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# Oritavancin for Adults with Acute Bacterial Skin and Skin Structure Infections

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Skin and skin-structure infections cause more than 15 million infections and account for 870,000 hospital admissions a year in the United States.[1] Acute bacterial skin and skin structure infections (ABSSSIs) are primarily caused by gram-positive pathogens including *Staphylococcus aureus*, which accounts for the vast majority of these infections. Other causative gram-positive pathogens are *Streptococcus pyogenes* and less frequently, *Enterococcus faecalis*.[2] Rates of these infections have been on the rise in the last 10 to 20 years due, in part, to the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA).[1] With the increasing incidence of infections due to antibiotic-resistant pathogens, new antimicrobial agents continue to be explored in order to establish dosing regimens that maximize benefits of therapy while containing the spread of resistance.[2]

Available treatment regimens for ABSSSIs due to presumed or confirmed gram-positive pathogens range from once daily dosing with daptomycin or telavancin for 7 to 14 days, to twice daily dosing with linezolid for 10 to 14 days, and intravenous (IV) vancomycin for 7 to 14 days, the latter of which must be frequently monitored for therapeutic drug levels.[2] Not surprisingly, the economic burden of ABSSSIs is quite substantial as it is driven by high hospitalization costs and by multiple days of dosing with the current agents. This economic burden is not overcome with the use of available treatment regimens in the outpatient setting. Furthermore, outpatient antibiotic use has its own disadvantages including the burden of multiple administrations, incomplete adherence to medication regimens, and the complexity of monitoring drug concentrations.[3]

Oritavancin is a novel, intravenous, semi-synthetic, lipoglycopeptide that has multiple mechanisms of action that result in concentration-dependent bactericidal activity, even against pathogens resistant to vancomycin.[3] The pharmacokinetic and pharmacodynamic profiles of oritavancin are unique and suggest that oritavancin can be given in a single dose, since the drug exhibits a prolonged terminal half-life.[2,3] The efficacy of a single dose regimen of oritavancin was confirmed in phase 2 and phase 3 trials leading to oritavancin becoming the first single-dose antibacterial agent granted an approved indication by the U.S. FDA in August 2014 for the treatment of ABSSSIs caused by susceptible gram-positive pathogens including both methicillin-susceptible *S. aureus* (MSSA) and MRSA, various *Streptococcus* species, and *Enterococcus faecalis*.[4] The single-dose regimen provided by oritavancin offers many theoretical advantages in the outpatient treatment of ABSSSIs and potentially provides an opportunity for effective and safe treatment with reduced costs of care.[5]

The purpose of this article is to review the pharmacology, efficacy, dosing and administration, and adverse events associated with oritavancin for the treatment of ABSSSIs caused by susceptible gram-positive pathogens.

**IN THIS ISSUE**



## Pharmacology

### *Mechanism of Action*

Oritavancin is a semi-synthetic, lipoglycopeptide antibacterial drug that has three mechanisms of action. First, like other glycopeptides (i.e., vancomycin), oritavancin disrupts bacterial cell wall synthesis by binding to the stem peptide of peptidoglycan precursors and inhibiting transglycosylation, the polymerization step of cell wall synthesis. Secondly, unlike vancomycin, oritavancin has a secondary binding site conferring activity against vancomycin-resistant strains and allowing the inhibition of transpeptidation, the crosslinking step of cell wall biosynthesis. Finally, oritavancin contains a hydrophobic group that can disrupt bacterial cell membrane activity and lead to cell death.[4,6,7]

### *Pharmacokinetics*

The pharmacokinetic properties of oritavancin are summarized in Table 1. Oritavancin is moderately (85%) bound to plasma proteins and has a volume of distribution of approximately 87.6 L, meaning that it is well distributed into tissues. In fact, concentration of oritavancin in skin blister fluid was evaluated in male volunteers, where the mean concentration of oritavancin was 1.5

**Table 1 | Pharmacokinetics of oritavancin.[4,6]**

| Characteristic | Oritavancin |
|---|---|
| **Protein Binding** | 85% |
| **Volume of Distribution** | 87.6 L |
| **Metabolism** | Not metabolized |
| **Half-life elimination** | 245 hours |
| **Excretion** | Unchanged in feces and urine |
| **$C_{max}$**[a] | 138 mcg/mL |
| **$AUC_{(0-\infty)}$**[a] | 2800 mcgh/mL |

