Formulary Drug Reviews

Dalbavancin

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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 October 2014 monograph topics are oritavancin diphosphate, insulin human inhalation powder, empaglifozin, efinaconazole topical solution, 10%, and tavaborole topical solution, 5%. The DUE/MUE is on oritavancin diphosphate.

Generic Name:	Dalbavancin
Proprietary Name:	Dalvance (Durata Therapeutics)
Approval Rating:	1P
Therapeutic Class:	Glycopeptide
Similar Drugs:	Telavancin, Vancomycin
Sound- or Look-Alike Names:	Dalalone, Telavancin

INDICATIONS

Dalbavancin is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus*

anginosus (including *Streptococcus intermedius* and *Streptococcus constellatus*).¹

To reduce the development of drug-resistant bacteria, dalbavancin should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.¹

CLINICAL PHARMACOLOGY

Dalbavancin is a novel, semisynthetic lipoglycopeptide with a pharmacokinetic profile that allows for once-weekly dosing.¹⁻³ Dalbavancin has been shown to be active in vitro and in vivo against gram-positive microorganisms including *S. aureus* (including methicillin-resistant isolates), *S. pyogenes*, *S. agalactiae*, and *S. anginosus* group.¹⁻⁴ Based on the results of 2 clinical trials, dalbavancin has a minimal inhibitory concentration (MIC) to inhibit the growth of 90% of the isolates for *S. aureus* and *S. pyogenes* of 0.06 mcg/mL.⁴ Additionally, in vitro at least 90% of vancomycin-susceptible isolates of *Enterococcus faecium* and *Enterococcus faecalis* exhibit MIC less than or equal to the dalbavancin susceptible

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breakpoint of 0.12 mcg/mL; however, the clinical significance is unknown.¹

Dalbavancin is an antibacterial drug and works by binding to the D-alanyl-D-alanine terminus of the stem pentapeptide in the bacterial cell wall peptidoglycan, which prevents crosslinking. This interferes with bacterial cell wall synthesis.^{1,4}

The antibacterial activity of dalbavancin best correlates with the ratio of area under the concentration-time curve (AUC) to MIC for *S. aureus*.¹ Resistance to dalbavancin was not observed.¹

PHARMACOKINETICS

The pharmacokinetics of dalbavancin can be best described using a 3-compartment model. Following a single intravenous (IV) dose of dalbavancin 1,000 mg in healthy patients, the maximum plasma concentration (C_{max}) was 287 mg/L, exposure (eg, AUC) from 0 to 24 hours was 3,185 mg•h/L, AUC_{0-24h} was 11,160 mg•h/L, and AUC_{0-inf} was 23,443 mg•h/L. Dalbavancin exhibits linear pharmacokinetics indicated by a proportional increase in both AUC_{0-24h} and C_{max} following single IV dalbavancin doses ranging from 140 to 1,500 mg. In healthy patients, IV infusion of dalbavancin 1,000 mg on day 1 followed by up to 7 weekly dalbavancin 500 mg IV infusions resulted in no apparent accumulation of dalbavancin.¹ After a single IV infusion of dalbavancin 1,000 mg, mean plasma concentrations were greater than 35 mg/L for 7 days.^{1,3}

Dalbavancin is primarily bound to albumin.^{1,3} Plasma protein binding is approximately 93% and is not affected by drug concentration, renal impairment, or hepatic impairment. Following dalbavancin 1,000 mg infused IV, the mean concentration in skin blister fluid is greater than 30 mg/L up to 7 days; from 0 to 144 hours, the mean exposure ratio of dalbavancin in skin blister fluid to plasma is 0.6.¹

The metabolism of dalbavancin is largely unknown. Dalbavancin is not a substrate, inhibitor, or inducer of cytochrome P450 (CYP-450) isoenzymes based on in vitro studies using human microsomal enzymes and hepatocytes. In the urine of healthy subjects, the hydroxy-dalbavancin metabolite of dalbavancin has been observed; however, quantifiable concentrations of the hydroxy-dalbavancin metabolite have not been detected in human plasma. Following single-dose administration of dalbavancin 1,000 mg in healthy patients, 20% was excreted in feces through 70 days post dose and 33% and 12% was excreted in urine as unchanged dalbavancin and the

hydroxy-dalbavancin metabolite through 42 days post dose, respectively. Following a single IV dose of dalbavancin 1,000 mg in healthy patients, dalbavancin clearance was 0.0513 L/h and terminal half-life was 346 hours.¹

