204 (83.3%)	169/201 (84.1%)
MSSA	222/268 (82.8%)	233/272 (85.7%)	231/268 (86.2%)	232/272 (85.3%)	220/268 (82.1%)	229/272 (84.2%)
Strep pyogenes	21/31 (67.7%)	25/32 (71.9%)	24/31 (77.4%)	24/32 (75%)	25/31 (80.6%)	23/32 (71.9%)

Summary of Efficacy

- In both SOLO I and SOLO II, oritavancin demonstrated non-inferior efficacy to vancomycin for the primary efficacy endpoint (early clinical response) and key secondary endpoints (≥20% reduction in lesion area from baseline at ECE and sustained clinical response at PTE).
- Across both SOLO trials, oritavancin demonstrated non-inferior early efficacy and sustained efficacy compared to vancomycin for patients with *S. aureus*.

Potential Off-Label Use

- Treatment of gram-positive infections other than ABSSSIs

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

	Comments
Boxed Warning	• None
Contraindications	• **Intravenous Unfractionated Heparin Sodium** – Use of intravenous unfractionated heparin sodium is contraindicated for 48 hours after oritavancin administration because the activated partial thromboplastin time (aPTT) test results are expected to remain falsely elevated for approximately 48 hours after oritavancin administration • **Hypersensitivity** – oritavancin is contraindicated in patients with known hypersensitivity to oritavancin
Warnings/Precautions	• **Potential Risk of Bleeding with Concomitant Use of Warfarin** – May result in higher exposure of warfarin, which may increase risk of bleeding. Use oritavancin in patients on chronic warfarin therapy only when benefits are expected to outweigh the risks. Monitor for signs and symptoms of bleeding frequently. • **Coagulation Test Interference –** *See Drug Interactions* Section for details. • **Hypersensitivity** – Serious hypersensitivity reactions have been reported. If an acute hypersensitivity reaction occurs during infusion, discontinue oritavancin immediately and institute appropriate supportive care. Due to possibility of cross-sensitivity with glycopeptides, carefully inquire about previous hypersensitivity reactions to glycopeptides. • **Infusion Related Reactions** – Infusion related reactions have been reported, including pruritis, urticarial, or flushing. If reactions do occur, consider slowing or interrupting oritavancin infusion. • ***Clostridium difficile*-associated Diarrhea (CDAD)** – CDAD has been reported for all systemic antibacterial drugs, including oritavancin, and may range in severity from mild diarrhea to fatal colitis. • **Osteomyelitis** – In Phase 3 ABSSSI clinical trials, more cases of osteomyelitis were reported in the oritavancin-treated arm than in the vancomycin-treated arm. If osteomyelitis is suspected or diagnosed, institute appropriate alternative antibacterial therapy. • **Development of Drug Resistant Bacteria** – Use of oritavancin in absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases risk of development of drug resistance.

Safety Considerations

The safety of oritavancin was evaluated in 23 clinical studies and included 703 subjects in phase I, 481 subjects in phase 2, and 3722 subjects in phase 3 clinical trials.[8,9] The Phase 3 SOLO trials were the first to utilize a single 1200 mg dose. The data from 1959 patients included in these Phase 3 trials are outlined below.[2,3,8] Please note that adverse events were defined as events with an onset or worsening severity at the time of or after the administration of the first dose of the study drug through the safety follow-up visit on day 60.[2,3]

- Overall, adverse events were reported in fewer patients treated with oritavancin than in those treated with vancomycin in the SOLO trials.[8,9]
    - 55.3% (n=539) of patients treated with oritavancin reported an adverse event compared to 56.9% (n=559) of patients treated with vancomycin. The majority of adverse events were classified as mild.
- The incidence of hypersensitivity was lower in the oritavancin group compared to the vancomycin group in the SOLO trials.[8]
    - 12.2% (n=119) of patients treated with oritavancin reported a hypersensitivity event compared to 18.7% (n=184) of patients treated with vancomycin. Six (0.61%) of these hypersensitivity reactions in the oritavancin group led to discontinuation compared to 14 (1.42%) hypersensitivity reactions in the vancomycin group.
    - The median time to onset of hypersensitivity was 2.2 days (range, 0 to 29 days) and 0.6 days