**$C_{max}$** = maximum concentration; **AUC** = area under the curve.
[a]After a single 1200 mg dose for ABSSSI.

to 3-fold higher than the $MIC_{90}$ for *S.aureus* (2 mcg/mL) at 24 hours after administration of oritavancin administered as 200 mg once daily for 3 days, or a single dose of 800 mg.[4] A population-predicted concentration-time profile of oritavancin showed a long terminal half-life of about 245 hours.[6] Population pharmacokinetic analyses demonstrated a clearance of 0.445 L/h.[6]

The drug is not metabolized prior to excretion but it is a non-specific, weak inhibitor of CYP2C9 and CYP2C19 and a weak inducer of CYP3A4 and CYP2D6. In humans, oritavancin is slowly excreted unchanged in urine and feces; after two weeks, <5% is recovered in urine and <1% in feces.[4,6]

*Spectrum of Activity*

Oritavancin is approved for the treatment of ABSSSIs caused by susceptible isolates of the following organisms: *S. aureus* (including MSSA and MRSA), *S. pyogenes*, *Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus group* (includes *S. anginosus, S. intermedius*, and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only). Oritavancin may be used to treat vancomycin-susceptible *Enteroccus faecium* but the safety and efficacy of the drug in treating these infections has not been examined in well-controlled trials. Serial passage studies showed resistance to oritavancin in *S. aureus* and *E. faecalis* isolates, but resistance has not been seen in clinical trials.[6]

## Clinical Trials

**Table 2** provides a summary of SIMPLIFI, SOLO I, and SOLO II, three clinical trials that played an integral role in oritavancin receiving an FDA-approved indication for treatment of ABSSSIs. In two early randomized, double-blind phase III studies, the efficacy of 3-7 days of treatment with oritavancin 180-330 mg/day was compared to treatment with 10-14 days of IV vancomycin followed by oral cephalexin in patients with complicated skin and skin structure infections.[2,4] Follow-up occurred after 21-35 days and oritavancin was found to be noninferior to the comparator with clinical cure achieved in 597 of 768 patients (77.7%) receiving oritavancin versus 347 of 458 patients (75.8%) in the vancomycin group.

These trials were followed by SIMPLIFI, a phase II, multicenter, randomized, double-blind, parallel, active-comparator, controlled study designed to evaluate noninferiority of two front-loaded treatment regimens: 1) a single 1200 mg dose, and 2) a dose of 800 mg on day 1 followed by an optional 400 mg on day 5 as determined by a blinded investigator based on clinical criteria, compared to oritavancin 200 mg administered for 3-7 days.[2] The primary objective of this study was to determine the clinical response of each treatment regimen in the clinically evaluable and intention-to-treat (ITT) populations at test of cure, which occurred on days 21-29. Clinical response at test of cure in the clinically evaluable population was 72.4% (55/76) in the daily-dose group, 81.5% (66/81) in the 1200-mg single-dose group, and 77.5% (55/71) in the infrequent-dose group. The difference in cure rates between the single- and daily-dose groups was 8.6% (90% CI = -2.5 to 18.2), and the difference in cure rates between the infrequent- and daily-dose groups was 5.2% (90% CI = -6.8 to 15.4). Thus, the single-dose and infrequent-dose regimens were found to be non-inferior to the daily-dose regimen. While no patients relapsed in the daily-dose group, 1/61 (1.6%) relapsed in the single-dose group, and 2/54 (3.7%) relapsed in the infrequent-dose group. Cure rates by disease category were comparable in each group for patients with wound infections and major abscesses. For patients with cellulitis, cure rates were similar in the infrequent- and daily-dose groups. However, there was a 29.2% (90% CI, 9.2 to 49.1) higher cure rate for patients with cellulitis in the 1200 mg single-dose group (87.5% [21/24]) compared to patients in the daily-dose group (58.3% [14/24]). Additionally, cure rates for patients with *S. aureus* (including both MSSA and MRSA) at baseline were 67.4% (31/46), 78.9% (45/57), and 79.5% (31/39) for the daily-dose, 1,200-mg-single-dose, and infrequent-dose groups, respectively; for patients with MRSA at baseline, cure rates were 78.3% (18/23), 73% (27/37), and 87% (20/23), respectively. It is important to keep in mind that the study was not powered to assess outcomes in these subpopulations and due to heterogeneity of the types of infections and small population size, it is difficult to determine whether differences in cure rates for these pathogens represent any true differences.[2]