Following a single dose of dalbavancin 500 or 1,000 mg, the mean plasma clearance was reduced 47% in patients with severe (less than 30 mL/min) renal impairment compared with healthy patients. Patients with severe renal impairment required a reduced dalbavancin dose.¹

The mean AUC_{0-336h} decreased 28% and 31% in patients with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, compared with healthy patients. The clinical significance of the decreased AUC_{0-336h} in patients with moderate and severe hepatic function is unknown, and there are no data available to determine appropriate dosing.¹

Pharmacokinetic parameters of medications used in the treatment of ABSSSI are summarized in Table 1.

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 Disease Society of America

Reference: Stevens DL, et al, 2005⁸

Comments: Recommends empiric treatment of minor skin and soft-tissue infections with semi-synthetic penicillin, first- or second-generation oral cephalosporins, macrolides, or clindamycin. For the outpatient treatment of community-acquired methicillin-resistant *S. aureus* (MRSA), trimethoprim-sulfamethoxazole, tetracycline, doxycycline, or minocycline are recommended with an 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 is progressing despite empirical antibiotic therapy, treatment strategy should be based upon 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, and to recommend treatment with agents effective against MRSA (eg, vancomycin, linezolid, daptomycin).

Table 1. Comparison of pharmacokinetic parameters of dalbavancin, linezolid, and vancomycin^{1,5-7}

	Dalbavancin 1,000 mg (IV; single dose)	Linezolid 600 mg (IV; single dose)	Linezolid 600 mg (oral; single dose)	Vancomycin 1,000 mg (IV; single dose)
C _{max}	287 mg/L	12.9 mcg/mL	12.7 mcg/mL	63 mcg/mL
T _{max}	NA	0.5 hours	1.28 hours	Immediately following a 60-minute infusion
Half-life	346 hours	4.4 hours	4.26 hours	4 to 6 hours
AUC _{0-inf}	23, 443 mcg•h/L	80.2 mcg•h/mL	91.4 mcg•h/mL	–
Clearance	0.0513 L/hour	138 mL/min	127 mL/min	0.048 L/h/kg
Volume of distribution	NA	40 to 50 L (at steady state)		0.864 L/kg ^a
Absolute bioavailability	NA	100%		NA
Protein binding	93%	31%		55%
Metabolism	No apparent metabolism	Oxidation		No apparent metabolism
Elimination	Feces: 20%, 70 days post dose Urine: 33% unchanged dalbavancin, 12% hydroxy-dalbavancin 42 days post dose	Feces: 6% hydroxyethyl glycine metabolite; 3% aminoethoxyacetic acid metabolite (at steady state) Urine: 30% unchanged linezolid; 40% hydroxyethyl glycine metabolite; 10% aminoethoxyacetic acid metabolite (at steady state)		Urine: 75% of dose excreted over 24 hours

Note: NA = not available in product labeling; T_{max} = time to maximum concentration.

^aMean dose of 1,500 mg/day.

Studies

Drug: Dalbavancin vs Vancomycin/Linezolid

Reference: Boucher HW, et al, 2013 (Discover 1)^{1,4,9}

Study Design: Phase 3, randomized, double-blind, double-dummy, noninferiority, multicenter, international study

Study Funding: Durata Therapeutics

Patients: 573 patients with ABSSSI. The mean age was 49 years; 60% of patients were male; 91% were White and 6% were Black or African American; and 43% were in the United States or Canada and 57% were in Europe, South Africa, or Asia. Thirteen percent of patients had a history of diabetes mellitus, 53% had cellulitis, 28% had a major abscess, 19% had a traumatic wound or surgical-site infection (median lesion size was 333 cm²), 85% had a fever, and 61% had systemic inflammatory response syndrome (SIRS).

