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Formulary Drug Reviews

Oritavancin Diphosphate

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Each month, subscribers to *The Formulary Monograph Service* receive 5 to 6 well-documented monographs on drugs that are newly released or are in late phase 3 trials. The monographs are targeted to Pharmacy & Therapeutics Committees. Subscribers also receive monthly 1-page summary monographs on agents that are useful for agendas and pharmacy/nursing in-services. A comprehensive target drug utilization evaluation/medication use evaluation (DUE/MUE) is also provided each month. With a subscription, the monographs are sent in print and are also available on-line. Monographs can be customized to meet the needs of a facility. A drug class review is now published monthly with *The Formulary Monograph Service*. Through the cooperation of *The Formulary, Hospital Pharmacy* publishes selected reviews in this column. For more information about *The Formulary Monograph Service,* call *The Formulary* at 800-322-4349. The December 2014 monograph topics are olodaterol, peginterferon beta-1a, testosterone nasal gel, ferric citrate corredination complex, and safinamide. The Safety MUE is on olodaterol.

Generic Name:	Oritavancin diphosphate
Proprietary Name:	*Orbactiv* (The Medicines Company)
Approval Rating:	1S
Therapeutic Class:	Antibacterials; glycopeptide
Similar Drugs:	Dalbavancin, telavancin, vancomycin
Sound- or Look-Alike Names:	Dalbavancin, *Orthovisc*

INDICATIONS

Oritavancin is approved for the treatment of adult patients with acute bacterial skin and skin structure infections (SSSIs) caused by or suspected to be caused by susceptible isolates of designated gram-positive microorganisms, including *Staphylococcus aureus* (methicillin susceptible [MSSA] and methicillin resistant [MRSA]), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only).[1] Oritavancin is also being evaluated using an in vitro model for *Clostridium difficile* infection and in vivo for use in the treatment of complicated SSSIs.[2,3] The US Food and Drug Administration (FDA)–approved indications for oritavancin, dalbavancin, telavancin, and vancomycin are compared in **Table 1**.

Dalbavancin is indicated for the treatment of adult patients with acute bacterial SSSIs caused by susceptible isolates of the following gram-positive microorganisms: *S. aureus* (including MSSA and MRSA strains), *S. pyogenes*, *S. agalactiae*, and *S. anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*).[4]

Telavancin is indicated for the treatment of adult patients with complicated SSSIs caused by susceptible isolates and hospital-acquired or ventilator-associated bacterial pneumonia caused by susceptible isolates of *S. aureus*. Telavancin should be reserved for use when alternative treatments are not suitable.[5]

Vancomycin is indicated for the treatment of serious or severe infections susceptible to strains

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Table 1. FDA-approved indications for dalbavancin, oritavancin, telavancin, and vancomycin[1,4,5,6]

Indication	Dalbavancin	Telavancin	Vancomycin	Oritavancin
Acute bacterial SSSIs (adults)	X			X
Complicated SSSIs (adults)		X		
Hospital-acquired or ventilator-associated bacterial pneumonia		X		
Serious or severe infections susceptible to strains of methicillin-resistant (beta-lactam resistant) staphylococci			X	
Endocarditis caused by staphylococci, *S. viridans*, *S. bovis*, enterococci, and diphtheroids			X	
Antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*			X	
Staphylococcal enterocolitis			X	

Note: FDA = US Food and Drug Administration; SSSIs = skin and skin structure infections.

of methicillin-resistant (beta-lactam resistant) staphylococci; treatment of endocarditis caused by staphylococci, *Streptococcus viridans*, *Streptococcus bovis*, enterococci, and diphtheroids; and oral treatment of antibiotic-associated pseudomembranous colitis produced by *C. difficile* and staphylococcal enterocolitis.[6]

To reduce the development of drug-resistant bacteria, all of these antibacterial agents should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.[1,4,5,6]