SOLO I was an international, randomized, double-blind study designed to compare the safety and efficacy of a single IV dose of 1200 mg of oritavancin to a regimen of IV vancomycin (1 g, or 15 mg/kg of body weight) administered every 12 hours for 7 -10 days in adults with acute bacterial skin and skin-structure infections.[3] The modified ITT population had 475 patients in the oritavancin group and 479 in the vancomycin group. The primary efficacy endpoint of this study was a composite outcome based on the early clinical evaluation which occurred 48-72 hours after initiation of the study treatment. This endpoint comprised the cessation of spreading or reduction in size of the lesion, absence of fever, or absence of the need for rescue antibiotics. There were two secondary endpoints: 1) clinical cure as assessed by the study investigator during the post-therapy evaluation that occurred day 7 to day 10, and 2) decrease in lesion area of 20% or more from baseline at the 48-72 hour evaluation. The mean age of the patients was 45 years. Demographic, clinical characteristics, and infection types were well balanced between groups. At least one pathogen was isolated at baseline from 60% of patient in each group; 96% of these patients had a gram-positive pathogen known to cause ABSSSI's. *Staphylococcus aureus* was the most common pathogen and MRSA was isolated from 204 patients.

The single dose of oritavancin had similar efficacy compared to vancomycin. The primary endpoint was achieved by 82.3% of patients treated with oritavancin versus 78.9% of patients treated with vancomycin, for a between-group difference of 3.4% (95% CI -1.6 to 8.4). With regard to secondary endpoints, clinical cure was achieved by 79.6% in the oritavancin treatment arm compared to 80% in the vancomycin treatment arm (between-group difference, 0.4%; CI -5.5 to 4.7). A reduction in lesion size by at least 20% was achieved by 86.9% and 82.9% of patients in each arm, respectively (between-group difference, 4%; 95% CI -0.5 to 8.6).

Both groups also had a similar incidence of treatment failure: 11.6% in the oritavancin group and 12.7% in the vancomycin group. For the majority of these patients (98.3%), treatment failure was due to patients not undergoing post-therapy evaluation. Additionally, in the subpopulation of patients with MRSA cultured at baseline, similar efficacy was observed in both groups. It is essential to note that the mean and median vancomycin concentrations in patients with a measurable trough were 15.4 mcg/mL and 11.1 mcg per mL, respectively.

SOLO II was a phase 3, global, multi-center, randomized, double-blind comparative efficacy and safety study also evaluating a single dose of IV oritavancin versus 7 to 10 days of vancomycin in adults with ABSSSI including wound infection, cellulitis, and major cutaneous abscess.[8] This study was similar in design to SO-

**TABLE 2 | Summary of oritavancin phase 2 and 3 clinical trials.**[2,3,8]

| Study | Treatment Arms | Primary Endpoints | Results | Conclusions |
|---|---|---|---|---|
| **SIMPLIFI**[2] | • Oritavancin single dose: 1200 mg IV on day 1 (n=99)<br>• Oritavancin infrequent dose: 800 mg IV on day 1 with an optional 400 mg on day 5 (n=103)<br>• Oritavancin daily dose: 200 mg IV daily for 3 to 7 days (n=100) | Clinical response rate at test of cure on days 21-29 | Clinical cure rates:<br>• Single dose: **81.5%**<br>• Infrequent dose: **77.5%**<br>• Daily dose: **72.4%**<br><br>Difference in cure rates:<br>• Single vs. daily dose groups: 8.6% (90% CI -2.5 to 18.2)<br>• Infrequent vs. daily dose groups: 5.2% (90% CI -6.8 to 15.4) | Single and infrequent dosing of oritavancin were as efficacious as daily administration |
| **SOLO I**[3] | • Oritavancin single IV dose of 1200 mg (n= 475)<br>• Vancomycin 1 g or 15 mg/kg of body weight every 12 hours for 7 to 10 days (n= 479) | Composite endpoint (cessation of spreading or reduction in lesion size; absence of fever; no need for rescue antibiotic) at 48-72 hours after study drug initiation | Primary outcome rate:<br>• **82.3%** with oritavancin<br>• **78.9%** with vancomycin<br><br>Difference in primary endpoint:<br>• 3.4% (95% CI -1.6 to 8.4) | Single dose oritavancin was non-inferior to twice-daily vancomycin x7-10 days for the treatment of Gram (+) ABSSSIs |
| **SOLO II**[8] | • Oritavancin single IV dose of 1200 mg (n= 503)<br>• Vancomycin 1 g or 15 mg/kg of body weight every 12 hours for 7 to 10 days (n= 502) | Composite endpoint (cessation of spreading or reduction in lesion size; absence of fever; no need for rescue antibiotic) at 48-72 hours after study drug initiation | Primary outcome rate:<br>• **80.1%** with oritavancin<br>• **82.9%** with vancomycin | Single dose oritavancin was non-inferior to twice-daily vancomycin x7-10 days for the treatment of Gram (+) ABSSSIs |