Intervention: Patients were randomized to dalbavancin 1 g IV infusion given over 30 minutes on day 1 followed by 500 mg IV infusion given over 30 minutes on day 8 or vancomycin 1 g or vancomycin 15 mg/kg IV infusion every 12 hours, for at least 3 days, with an option to switch to oral linezolid 600 mg

twice daily. All patients received matching placebo. The end of treatment was planned to occur on day 14 or 15.

Results

Primary Endpoint(s)

- The proportion of patients in the intention-to-treat (ITT) population (all randomized patients) achieving early response (defined by the cessation of spread of infection related erythema at 48 to 72 hours after treatment initiation and a temperature of 37.6°C [99.7°F] or lower at 3 consecutive recordings assessed every 6 hours) was 240 of 288 (83.3%) for dalbavancin and 233 of 285 (81.8%) for vancomycin/linezolid; between-treatment difference was 1.5% (95% confidence interval [CI], –4.6 to 7.9).

Secondary Endpoint(s)

- Proportion of patients with a reduction in lesion area of at least 20% within 48 to 72 hours after initiation of therapy in the ITT population was 259 of 288 (89.9%) for dalbavancin and 259 of 285 (90.9%) for vancomycin/linezolid; between-group difference was –1% (95% CI, –5.7 to 4).

- Proportion of patients achieving clinical success (defined as a decrease in lesion size, temperature of 37.6°C [99.7°F] or lower, and meeting prespecified criteria for local signs, ie, purulent discharge and drainage absent or mild and improved from baseline, heat/warmth and fluctuance absent, swelling/induration and tenderness to palpation absent or mild) between days 26 to 30 in the ITT population was 241 of 288 (83.7%) for dalbavancin and 251 of 285 (88.1%) for vancomycin/linezolid; between-group difference was -4.4% (95% CI, -10.1 to 1.4). In the clinically evaluable population, it was 212 of 226 (93.8%) for dalbavancin and 220 of 229 (96.1%) for vancomycin/linezolid; between-group difference was -2.3% (95% CI, -6.6 to 2).

Endpoint(s)

- Clinical success at day 26 to 30 per pathogen in the microbiologically evaluable population for MRSA was 30 of 32 (93.8%) and 25 of 25 (100%), for methicillin-sensitive *S. aureus* (MSSA) was 57 of 60 (95%) and 78 of 78 (100%), for *S. pyogenes* was 8 of 8 (100%) and 9 of 11 (81.8%), for *S. agalactiae* was 2 of 3 (66.7%) and 2 of 2 (100%), and for *E. faecalis* was 1 of 1 (100%) and 2 of 2 (100%), for dalbavancin and vancomycin/linezolid, respectively.

Comments: The study was conducted from 2011 to 2012 at 54 sites. Noninferiority of dalbavancin to vancomycin/linezolid for the primary endpoint was declared if the lower limit of the difference in success rates was greater than a difference of 10% based on the US Food and Drug Administration (FDA) guidance.¹⁰ Patients with an invasive infection, venous catheter infection, ABSSSI that required surgical drainage for cure, and infections caused by gram-negative bacteria were excluded. Patients with missing data in which treatment success could not be determined were considered to be treatment failures. In the dalbavancin and vancomycin/linezolid groups, 27 and 28 patients, respectively, prematurely discontinued treatment mostly due to loss to follow-up. There was no between-group difference in frequency of infusion-related reactions. Two clinical trials, Discover 1 and Discover 2, were conducted to meet new FDA requirements and included patients with an ABSSSI or abscess of a minimum size or complexity, which was greater than the historical standard. Early

response rates and clinical success rates at the end of treatment were comparable in both the North America and Europe/Asia regions.¹¹

Limitations: Clinical success was based on subjective judgment of improvement of ABSSSI (eg, warmth, fluctuance, induration).

Reference: Wilcox M, et al, 2013 (Discover 2)^{1,4,12}

Study Design: Phase 3, randomized, double-blind, double-dummy, noninferiority, multicenter, international study

Study Funding: Durata Therapeutics

Patients: 739 patients with ABSSSI. Mean age was 50 years; 57% of patients were male; 88% were White and 4% were Black or African American; and 31% were in the United States or Canada and 69% were in Europe, South Africa, or Asia. Eighteen percent had a history of diabetes mellitus, 54% had cellulitis, 24% had a major abscess, 22% had a traumatic wound or surgical-site infection (median lesion size was 313 cm²), 84% had a fever, and 43% had SIRS.