CLINICAL PHARMACOLOGY

All semisynthetic lipoglycopeptide antibacterials share similar mechanisms of action and spectrums of activity. All work by inhibiting the transpeptidase and transglycosylase steps in bacterial cell-wall synthesis of gram-positive bacteria by binding to the terminal D-alanyl-D-alanine of the stem pentapeptide of the nascent peptidoglycan. Differences in binding and anchoring to the cell membrane and dimerization may alter each agent's potency against various bacteria.[4-9]

In vitro testing with oritavancin indicates activity against a number of gram-positive bacteria, including *S. aureus* (coagulase positive and coagulase negative), *Streptococcus* spp., *Enterococcus*, *Bacillus*, *Corynebacterium* spp., *Lactobacillus* spp., *Leuconostoc* spp., *Listeria monocytogenes*, *Pediococcus* spp., viridans group *Streptococcus*, *C. difficile*, *Clostridium perfringens*, *Peptostreptococcus* spp., and *Propionibacterium* spp.[8,10-35] Oritavancin appears to have no activity against gram-negative bacteria.[12]

In vitro testing indicates that oritavancin has synergistic effects against some strains of *S. aureus* when given with gentamicin, linezolid, or rifampicin (mixed results); against *E. faecium* (vancomycin intermediate and vancomycin resistant) when given with ampicillin, ciprofloxacin, gentamicin, or daptomycin; and against multidrug-resistant *Acinetobacter baumannii* when given with colistin.[36-42] Moxifloxacin showed variable results.[36]

PHARMACOKINETICS

The pharmacokinetics of oritavancin are best characterized with a 3-compartment model with linear elimination.[43,44] Time to maximum plasma concentration (T_{max}) is 1 to 1.5 hours.[45] Plasma protein binding is 85% to 90%.[1,46] The volume of the central compartment is influenced by the patient's body surface area (BSA) and increases by 85% as the BSA increases from 1.3 to 3.5 m^2. The volume of the central compartment is 5.88 L. The volumes of the other 2 compartments are 14.8 L (V2) and 90 L (V3). Systematic clearance is 0.445 L/h.[43]

Oritavancin is not metabolized but is excreted unchanged in both the urine and feces.[43] The distribution half-life is 2.18 hours for the alpha phase and 17.6 hours for the beta phase.[47] The terminal half-life is 245 to 404 hours.[1,43,47]

Maximum concentration (C_{max}) in blister fluid occurred at about 10 hours.[45] The mean oritavancin C_{max} in plasma is approximately 8-fold higher than in blister fluid following a 200 mg dose and 11-fold higher following an 800 mg dose.[45] However, the mean drug concentration in the blister fluid is higher

Table 2. Comparison of pharmacokinetic parameters of dalbavancin, oritavancin, telavancin, and vancomycin[1,4,5,6,43]

	Dalbavancin 1,000 mg (IV; single dose)	Oritavancin	Vancomycin 1,000 mg (IV; single dose)	Telavancin 10 mg/kg (IV; single dose)
C_{max}	287 mcg/mL	138 mcg/mL	63 mcg/mL	93.6 mcg/mL
T_{max}	NA	Immediately following a 3-h infusion	Immediately following a 60-min infusion	Immediately following a 60-min infusion
Half-life	346 h	393 h	4 to 6 h	8 h
$AUC_{0\text{-infinity}}$	23,443 mg•h/L	2,800 mcg•h/mL	—	747 mcg•h/mL
Clearance	0.0513 L/h	0.456 L/h	0.058 L/h/kg	13.9 mL/h/kg
Volume of distribution	NA	5.88 L (central compartment); 14.8 L (V2); 90 L (V3)	0.864 L/kg	145 mL/kg
Protein binding	93%	85% to 90%	55%	90%
Metabolism	No apparent metabolism	No apparent metabolism	No apparent metabolism	No apparent metabolism
Elimination	Urine: 33% unchanged for dalbavancin, 12% for hydroxy-dalbavancin 42 days postdose Feces: 20%, 70 days postdose	Unchanged in urine and feces	Urine: 75% excreted over 24 h	Urine: 76% Feces: < 1%

Note: AUC = area under the curve; NA = not available in product labeling.

than the 90% minimum inhibitory concentration (2 mcg/mL) by 2- to 5.5-fold at 12 hours and by 1.5- to 3-fold at 24 hours.[45]

Pharmacokinetic parameters of glycopeptide antibacterial medications used in the treatment of acute bacterial SSSIs are summarized in **Table 2**.