**ABSSSIs =** acute bacterial skin and skin structure infections; **IV =** intravenous.

LO I, but there were several differences that primarily center on when clinical evaluations were performed and how these clinical evaluations factor into the primary and secondary endpoints. In SOLO II, the primary endpoint was a composite outcome of the same outcomes as studied in SOLO I: cessation of spreading or reduction in size of the lesion, absence of fever, or absence of the need for rescue antibiotics. The key secondary endpoint in SOLO II was also investigator-assessed clinical cure as in SOLO I; however, instead of clinical cure being assessed at the end of therapy, it was assessed 7-14 days after the end of therapy in SOLO II. The additional secondary endpoint of lesion area decrease by at least 20% at 48-72 hours of treatment was also the same as in SOLO I. The modified ITT population had 503 patients (mean age 45 years) in the oritavancin group and 502 (mean age 44 years) in the vancomycin group. All patients had similar demographic and clinical characteristics and infection types were well balanced between groups. Baseline characteristics for both SOLO I and SOLO II can be found in TABLE 3. In each group, 70% of patients had a pathogen isolated at baseline; 97% of these patients had a gram-positive pathogen known to cause ABSSSI's. *Staphylococcus aureus* was the most common pathogen and MRSA was isolated from 201 patients.

The single dose of oritavancin had similar efficacy compared to vancomycin.[8] The primary composite endpoint was achieved by 80.1% of patients treated with oritavancin versus 82.9% of patients treated with vancomycin. The endpoint of clinical cure was achieved by 82.7% in the oritavancin treatment arm compared to 80.5% in the vancomycin treatment arm. The end-point of reduction in lesion size by at least 20% was achieved by 85.9% and 85.3% in both arms, respectively.

Both groups also had similar treatment failure: 9.9% in the oritavancin group vs 12% in the vancomycin group. For the majority of these patients (99.1%), treatment failure was due to patients not undergoing post-therapy evaluation. Additionally, in the subpopulation of patients with MRSA, similar efficacy was observed in both groups. Of note, mean ± SD and median vancomycin concentrations in patients with a measurable trough were 14.2 ± 12.37 mcg/mL and 10.5 mcg/mL.

Data regarding the use of oritavancin in pediatric patients are not available. However, a phase 1, multicenter, non-randomized, open-label, dose-finding, pharmacokinetics study (NCT02134301) is currently being performed to examine the safety and tolerability of oritavancin in pediatric patients aged <18 years with suspected or confirmed Gram-positive bacterial infections.[9]

## ADVERSE EFFECTS

Adverse events occurring in ≥1.5% of patients receiving oritavancin in a pooled analysis of SOLO I and SOLO II are summarized in TABLE 4. The most commonly reported side effects seen in SIMPLIFI, SOLO I, and SOLO II were nausea, phlebitis, diarrhea, headache, vomiting, constipation, limb and subcutaneous abscesses, and infusion site extravasation.[2,3,6,8] In a pooled analysis of SOLO I and SOLO II, serious adverse events were reported in 5.8% versus 5.9% of patients treated with oritavancin and vancomycin, respectively. The most commonly reported serious adverse event was cellulitis which affected 1.1% in the oritavancin group and 1.2% in the vancomycin arm. Oritavancin was discontinued in 3.7% of patients. The most common adverse reactions leading to discontinuation of the drug was cellulitis occur-