Intervention: Patients were randomized to dalbavancin 1 g IV infusion given over 30 minutes on day 1 followed by 500 mg IV infusion given over 30 minutes on day 8 or vancomycin 1 g or vancomycin 15 mg/kg IV infusion every 12 hours, for at least 3 days, with an option to switch to oral linezolid 600 mg twice daily. All patients received matching placebo. End of treatment was planned to occur on day 14 or 15.

Results

Primary Endpoint(s)

- The proportion of patients in the ITT population (all randomized patients) achieving early response (defined by the cessation of spread of infection related to erythema at 48 to 72 hours after treatment initiation and a temperature of 37.6°C [99.7°F] or lower at 3 consecutive recordings assessed every 6 hours) was 285 of 371 (76.8%) for dalbavancin and 288 of 368 (78.3%) for vancomycin/linezolid; between-treatment difference was -1.5 (95% CI, -7.4 to 4.6).

Secondary Endpoint(s)

- Proportion of patients with a reduction in lesion area of at least 20% within 48 to 72 hours after initiation of therapy in the ITT population was 325 of 371 (87.6%) for dalbavancin and 316 of 368 (85.9%) for vancomycin/linezolid; between-group difference was 1.7% (95% CI, -3.2 to 6.7).

- Proportion of patients achieving clinical success (defined as decrease in lesion size, temperature of 37.6°C [99.7°F] or lower, and meeting prespecified criteria for local signs, ie, purulent discharge and drainage absent or mild and improved from baseline, heat/warmth and fluctuance absent, swelling/induration and tenderness to palpation absent or mild) between days 26 to 30 in the ITT population was 327 of 371 (88.1%) for dalbavancin and 311 of 368 (84.5%) for vancomycin/linezolid; between-group difference was 3.6% (95% CI, -1.3 to 8.7). In the clinically evaluable population, it was 283 of 294 (96.3%) for dalbavancin and 257 of 272 (94.5%) for vancomycin/linezolid; between-group difference was 1.8% (95% CI, -1.8 to 5.6).

Endpoint(s)

- Clinical success at day 26 to 30 per pathogen in the microbiologically evaluable population for MRSA was 32 of 32 (100%) and 22 of 22 (100%), for MSSA was 73 of 76 (96.1%) and 71 of 76 (93.4%), for *S. pyogenes* was 21 of 22 (95.5%) and 17 of 19 (89.5%), for *S. agalactiae* was 8 of 9 (88.9%) and 3 of 4 (75%), for *Streptococcus anginosus-milleri* was 9 of 9 (100%) and 9 of 9 (100%), and for *E. faecalis* was 8 of 8 (100%) and 3 of 3 (100%), for dalbavancin and vancomycin/linezolid, respectively.

Comments: Study conducted from 2011 to 2012 at 86 sites. Noninferiority of dalbavancin to vancomycin/linezolid for the primary endpoint was declared if the lower limit of the difference in success rates was greater than a difference of 10% based on FDA guidance.¹⁰ Patients with an invasive infection, venous catheter infection, ABSSSI that required surgical drainage for cure, and infections caused by gram-negative bacteria were excluded. Patients with missing data in which treatment success could not be determined were considered to be treatment failures. In the dalbavancin and vancomycin/linezolid groups, 39 and 35 patients prematurely discontinued treatment, respectively, mostly due to loss to follow-up. There was no between-group difference in frequency of infusion-related reactions. Discover 1 and Discover 2 were conducted to meet new FDA requirements that included patients with an ABSSSI or abscess of a minimum size or complexity, which was greater than the historical standard. Early response rates and clinical success rates at end of treatment were comparable in both the North America and Europe/Asia regions.¹¹

Limitations: Clinical success was based on subjective judgment of improvement of ABSSSI (eg, warmth, fluctuance, induration).