COMPARATIVE EFFICACY

Indication: Acute Bacterial Skin and Skin Structure Infections

Guidelines

Guideline: Practice guidelines for the diagnosis and management of skin and soft-tissue infections, Infectious Diseases Society of America

Reference: Stevens DL, et al, 2005[48]

Comments: The guidelines recommend empiric treatment of minor skin and soft-tissue infections with semisynthetic penicillin, first- or second-generation oral cephalosporins, macrolides, or clindamycin. For outpatient treatment of community-acquired MRSA, trimethoprim-sulfamethoxazole, tetracycline, doxycycline, or minocycline is recommended, with evaluation 48 to 72 hours after initial dose to verify a clinical response. For patients with an infection severe enough to require hospitalization or with an infection that progresses despite empirical antibiotic therapy, treatment strategy should be based on results of appropriate gram stain, culture, and drug-susceptibility analysis. When treating *S. aureus*, it is appropriate to assume that the organism is methicillin resistant, due to the high prevalence of community-associated MRSA strains; treatment with agents effective against MRSA, such as vancomycin, linezolid, or daptomycin, is recommended.

Studies

Drug: Oritavancin vs Vancomycin

Reference: Corey GR, et al, 2014 (SOLO-I study)[49]

Study Design: International, randomized, double-blind, multicenter noninferiority study

Study Funding: The Medicines Company

Patients: 968 adult patients (18 years and older)

with acute bacterial SSSIs (wound infection, cellulitis, or major cutaneous abscess) thought to be caused by gram-positive bacteria were enrolled and included in the intent-to-treat population; 954 of these patients were included in the safety population and the modified intent-to-treat (received any dose of antibiotic) population. The study population was about 45 years of age with 9% being 65 years and older; 63% were male; 58% of patients were White, 9% were Black, and 32% were Asian; body weight was 82 kg and body mass index (BMI) was about 29; and 20% of patients had diabetes, 20% had wound infections, 50% had cellulitis infections, and 29.5% had abscesses. Each infection site had to be at least 75 cm^2 with signs and symptoms of systemic inflammation.

Intervention: Patients were randomized (1:1) to a single oritavancin dose of 1,200 mg intravenously (IV) followed by IV placebo or IV vancomycin (1 g or 15 mg/kg of body weight) every 12 hours for 7 to 10 days. The study populations were stratified based on geographic region, study site, and presence or absence of diabetes. Thirty percent of major cutaneous abscesses were included from the study sample. Adjunctive antibiotics were allowed in patients with gram-negative (aztreonam) and anaerobic (metronidazole) coverage. In the oritavancin group, 10.9% received aztreonam and 3.2% received metronidazole; in the vancomycin group, 9.8% received aztreonam and 3.5% received metronidazole. The mean total daily dose of vancomycin was 2.3 g, mean duration of therapy was 8.1 days, and mean measurable trough level was 15.4 mcg/mL.

Results

Primary Endpoint(s)

- Composite outcome, including cessation of spreading or reduction in size of baseline lesion, absence of fever, and absence of a need for rescue antibiotic medication at early clinical evaluation, occurred in 82.3% of the oritavancin group and 78.9% of the vancomycin group (difference, 3.4%; 95% confidence interval [CI], –1.6 to 8.4). Noninferiority margin was 10% on the lower bounds), with an alpha level of 0.025 with at least a 75% rate for the primary outcome in both groups.

Secondary Endpoint(s)

- Investigator-assessed clinical cure at posttherapy evaluation was 79.6% in the oritavancin group and 80% in the vancomycin group (difference, –0.4%; 95% CI, –5.5 to 4.7). Noninferiority margin was 10%, with an alpha level of 0.025 with at least a 65% rate for the primary outcome in both groups.
- Decrease in lesion area of 20% or more from baseline to early clinical evaluation was 86.9% in the oritavancin group and 82.9% in the vancomycin group (difference, 4.1%; 95% CI, –0.5 to 8.6).