(range, 0 to 63 days) in the oritavancin and vancomycin groups, respectively.
    - The median duration of hypersensitivity was 2.4 days (range, 0 to 55 days) and 1.5 days (range, 0-69 days) in the oritavancin and vancomycin groups, respectively.
- In the SOLO trials, infusion site reactions occurred with similar frequencies in the oritavancin and vancomycin groups.[8]
    - Infusion site-related reactions were observed in 10% (n=99) of patients treated with oritavancin and 11% (n=109) of patients treated with vancomycin.
    - No oritavancin-treated patients developed red man syndrome compared to 2 vancomycin-treated patients.
    - The median time to onset of infusion site reactions/phlebitis was 3.1 days in both groups.
    - The median duration of infusion site reactions/phlebitis was 2 days (range, 0 to 25 days) and 1.9 days (range, 0 to 512 days) in the oritavancin and vancomycin groups, respectively.
- A 60 day follow up did not reveal prolonged or delayed adverse effects associated with the extended half-life of oritavancin.[2,3,8]

Adverse Reactions

Common adverse reactions[1]	• **Incidence ≥5%:** headache, nausea • **Incidence 1.5 – 5%:** diarrhea, vomiting, dizziness, infusion site phlebitis, abscess (limb and subcutaneous), ALT and AST increased, tachycardia, infusion site reaction
Death/Serious adverse reactions[8,9]	• Serious AE occurred in 5.8% (n=57) of patients treated with oritavancin vs. 5.9% (n=58) of patients treated with vancomycin in Phase 3 trials. • Five deaths occurred during the Phase 3 studies: 0.2% (n=2) with oritavancin vs. 0.3% (n=3) with vancomycin; none of the deaths were related to oritavancin or vancomycin.
Discontinuations due to adverse reactions[8]	• Discontinuation due to AE occurred in 3.4% (n=33) of patients treated with oritavancin vs. 3.3% (n=32) of patients treated with vancomycin in Phase 3 trials. There were 8 patients (0.8%) in the oritavancin arm and 19 patients (1.9%) in the vancomycin arm who had an AE which led to treatment discontinuation related to study drug.
Laboratory abnormalities[8,9]	• In phase 3 trials, 1.8% (n=18) of patients in the oritavancin group had ALT elevations from baseline to 3-5 times the ULN compared to 1.4% (n=14) in the vancomycin group

Drug Interactions

Drug-Drug Interactions

- Oritavancin is a non-specific, weak inhibitor of CYP2C9, CYP2C19 and weak inducer of CYP3A4, CYP2D6.[1,8,9]
- Results from drug-drug interaction study in healthy subjects demonstrated a 30% increase in the mean AUC of warfarin (CYP2C9 substrate) when administered concomitantly with oritavancin.[8,9] Due to the interaction between oritavancin and warfarin, there may be an increased risk for bleeding. Patients should be monitored for bleeding if concomitantly receiving oritavancin and warfarin.[1,8,9]
- Caution should be used during concomitant administration of oritavancin and drugs with narrow therapeutic windows predominantly metabolized by one of the affected CYP450 enzymes (e.g., warfarin).[1,8,9] Oritavancin may increase the concentration of drugs metabolized by CYP2C9 and CYP2C19 and decrease the concentrations of drugs metabolized by CYP3A4 and CYP2D6. Patients should be monitored for signs of toxicity or lack of efficacy during concomitant administration.

Drug-Lab Interactions

- Oritavancin has been shown to artificially prolong aPTT for 48 hours and PT/INR for up to 24 hours by binding to and preventing action of phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests.[1,8,9] Similar effects by oritavancin on ACT are expected since this laboratory coagulation test utilizes phospholipids as well. Oritavancin has no effect on the coagulation system.

Risk Evaluation

Sentinel event advisories	• None
Look-alike/sound-alike error potentials	• Sources: Based on clinical judgement and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgement
Oritavancin	None	None	None	Dalbavancin, Telavancin
Orbactiv	None	None	None	Vibativ, Factive, Rectiv, Zorbtive

Other Considerations

Pharmacokinetics[1,8]

Parameter	Oritavancin
Cmax	138 mg/L
Clearance	0.445 L/hour
AUC_{0-24}	1110 mg·hr/L
$T_{1/2}$ (terminal)	245 hours
Protein Binding	85%
Metabolism	Not metabolized
Elimination	Feces (<1%) and urine (5% unchanged oritavancin)