Drug: Dalbavancin vs Linezolid

Reference: Jauregui LE, et al, 2005²

Study Design: Randomized, double-blind, noninferiority, multicenter, international study

Study Funding: Vicuron Pharmaceuticals

Patients: 854 patients with skin and skin structure infections (SSSIs) due to gram-positive pathogens that required treatment with parenteral antibiotic therapy. Mean age was 47 years; 61.5% of patients were male; and 68.4% were White, 18% were Hispanic/Latino, and 10.7% were Black. Of these patients, 32.3% had a major abscess, 28.2% had cellulitis, 16.6% had some other type of deep soft-tissue infection, 11.2% had traumatic wound infection, 8.7% had a surgical wound infection, 23.3% had diabetes mellitus, 63.3% were hospitalized at baseline, and 87% of patients were enrolled from centers in North America. There were 550 patients in the microbiological ITT population that had a positive culture at baseline; of these, 51% were MRSA, 6% were *S. pyogenes*, 5% were *S. agalactiae*, and 4% were viridans *Streptococcus* spp.

Intervention: Patients were randomized in a 2:1 ratio to receive dalbavancin 1,000 mg on day 1 and dalbavancin 500 mg on day 8 IV infused over 30 minutes with a possible switch to oral placebo ($n = 571$) or linezolid 600 mg IV every 12 hours with the possibility of switching to oral linezolid (600 mg every 12 hours) after at least 24 hours of IV therapy ($n = 283$). The total course of treatment was 14 days. Aztreonam and/or metronidazole were allowed as empirical treatment for suspected mixed infections due to gram-negative pathogens; these agents were discontinued if the etiology was determined to be only gram-positive pathogens.

Results

Primary Endpoint(s)

- Proportion of clinically evaluable patients achieving clinical success 14 to 16 days after completion of treatment (test of cure [TOC]) was 88.9% for dalbavancin ($n = 434$) and 91.2% for linezolid ($n = 226$); the lower limit of the 95% CI was -7.28%, which was greater than the noninferiority margin of -12.5%.

- Proportion of clinically evaluable patients achieving clinical success within 3 days of completion of treatment was 92.3% for dalbavancin and 94.2% for linezolid.

Secondary Endpoint(s)

- Proportion of microbiological ITT population achieving microbiological success 14 to 16 days after completion of treatment was 89.5% for dalbavancin and 87.5% for linezolid.
- Proportion of microbiological ITT population achieving microbiological success within 3 days of completion of treatment was 87.5% for dalbavancin and 90.2% for linezolid.

Comments: The proportion of clinically evaluable patients was 88.9% in the dalbavancin group and 91.2% in the linezolid group. Patients were excluded from analysis for receiving prohibited antibiotics (10% for each group), having indeterminate clinical response at TOC (7% for each group), and receiving less than 3 days of treatment (4% and 1% for dalbavancin and linezolid, respectively). The microbiologically evaluable ITT population included 358 dalbavancin patients and 192 linezolid patients. Common adverse reactions were nausea (3.2% and 5.3%), diarrhea (2.5% and 5.7%), and infusion-site reactions (2.8% and 3.9%) for dalbavancin and linezolid, respectively.

Limitations: Study used a large noninferiority margin (12.5%); 10% is commonly used in infectious disease studies. Compared with linezolid only, no conclusions for efficacy and safety in patients treated with vancomycin can be concluded. Study was conducted from 2003 to 2004 and was limited by changes in microbiological resistance patterns. A power calculation was not done to estimate a sample size.

Drug: Dalbavancin vs Other Antimicrobial Agents

Reference: Seltzer E, et al, 2003³

Study Design: Phase 2, randomized, open-label, dose-ranging, multicenter study

Study Funding: Vicuron Pharmaceuticals

Patients: 62 patients with skin and soft-tissue infections (SSTI), caused by a gram-positive bacteria, involving deep soft tissue and/or required surgical intervention.