**TABLE 3 | Baseline characteristics of patients in the SOLO I and SOLO II trials according to randomized treatment strategy.[3,8]**

| Characteristic | SOLO I | | SOLO II | |
|---|---|---|---|---|
| | Oritavancin (N=475) | Vancomycin (N=479) | Oritavancin (N=503) | Vancomycin (N=502) |
| **Age, years** | 46.2 (14.2)[a] | 44.3 (14.5)[a] | 45.0 (13.4) | 44.4 (14.3) |
| **Male** | 63.4% | 62.8% | 67.2% | 68.3% |
| **Race** | | | | |
| **White** | 57.7% | 57.4% | 70.8% | 70.9% |
| **Black** | 9.1% | 8.4% | 2.8% | 3.4% |
| **Asian** | 33.2% | 32.2% | 24.3% | 24.3% |
| **Other** | 1.1% | 2.1% | 2.2% | 1.4% |
| **Body Weight, kg** | 81.9 (24.4) | 82.7 (26.5) | 76.2 (20.6) | 78.0 (23.2) |
| **BMI, kg/m$^2$** | 28.7 (8.33) | 28.8 (8.67) | 26.8 (6.74) | 26.8 (7.07) |
| **Infection Type** | | | | |
| **Wound infection** | 19.4% | 21.9% | 38.0% | 35.1% |
| **Confirmed MRSA** | 22.1% | 20.0% | 20.4% | 25.6% |
| **Cellulitis** | 51.2% | 48.6% | 28.6% | 33.3% |
| **Confirmed MRSA** | 19.2% | 23.0% | 8.3% | 10.8% |
| **Abscess** | 29.5% | 29.4% | 33.4% | 31.7% |
| **Confirmed MRSA** | 58.7% | 27.0% | 29.2% | 23.9% |
| **Diabetes mellitus** | 19.6% | 19.8% | 9.1% | 9.0% |
| **Temperature ≥38.0°C** | 14.3% | 16.5% | 23.5% | 21.2% |
| **White Blood Cell count >12,000/mm$^3$** | 24.0% | 19.8% | 24.0% | 19.8% |
| **Lesion area, cm$^3$** | | | | |
| **Median (range)** | 248 (47-3249) | 225.6 (75-3417) | 287.8 (19-4250) | 308.8 (57-2184) |
| **≥75 cm$^3$** | 99.6% | 100.0% | 99.2% | 99.2% |
| **Receipt of permitted medications** | | | | |
| **Aztreonam** | 10.9% | 9.8% | 9.1% | 9.0% |
| **Metronidazole** | 3.2% | 3.5% | 6.4% | 4.4% |
| **Cultures** | | | | |
| **Positive infection-site culture** | 61.1% | 60.5% | 69.8% | 70.1% |
| **Any gram(+) pathogen** | 96.2% | 95.5% | 96.9% | 97.7% |
| ***S. aureus*** | 78.1% | 75.8% | 73.5% | 75.0% |
| **Positive blood cultures** | 3.8% | 1.9% | 2.0% | 2.0% |

Data represent mean (SD) or percent unless otherwise noted.
**BMI =** body mass index; **MRSA =** methicillin-resistant *S. aureus*.
[a]p=0.04 comparing treatment groups.

ring in 0.4% and osteomyelitis occurring in 0.3%.[4,6]

*Contraindications*

Per package insert, the use of IV unfractionated heparin is contraindicated for 48 hours after administering oritavancin since oritavancin can cause false elevation of the activated partial thromboplastin time (aPTT) for ~48 hours. Oritavancin is also contraindicated in patients who have hypersensitivity to the drug.[6]

*Warnings and Precautions*

Administration of oritavancin with warfarin may potentiate the effects of warfarin due to pharmacokinetic interactions (see *Drug-Drug Interactions* below) and increase the risk of bleeding.[6] Additionally, oritavancin can artificially prolong PT and INR for up to 24 hours rendering INR monitoring of the anticoagulation effects of warfarin unreliable for up to 24 hours after administration of oritavancin. For patients who must have aPTT monitoring within 48 hours of oritavancin, use of a non-phospholipid-dependent coagulation test such as the Factor Xa assay is to be considered per the manufacturer.