Endpoint(s)

- The efficacy rate of the primary endpoint was similarly based on several subgroup analyses (BMI, presence or absence of diabetes, presence or absence of MRSA infection, sex, race, or lesion type).

Comments: The pathogens detected in patients were *S. aureus* (MRSA and MSSA), *S. anginosus* group (*S. agalactiae*, *S. pyogenes*, and *S. dysgalactiae*), and *E. faecalis*. The most common pathogen was *S. aureus*.[49] The study protocol was amended to allow patients to complete antimicrobial therapy in the ambulatory setting at the discretion of the investigator. After this amendment, 345 of 954 (36%) patients were not admitted to the hospital during the study; instead, the study medication was administered to the patient in the emergency department, with follow-up treatment at the patient's home or an outpatient antimicrobial treatment center. An early clinical response at early clinical evaluation occurred in 82.6% of the oritavancin group and 75.7% of the vancomycin group (difference, 6.8%; 95% CI, –1.7 to 15.4). In those treated in the hospital, an early clinical response at early clinical evaluation occurred in 82.2% of the oritavancin group and 80.7% of the vancomycin group (difference, 1.5%; 95% CI, –4.7 to 7.6).[50]

Reference: Corey R, et al, 2013 (SOLO II study)[51,52]

Study Design: International, randomized, double-blind, multicenter noninferiority study

Study Funding: The Medicines Company

Patients: 1,019 adult patients (18 years and older) with acute bacterial SSSIs (wound infection, cellulitis, or major cutaneous abscess) thought to be caused by gram-positive bacteria were enrolled and included in the intent-to-treat population; 1,005 of these patients were included in the modified intent-to-treat (received any dose of antibiotic) population.

Intervention: Patients were randomized (1:1) to a single oritavancin dose of 1,200 mg IV followed

by IV placebo or IV vancomycin (1 g or 15 mg/kg of body weight) every 12 hours for 7 to 10 days. Adjunctive antibiotics were allowed in patients with gram-negative (aztreonam) and anaerobic (metronidazole) coverage.

Results

Primary Endpoint(s)

- Composite outcome, including cessation of spreading or reduction in size of baseline lesion, absence of fever, and absence of a need for rescue antibiotic medication at early clinical evaluation, occurred in 80.1% of the oritavancin group and 82.9% of the vancomycin group (difference, 2.8%).

Secondary Endpoint(s)

- Investigator-assessed clinical cure at posttherapy evaluation was 82.7% in the oritavancin group and 80.5% in the vancomycin group (difference, 2.3%).
- Decrease in lesion area of 20% or more from baseline to early clinical evaluation was 85.9% in the oritavancin group and 85.3% in the vancomycin group (difference, 0.6%).

Comments: The SOLO I and SOLO II studies have identical study designs. The pathogens detected in patients were *S. aureus* (MRSA and MSSA), *S. anginosus* group (*S. agalactiae*, *S. pyogenes*, and *S. dysgalactiae*), and *E. faecalis*. The most common pathogen was *S. aureus*.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Administration of IV unfractionated heparin sodium is contraindicated within 48 hours after oritavancin administration; activated partial thromboplastin time (aPTT) test may be falsely elevated for about 48 hours. An alternative anticoagulant that does not require aPTT monitoring or the use of nonphospholipid-dependent coagulation test (eg, factor Xa [chromogenic]) may be necessary.[1]

Oritavancin is contraindicated in patients with known hypersensitivity reactions to the drug.[1]

Contraindications for medications used in the treatment of acute bacterial SSSIs are summarized in **Table 3**.