Intervention: Patients were randomized 1:1:1 to receive a single dose of dalbavancin 1,100 mg ($n = 20$), dalbavancin 1,000 mg on day 1 and dalbavancin 500 mg on day 8 ($n = 21$), or a compara-

tor regimen administered over 7 to 21 days, which was determined by the investigator before randomization ($n = 20$). Dalbavancin was administered as an IV infusion over 30 minutes. Comparator treatment included ceftriaxone alone or in combination ($n = 6$), cefazolin alone or in combination ($n = 4$), vancomycin alone or in combination ($n = 4$), piperacillin/tazobactam ($n = 3$), clindamycin ($n = 2$), linezolid ($n = 1$), and cephalexin ($n = 1$). Patients in the comparator group could be switched to oral therapy at the investigator's discretion (oral switch occurred in 13 of 20 patients). Additionally, if it was determined that gram-negative aerobic or anaerobic bacterial coverage was required, patients could also receive aztreonam, ceftazidime, or metronidazole.

Results

Primary Endpoint(s)

- The proportion of patients in the clinically evaluable population achieving clinical success at follow-up visit (day 24 for 1-dose dalbavancin, day 34 for 2-dose dalbavancin, and 2 weeks after the last dose for comparator regimens) was 8 of 13 (62%) for 1-dose dalbavancin, 16 of 17 (94%) for 2-dose dalbavancin, and 16 of 21 (76%) for comparator.

Secondary Endpoint(s)

- Proportion of patients in the microbiologically evaluable population (clinically evaluable patients with gram-positive pathogens at baseline) achieving clinical success at follow-up visit in patients with *S. aureus* isolates was 5 of 10 (50%) for 1-dose dalbavancin, 9 of 10 (90%) for 2-dose dalbavancin, and 6 of 10 (60%) for comparator; in patients with miscellaneous streptococcal isolates, it was 2 of 3 (67%) for 1-dose dalbavancin, 4 of 5 (80%) for 2-dose dalbavancin, and 5 of 7 (71%) for comparator. Clinical success at follow-up for patient with MRSA was 4 of 5 (80%) for 1-dose dalbavancin, 3 of 6 (50%) for 2-dose dalbavancin, and 1 of 2 (50%) for comparator.

Comments: Conducted at 10 centers in the United States from July 2001 to May 2002. Three patients did not complete the study, 1 patient in each of the dalbavancin groups discontinued due to noncompliance, and 1 patient in the single-dose dalbavancin group received a prohibited medication. Reasons patients were excluded from the clinically evaluable population were a need for concomitant antibacterial agents and/or corticosteroids ($n = 5$), no evidence

of gram-positive pathogen found at baseline ($n = 3$), missing end of treatment or follow-up visit ($n = 2$), and SSTI with compromised vascularity ($n = 1$).

Limitations: Study was conducted from 2001 to 2002 and was limited by changes in microbiological resistance patterns. Investigator chose comparator treatment, which is an inconsistent comparison.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Dalbavancin is contraindicated in patients with known hypersensitivity to dalbavancin. There are no data available on cross-reactivity between dalbavancin and other glycopeptides.¹

Contraindications for medications used in the treatment of ABSSSI are summarized in **Table 2**.

Warnings and Precautions

In patients treated with dalbavancin, serious hypersensitivity and skin reactions have been reported. Use caution in patients with a history of glycopeptide allergy due to the possibility of cross-sensitivity. If an allergic reaction occurs, treatment with dalbavancin should be discontinued.¹

To minimize the risk of infusion-related reactions, dalbavancin is administered via IV infusion over 30 minutes. Rapid IV infusions of dalbavancin can cause reactions resembling “red-man syndrome” (eg, flushing of the upper body, urticaria, pruritus, and/or rash). Discontinuing or slowing the infusion may result in cessation of these reactions.¹

Table 2. Comparison of contraindications of dalbavancin, linezolid, and vancomycin^{1,5,6}

	Dalbavancin	Linezolid	Vancomycin
Known hypersensitivity to drug product	X	X	X
Use in patients taking any medicinal product that inhibits monoamine oxidases A or B or within 2 weeks of use of such product		X	

In clinical trials, more dalbavancin-treated patients with normal baseline transaminase levels had postbaseline alanine aminotransferase (ALT) elevation greater than 3 times the upper limit of normal (ULN) than patients treated with a comparative agent. Abnormalities in other liver tests (eg, ALT, aspartate aminotransferase [AST], bilirubin) were reported with similar frequency in the dalbavancin and comparator groups.¹