The development of *Clostridium difficile*-associated diarrhea (CDAD) has been reported for almost all antibacterial agents. If CDAD is suspected or confirmed after use of oritavancin, antibiotics not directed against *C. difficile* may need to be continued and appropriate management of CDAD should be instituted as clinically indicated. Additionally, prescribing oritavancin in the absence of a proven or strongly suspected bacterial infection can increase the risk of bacterial resistance and provide little benefit to the patient.[6]

*Drug-Drug Interactions*

Oritavancin is a nonspecific, weak inhibitor of CYP2C9 and

**TABLE 4 | Adverse reactions occurring in ≥1.5% of patients receiving oritavancin.[6]**

| Adverse Reactions | Oritavancin (N= 976) | Vancomycin (N=983) |
|---|---|---|
| **GI Adverse Effects** | | |
| Diarrhea | 3.7% | 3.4% |
| Nausea | 9.9% | 10.5% |
| Vomiting | 4.6% | 4.7% |
| **CNS Adverse Effects** | | |
| Dizziness | 2.7% | 2.6% |
| Headache | 7.1% | 6.7% |
| **Administration reaction** | | |
| Infusion site phlebitis | 2.5% | 1.5% |
| Infusion site reaction | 1.9% | 3.5% |
| **Infections** | | |
| Abscess | 3.8% | 2.3% |
| **Lab abnormalities** | | |
| ALT increase | 2.8% | 1.5% |
| AST increase | 1.8% | 1.5% |
| **Cardiac disorders** | | |
| Tachycardia | 2.5% | 1.1% |

**ALT =** alanine aminotransferase; **AST =** aspartate aminotransferase; **CNS =** central nervous system; **GI =** gastrointestinal.

CYP2C19 and inducer of CYP3A4 and CYP2D6. *In vitro* studies have shown that oritavancin may also inhibit other CYP450 enzymes such as 1A2 and 2B6. Caution should be used when administering oritavancin with narrow therapeutic index drugs that are metabolized by any of the affected CYP450 enzymes such as midazolam, dextromethorphan, omeprazole, or warfarin just to name a few.[6] In vitro studies demonstrate no antagonism between oritavancin and other antibiotics.[4]

Synergistic bactericidal activity was found when oritavancin was combined with: 1) gentamicin, moxifloxacin, or rifampicin against methicillin-susceptible *S. aureus* (MSSA); 2) gentamicin or linezolid against heterogeneous vancomycin intermediate *S. aureus* (hVISA), VISA, and vancomycin-resistant *S. aureus* (VRSA); and, 3) rifampin against VRSA.[6,10]

## Dosing and Administration

Oritavancin is supplied in a single use 50-mL clear glass vial containing white to off-white lyophilized powder equivalent to 400 mg of oritavancin. The FDA-approved labeling recommends administration of oritavancin as a single, 1200-mg dose over a 3 hour IV infusion in patient's aged ≥18 years.[6] Three of the 400-mg vials of oritavancin must be reconstituted with sterile water and diluted with 5% dextrose in sterile water (D5W), using aseptic technique, to prepare the single 1200 mg dose. Oritavancin should only be diluted with D5W. Normal saline causes precipitation of the drug. Other IV solutions, additives or other medications mixed in normal saline should not be added to the oritavancin vial and should not be administered through the same IV line or port. If the same IV line must be used, the line should be flushed with D5W before and after the oritavancin infusion.[6]

### *Special Populations*

Oritavancin is classified in FDA pregnancy category C. Though animal studies have shown no harm to the fetus, doses in these reproduction studies were equivalent to a human dose of 300 mg, 25% of the recommended single clinical dose of 1200 mg. No adequate or well-controlled trials are available in pregnant women and oritavancin should only be used in pregnant women if the benefits outweigh the risks. Additionally, although it is unknown whether oritavancin is excreted in human breastmilk, a study in rats showed that oritavancin was excreted in milk. Therefore caution should be used when administering this drug to nursing mothers.

Safety and effectiveness in pediatric patients is currently being studied.[9] Phase 3 studies have enrolled a low number (<10%) of patients aged 65 years or older. Thus, clinical experience with this age group is limited and greater sensitivity of older patients to oritavancin cannot be ruled out.[6]

No dosage adjustments are needed in patients with mild-to-moderate renal impairment. Oritavancin has not been studied in patients with severe renal impairment. Additionally, the drug is not removed by hemodialysis.[6] Likewise, no dosage adjustment is needed in mild-to-moderate hepatic impairment. Oritavancin has not been studied in severe hepatic insufficiency.[4,6]