Warnings and Precautions

To minimize the risk of infusion-related reactions, oritavancin is administered via IV infusion over 3 hours.[1] More rapid IV infusions can cause infusion-related reactions (eg, flushing, urticaria, pruritus). Infusion interruption or slowing may result in cessation of these reactions.[1]

Tests used to monitor anticoagulant status (eg, prothrombin time [PT], international normalized ratio [INR], aPPT, activated clotting time [ACT]) may be altered for up to 48 hours after oritavancin administration.[1]

Hypersensitivity reactions may occur after oritavancin administration; median onset was 1.2 days, and median duration was 2.4 days. If the reaction occurs during IV infusion, the infusion should be discontinued immediately and appropriate supportive care should be started. There is a possibility of cross-sensitivity reactions with other glycopeptides (eg, vancomycin).[1]

Systemic antibacterial drugs, including dalbavancin, oritavancin, telavancin, and vancomycin, are associated with *C. difficile*–associated diarrhea (CDAD), with severity ranging from mild diarrhea to fatal colitis. CDAD has been reported in patients treated with these drugs. Treatment with antibacterial agents can alter the normal flora of the colon and may permit overgrowth of *C. difficile*. CDAD must be considered in patients who present with diarrhea following antibacterial use. CDAD has been reported to occur more than 2 months after use of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* should be discontinued, if possible.[1,4-6]

Use of dalbavancin, oritavancin, telavancin, or vancomycin in patients without proven or strongly suspected bacterial infection is unlikely to provide benefit and increases the risk of development of drug-resistant bacteria.[1,4-6]

Table 3. Comparison of contraindications of dalbavancin, telavancin, oritavancin, and vancomycin[1,4,5,6]

Contraindications	Dalbavancin	Oritavancin	Telavancin	Vancomycin
Known hypersensitivity to drug	X	X	X	X
Unfractionated heparin sodium therapy within 48 hours		X		

Table 4. Comparison of warnings and precautions for dalbavancin, oritavancin, telavancin, and vancomycin[1,4,5,6]

Warnings and precautions	Dalbavancin	Oritavancin	Telavancin	Vancomycin
ALT elevation	X			
CDAD	X	X	X	X
C. difficile-induced pseudomembranous colitis				X
Chemical peritonitis associated with intraperitoneal administration				X
Development of drug-resistant bacteria	X	X	X	X
Hypersensitivity reactions	X	X	X	
Hypersensitivity reactions with prior vancomycin or other glycopeptide therapy	X	X	X	X
Increased mortality in patients with hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia			X	
Infusion-related events (eg, flushing, erythema, urticaria, pruritus)	X	X	X	X
Injection-site pain				X
Interference with coagulation test results		X	X	
Intrathecal or intraperitoneal administration[a]				X
Nephrotoxicity			X	X
Neutropenia, reversible				X
Osteomyelitis		X		
Ototoxicity				X[b]
QTc prolongation			X	
Rapid bolus administration	X		X	X
Reduced efficacy in patient with moderate/severe preexisting renal impairment			X	
Renal impairment, dosage adjustment			X	X
Thrombophlebitis				X
Special populations				
Pregnancy Category	Category C	Category C	Category C	Category C
Breast-feeding	Unknown	Unknown	Unknown	Caution
Pediatric use	No data	No data	No data	Yes

Note: ALT = alanine aminotransferase; CDAD = *C. difficile*–associated diarrhea; *C. difficile* = *Clostridium difficile*.
[a]Efficacy not established by adequate and well-controlled trials.
[b]Patients receiving excessive doses, who have underlying hearing loss, or who are receiving concurrent therapy with another ototoxic drug (eg, aminoglycosides).

In clinical trials, osteomyelitis occurred in the oritavancin treatment arm more than in the vancomycin treatment arm. Patients treated with oritavancin should be monitored for signs and symptoms of osteomyelitis during the course of therapy and at follow-up.[1]

Oritavancin is classified as Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women.[1]

It is not known whether oritavancin or its metabolite is excreted in human milk. Caution should be

exercised when oritavancin is administered to a breast-feeding woman.[1]

The safety and efficacy of oritavancin in pediatric patients have not been established. However, studies are ongoing to evaluate the safety and tolerability of oritavancin in pediatric patients with suspected or confirmed bacterial infections.[1,53]

Warnings and precautions for medications used in the treatment of acute bacterial SSSIs are summarized in **Table 4**. Only telavancin has a required black box warning regarding patients with preexisting moderate/severe renal impairment treated for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, the risk of nephrotoxicity, and pregnancy test recommendations.[1,4-6]

ADVERSE REACTIONS

The most common adverse reactions reported with oritavancin therapy are nausea, headache, diarrhea, and limb and subcutaneous abscesses.[1,49] See **Tables 5**, **6**, and **7** for comparisons with other glycopeptide antibiotics.