Systemic antibacterial drugs, including dalbavancin, are associated with *Clostridium difficile*-associated diarrhea (CDAD) with severity ranging from mild diarrhea to fatal colitis. CDAD has been reported in patients using dalbavancin. 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 have diarrhea following antibacterial use. CDAD has been reported to occur more than 2 months after the use of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* should be discontinued, if possible.¹

Use of dalbavancin in a patient without a proven or strongly suspected bacterial infection is unlikely to provide any benefit and increases the risk of the development of drug-resistant bacteria.¹

Dalbavancin is Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Dalbavancin should only be used during pregnancy if the benefit justifies the potential risk to the fetus. No evidence of embryo or fetal toxicity was found in rats or rabbits given dalbavancin 15 mg/kg/day (1.2 and 0.7 times the human dose on an exposure basis, respectively). Delayed fetal maturation was observed in rats given dalbavancin 45 mg/kg/day (3.5 times the human dose on an exposure basis). In rats given dalbavancin 45 mg/kg/day (3.5 times the human dose on an exposure basis), increased embryo lethality and increased offspring deaths during the first week postpartum was observed.¹

It is not known whether dalbavancin or its metabolite is excreted in human milk. Dalbavancin is excreted in the milk of lactating rats; therefore, caution should be exercised when dalbavancin is administered to a breast-feeding woman.¹

The safety and efficacy of dalbavancin in pediatric patients have not been established.¹

Dalbavancin is mainly excreted by the kidney; therefore, the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dosage selection.¹

Table 3. Comparison of warnings and precautions of dalbavancin, linezolid, and vancomycin^{1,5,6}

	Dalbavancin	Linezolid	Vancomycin
ALT elevation	X		
Blood pressure; elevation		X	
CDAD	X	X	X
<i>Clostridium difficile</i> –induced pseudomembranous colitis			X
Chemical peritonitis; associated with intraperitoneal administration			X
Development of drug-resistant bacteria	X	X	X
Hypersensitivity reactions	X		
Hypoglycemia		X	
Infusion-related events (eg, flushing, erythema, urticaria, pruritus)	X		X
Injection-site pain			X
Rapid bolus administration	X		X
Intrathecal or intraperitoneal administration ^a			X
Lactic acidosis		X	
Myelosuppression		X	
Neutropenia; reversible			X
Nephrotoxicity			X
Neuropathy; peripheral and optic		X	
Ototoxicity			X ^b
Renal impairment, dosage adjustment			X
Seizures		X	
Serotonin syndrome		X	
Thrombophlebitis			X

Note: ALT = alanine aminotransferase; CDAD = *Clostridium difficile*–associated diarrhea.

^aEfficacy not established by adequate and well-controlled trials.

^bPatients receiving excessive doses, who have underlying hearing loss, or who are receiving concurrent therapy with another ototoxic drug (eg, aminoglycosides).

In patients with renal impairment with a creatinine clearance (CrCl) less than 30 mL/min, not receiving regularly scheduled hemodialysis required a reduced dose of dalbavancin. However, for patients receiving regularly scheduled hemodialysis, no dosage adjustment is recommended.¹

No dosage adjustment of dalbavancin is recommended for patients with mild hepatic impairment (Child-Pugh class A). There are no data available to determine appropriate dalbavancin dosing in patients with moderate or severe hepatic impairment (Child-Pugh class B or C); therefore, use caution when prescribing dalbavancin to these patients.¹

Warnings and precautions sections for medications used in the treatment of ABSSSI are summarized in Table 3.

ADVERSE REACTIONS

Common adverse reactions in patients treated with dalbavancin were nausea (5.5%), headache (4.7%), and diarrhea (4.4%). Adverse reactions lasted for a median of 4 days.¹ Proportion of patients in clinical trials that discontinued treatment due to adverse events was 3% for dalbavancin and 2.8% for the comparator treatment.¹

Postbaseline ALT elevations were greater than 3 times the ULN in 12 (0.8%) dalbavancin patients and 2 (0.2%) comparator treatment patients. Eight of 12 patients treated with dalbavancin and 1 of 2 patients treated with comparator drug had concomitant conditions that could elevate liver enzymes.¹

Adverse reactions for some medications used in the treatment of ABSSSI are summarized in Table 4.