Microbiology

Surveillance data have evaluated the MIC_{50} and MIC_{90} of oritavancin and other antibiotics against Gram-Positive Agents collected in the United States (See Table D).[10]

Table D. In Vitro Activity of Oritavancin and other Agents Reported in a Surveillance Study (US Institutions)

Organism	Drug Name	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)
MSSA (n=2853)	oritavancin	0.03	0.06
	vancomycin	1	1
	linezolid	1	2
	daptomycin	0.25	0.5
MRSA (n=2874)	oritavancin	0.03	0.06
	vancomycin	1	1
	linezolid	1	1
	daptomycin	0.25	0.5
Coagulase negative staphylococci (n=188)	oritavancin	0.015	0.06
	vancomycin	1	2
	linezolid	0.5	1
	daptomycin	0.25	0.5
Streptococcus pyogenes (n=430)	oritavancin	0.03	0.12
	vancomycin	0.25	0.5
	linezolid	1	1
	daptomycin	≤0.06	≤0.06
Streptococcus agalactiae (n=242)	oritavancin	0.03	0.12
	vancomycin	0.5	0.5
	linezolid	1	1
	daptomycin	0.25	0.25
Viridans group *Streptococci*	oritavancin	≤0.008	0.015
	vancomycin	0.5	1
	linezolid	1	1
	daptomycin	0.25	0.5

Enterococcus faecalis (n=272)	oritavancin vancomycin linezolid daptomycin	0.015 1 1 1	0.06 2 2 2
Enterococcus faecium, Vancomycin-Resistant (n=70)	oritavancin vancomycin linezolid daptomycin	0.06 >16 1 2	0.12 >16 1 2

Dosing and Administration[1]

The recommended dosing for oritavancin is a single 1200 mg dose administered by intravenous infusion over 3 hours in patients 18 years and older.

Special Populations (Adults)[1]

Elderly	• Clinical studies of oritavancin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.
Pregnancy	• Pregnancy Category C.
Lactation	• Oritavancin is excreted in the breast milk of rats. It is not known whether oritavancin is excreted in human milk. Caution should be exercised when oritavancin is administered to a nursing woman.
Renal Impairment	• No dosage adjustment is needed in patients with mild or moderate renal impairment. The pharmacokinetics of oritavancin in severe renal impairment have not been evaluated. Oritavancin is not removed from blood by hemodialysis.
Hepatic Impairment	• No dosage adjustment is needed in patients with mild or moderate hepatic impairment. The pharmacokinetics of oritavancin in severe hepatic insufficiency have not been studied.
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy

- The CDC estimates that MRSA caused 80,461 invasive infections and 11,285 deaths in 2011.[11]
- The Infectious Diseases Society of America (IDSA) Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections and IDSA Practice Guidelines for the Management of Patients with Infections caused by MRSA are currently the only two national clinical practice guidelines that discuss MRSA ABSSSIs (FDA labeled indication for oritavancin) and both were published prior to the approval of oritavancin.[4,5]
    - The IDSA Clinical Practice Guidelines for the Management of MRSA Infections recommend clindamycin (A-II), trimethoprim-sulfamethoxazole (A-II), a tetracycline (A-II), and linezolid (A-II) for empirical coverage of community-acquired MRSA in outpatients for the management of skin and soft-tissue infections.[5] IV options for complicated skin and soft-tissue infections requiring hospitalization due to MRSA include vancomycin (A-I), oral or IV linezolid (A-I), daptomycin (A-I), telavancin (A-I), and clindamycin IV or oral (A-III).
    - The IDSA Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections lists vancomycin, linezolid, clindamycin, daptomycin, ceftaroline, doxycycline/minocycline, and trimethoprim/sulfamethoxazole as antimicrobial treatment options for MRSA.[4]
    - Treatment duration discussed in available guidelines varies from 5 – 14 days depending on guideline and severity of infection.[4,5] Additional agents with FDA labeled indications for MRSA ABSSSIs not included in the guidelines include recently approved tedizolid phosphate and dalbavancin.
- Phase 3 clinical studies demonstrated non-inferiority of a single dose of oritavancin vs 7-10 days of vancomycin (FDA approved duration) for treatment of ABSSSI.[2,3] Oritavancin's prolonged half-life allows for unique dosage regimen that may facilitate parenteral administered therapy for ABSSSI in the emergency department or outpatient setting; however, the impact of this prolonged half-life on adverse events needs further surveillance during clinical use.

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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.