DRUG INTERACTIONS

Coadministration with warfarin may result in increased warfarin levels and increased risk of bleeding. Patients can be treated with the combination but should be monitored for signs of bleeding.[1] Coagulation tests (eg, PT, INR) may be unreliable for up to 24 hours after the oritavancin administration; aPPT may be altered for up to 48 hours, and ACT may be affected.[1]

Oritavancin is a nonspecific, weak inhibitor of cytochrome P450 (CYP-450) 2C9 and CYP2C19 and is an inducer of CYP3A4 and CYP2D6. Oritavancin may also inhibit the activity of CYP1A2, CYP2B6, CYP2D6, and CYP3A4, based on in vitro studies. Therefore, caution should be observed if oritavancin

Table 5. Comparison of adverse reactions from the SOLO I study of oritavancin and vancomycin in adult patients with acute bacterial skin and skin structure infection[49]

Adverse reactions	Oritavancin (n = 473)	Vancomycin (n = 481)
Nausea	11%	8.9%
Headache	7.2%	7.9%
Pruritus	3.4%	9.1%
Infusion-site reaction	4%	7.1%
Infusion-site extravasation	3.8%	4.8%
Vomiting	4.9%	3.7%
Constipation	4%	4.4%
Diarrhea	4.9%	3.5%
Cellulitis	4.2%	3.5%
Pyrexia	3.2%	4.2%
Dizziness	3.2%	3.1%
Insomnia	3%	2.7%
Chills	2.1%	2.5%
Urticaria	1.5%	3.1%
Pruritus, generalized	2.3%	1.9%
Subcutaneous abscess	1.9%	2.3%
Abscess on limb	2.7%	1%
Infusion-site phlebitis	1.7%	2.1%
ALT elevation	2.3%	1%
Fatigue	2.1%	1.2%

Note: ALT = alanine aminotransferase.

Table 6. Comparison of adverse reactions of dalbavancin, oritavancin, and telavancin in adult patients with skin and skin structure infection[a,1,4,5,49]

Adverse reactions	Dalbavancin	Oritavancin	Telavancin	Vancomycin
Nausea	5.5%	9.9% to 11%	27%	
Headache	4.7%	7.1% to 7.2%		
Diarrhea	4.4%	3.7% to 4.9%	7%	
Vomiting	2.8%	4.6% to 4.9%	14%	
Rash	2.7%			X
Pruritus	2.1%			
Rigors			4%	
Taste disturbance			33%	
Foamy urine			13%	

[a]Data extracted from product labeling; therefore, patient types, indications, and duration of therapy may be different from clinical use.

Table 7. Comparison of adverse reactions with oritavancin and vancomycin in adult patients treated for acute bacterial skin and skin structure infection in clinical trials[1,4,5,49]

Adverse events	Oritavancin (*n* = 976)	Vancomycin (*n* = 983)
Abscess (limb and subcutaneous)	3.8%	2.3%
Diarrhea	3.7%	3.4%
Dizziness	2.7%	2.6%
Headache	7.1%	6.7%
Infusion-site phlebitis	2.5%	1.5%
Infusion-site reaction	1.9%	3.5%
Nausea	9.9%	10.5%
Tachycardia	2.5%	1.1%
Vomiting	4.6%	4.7%

is used to treat patients receiving a narrow therapeutic index drug metabolized by these CYP isoforms. Oritavancin is not a substrate nor an inhibitor of the efflux transporter P-glycoprotein.[1]