## Opportunities for Outpatient Treatment

Single-dose IV therapy with oritavancin may significantly alter antibiotic therapy in the outpatient setting. The **BOX** summarizes the potential advantages and limitations to outpatient management of serious infections with oritavancin. Hypothetically, a single infusion that provides therapeutic drug levels for weeks can provide potential cost-savings and eliminate the need for repeated infusions and adherence concerns. Furthermore, patients and families may benefit from better quality of life and reduced costs while hospitals and insurance providers may benefit from early discharges. The burden of hospital-acquired infections could, in theory, be reduced and more efficient use of emergency departments, observation units, and urgent care centers may be possible.[5]

Some limitations include the risk of a sudden complication that needs urgent care, which may not be easily obtained at home. Additionally, elimination of IV administrations can result in reduction in staff and reimbursement. If the drug is priced high, conflicts as to who will absorb the costs may occur. Patients also may not return for follow-up care if they feel better. Laboratory tests to monitor response and adverse effects may be important, but this importance may not be appreciated by payers. Another concern is appropriate antibiotic use. It may not always be easy to

**BOX | Potential advantages and limitations of outpatient therapy with oritavancin for serious infections.[5]**

| Potential Advantages |
|---|
| • Single infusion |
| • Improved quality of life, patient satisfaction |
| • Return to work |
| • Potential cost savings |
| • Therapeutic levels and compliance assured |
| • Reduced length of hospital stay |
| • Reduced hospital-acquired infections |

| Potential Limitations |
|---|
| • No immediate access to medical care |
| • Reduced provider visits |
| • Limited home care resources |
| • Family and patient education and training |
| • Overuse of antibiotic |

determine whether a patient has a serious infection that should be treated in the outpatient setting with an IV antibiotic or an oral antibiotic. Overuse of oritavancin in these situations may breed resistance.

With the potential changes in outpatient therapy that oritavancin may bring, there is a need to develop systems to determine and monitor outcomes. Registries that have been developed for outpatient therapy can be used and quality assurance can provide ongoing information concerning appropriate use and adverse effects.[5]

## Summary

Oritavancin is the first single dose antibacterial agent granted an approved indication by the U.S. FDA for the treatment of ABSSSIs caused by susceptible gram-positive pathogens including both MSSA and MRSA, various *Streptococcus* species, and *Enterococcus faecalis*. The recommended dosing of oritavancin is a single 1200 mg dose over a 3 hour IV infusion in patient's ≥18 years old. No differences in response to oritavancin have been elucidated between elderly and younger patients, although few older patients have been included in trials; the safety and efficacy of oritavancin in the pediatric population is currently being examined. No specific dose adjustments are required in patients with mild to moderate renal or hepatic impairment. Currently, no data exist for patients with severe renal or hepatic impairment.

Clinical trials have shown that oritavancin is noninferior to vancomycin for the treatment of ABSSSIs. Single-dose IV therapy with oritavancin may potentially reduce costs of care without sacrificing quality, improve patient satisfaction, and limit the spread of hospital-acquired infections. The benefits, however, do not come without risks, including: 1) side effects, the most common of which are nausea, phlebitis, diarrhea, headache, vomiting, constipation, limb and subcutaneous abscesses, and infusion site extravasation; and 2) the potential for inappropriate use and overuse which can breed increasing resistance and waste valuable resources.

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# Editor's Corner

## Time to Blood Pressure Control

A study published this month in the *British Medical Journal* examined several aspects of blood pressure control including time to treatment intensification following an elevated blood pressure and subsequent time to next blood pressure measurement following treatment intensification.

Dr. Xu and colleagues studied a retrospective cohort of 88,756 patients with hypertension treated by primary care practitioners in the United Kingdom from 1986 to 2010. The primary outcome was acute cardiovascular events or death from any cause. Hazard ratios were adjusted for age, sex, smoking status, socioeconomic deprivation (a measure of socioeconomic status), diabetes, cardiovascular disease, CKD, Charlson comorbidity index, BMI, medication possession ratio, and baseline blood pressure.

During a median follow-up of 37.4 months, 9,985 acute cardiovascular events or deaths occurred. Slower time to treatment intensification (1.45 to 4.68 months versus ≤1.44 months) was associated with increased risk for the primary outcome (HR 1.12; 95% CI 1.05-1.20), as was longer interval until next follow-up (≥2.7 months versus 0.7-1.0 months) (HR 1.18; 95% CI 1.11-1.25).

*Reference*:


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Weber MA, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE TRIAL. *Lancet* 2004;363:2049–51.


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