In vitro compatibility studies have been conducted with oritavancin using a simulated Y-site administration model and detection of visual incompatibilities. The aqueous solubility of oritavancin was best at an acidic pH and poor in a neutral or alkaline medium. Drugs compatible with oritavancin were calcium gluconate, cimetidine, ciprofloxacin, dexmedetomidine, dobutamine, dopamine, epinephrine, famotidine, fentanyl citrate, fluconazole, gentamicin, haloperidol lactate, insulin (human regular), lorazepam, midazolam, morphine, nitroglycerin, norepinephrine, pancuronium, phenylephrine, potassium chloride, ranitidine, and tobramycin. Drugs formulated at a basic or neutral pH (eg, aminophylline, amphotericin B, aztreonam, bumetanide, clindamycin, furosemide, heparin sodium, hydrocortisone sodium succinate, meropenem, metronidazole, sodium nitroprusside, phenytoin sodium, sodium bicarbonate, trimethoprim-sulfamethoxazole) were more likely to be classified as incompatible with oritavancin.[54]

Oritavancin should only be reconstituted with sterile water for injection and only diluted with dextrose 5% in water. Dilution with normal saline for injection can result in the formation of a precipitate. Therefore, oritavancin should not be infused simultaneously or mixed with other drugs that are prepared

with normal saline. Oritavancin should also not be infused in the same IV line or through a common IV port that contains normal saline.[1]

RECOMMENDED MONITORING

None.

DOSING

The recommended dose for adults 18 years and older is oritavancin 1,200 mg administered as a single IV infusion over 3 hours.[1]

No dosage adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment were not evaluated. Oritavancin is not removed from blood by hemodialysis.[1]

No dosage adjustment is recommended for patients with mild or moderate hepatic impairment. There are no data available to determine appropriate oritavancin dosing in patients with severe hepatic impairment; therefore, use caution when prescribing oritavancin to these patients.[1]

See **Table 8** for a comparison of recommended dosing regimens for the various glycopeptide antibiotics.

PRODUCT AVAILABILITY

The New Drug Application for oritavancin was filed in February 2014 and was classified as a priority review by the FDA.[55] Oritavancin was also classified as a "qualified infectious disease product" in December 2013.[55] It was approved for use on August 6, 2014.[56]

Oritavancin is supplied in a single-use 50 mL vial containing oritavancin diphosphate 449 mg (equivalent to oritavancin 405 mg) lyophilized powder. The vial contains an extra 5 mg of oritavancin to ensure withdrawal of the recommended 400 mg dose after the lyophilized powder is reconstituted with sterile water for injection.[1]

The unreconstituted vial should be stored at 68°F to 77°F (20°C to 25°C), with excursions permitted to 59°F to 86°F (15°C to 30°C).[1]

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for oritavancin.[56]

CONCLUSION

Oritavancin is a semisynthetic lipoglycopeptide antibacterial indicated for acute bacterial SSSIs caused by certain susceptible bacterial strains. Oritavancin has a pharmacokinetic and antibacterial

Table 8. Recommended dosing regimens for FDA-approved indications for dalbavancin, oritavancin, telavancin, and vancomycin[1,4,5,6,49]

Indication	Dalbavancin	Oritavancin	Telavancin	Vancomycin
Acute bacterial SSSIs (adults)	1,000 mg IV infusion over 60 min, followed 1 wk later by 500 mg; adjust based on renal function	Single 1,200 mg IV dose over 3 h		
Complicated SSSIs (adults)			10 mg/kg IV infusion over 60 min every 24 h for 7 to 14 days; adjust based on renal function	
Hospital-acquired or ventilator-associated bacterial pneumonia			10 mg/kg IV infusion over 60 min every 24 h for 7 to 21 days; adjust based on renal function	
Various infections				500 mg every 6 h **or** 1 g every 12 h infused over 60 min; adjust based on renal function

Note: FDA = US Food and Drug Administration; IV = intravenous; SSSIs = skin and skin structure infections.

profile that allows for single-dose administration. In 2 clinical trials (SOLO I and SOLO II) enrolling 1,959 adults with acute bacterial SSSIs, oritavancin was as effective as vancomycin for the treatment of acute bacterial SSSIs. Common adverse effects associated with oritavancin were similar to vancomycin. Oritavancin will not replace vancomycin on a formulary but will allow some patients with acute bacterial SSSIs to receive a single dose of the medication during a hospitalization or a clinic visit.

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