Table 4. Comparison of adverse reactions of dalbavancin, linezolid, and vancomycin in adult patients with skin and skin structure infection^{1,5,a}

	Dalbavancin (n = 1,778)	Comparator ^b (n = 1,224)	Linezolid 400 mg every 12 hours (n = 548)
Nausea	5.5%	6.4%	5.1%
Headache	4.7%	4.8%	8.8%
Diarrhea	4.4%	5.9%	8.2%
Vomiting	2.8%	3%	2%
Rash	2.7%	2.4%	1.1%
Pruritus	2.1%	3.3%	–

^aAdverse reactions are collected from different studies under varying conditions and are not necessarily comparable.

^bComparators included linezolid, cefazolin, cephalexin, and vancomycin in clinical trials with dalbavancin.

Other adverse reactions reported in dalbavancin-treated patients at a rate of less than 2% included dizziness, generalized abdominal pain, localized abdominal pain, oral candidiasis, vaginal candidiasis/mycotic infection, hemorrhagic anemia, anemia, leucopenia, neutropenia, thrombocytopenia, petechiae, eosinophilia, thrombocytosis, gastrointestinal hemorrhage, melena, hematochezia, infusion-related reactions, hepatotoxicity, anaphylactoid reaction, *C. difficile* colitis, abnormal liver function test, blood alkaline phosphatase increased, increased international normalized ratio, hypoglycemia, bronchospasm, urticaria, flushing, phlebitis, wound hemorrhage, and spontaneous hematoma.¹

DRUG INTERACTIONS

No clinical drug-drug interaction studies have been conducted with dalbavancin. Nonclinical, in vitro studies using human microsomal enzymes and hepatocytes indicate that dalbavancin is not a substrate, inhibitor, or inducer of CYP-450. Dalbavancin did not result in changes in dalbavancin pharmacokinetic parameters when coadministered with known CYP-450 substrates, inducers, or inhibitors in a population pharmacokinetic study. Additionally, dalbavancin pharmacokinetics were not affected by individual medications, including acetaminophen, aztreonam, fentanyl, metronidazole, furosemide, omeprazole, esomeprazole, pantoprazole, lansoprazole, midazolam, or simvastatin. There is minimal potential for drug-drug interactions between dalbavancin and CYP-450 substrates, inhibitors, or inducers.¹

In contrast, linezolid has the potential for a number of clinically important drug interactions. In addition to antibiotic properties, linezolid is a reversible, nonselective monoamine oxidase inhibitor (MAOI).

Concurrent use of linezolid with medications that inhibit either monoamine oxidase A or B or use of linezolid within 2 weeks of taking MAOIs is contraindicated because of the risk of severe hypertensive crisis and possible serotonin syndrome. Additionally, linezolid should not be used with drugs that possess MAOI-like activity or tyramine intake greater than 100 mg.⁵ Linezolid may interact with adrenergic and serotonergic agents (eg, selective serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT₁ receptor agonists, meperidine, bupropion, buspirone). Use may result in serotonin syndrome or neuroleptic malignant syndrome-like reactions.⁵

Coadministration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing and anaphylactoid reactions.⁶ Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs (eg, amphotericin B, aminoglycosides, bacitracin, polymyxin B, colistin, viomycin, cisplatin) with vancomycin, when indicated, requires careful monitoring for toxic effects.⁶

RECOMMENDED MONITORING

Monitor for a clinical response (eg, reduction in lesion size, resolution of fever) 48 to 72 hours after treatment initiation. During dalbavancin infusion, monitor for infusion-related reactions (eg, flushing of the upper body, urticaria, pruritus, and/or rash). Stopping or slowing the infusion may result in cessation of reaction.¹ Monitor for signs and symptoms of CDAD for up to 2 months after dalbavancin administration.¹

DOSING

For treatment of adults with ABSSSI from susceptible gram-positive microorganisms, the recommended 2-dose regimen is dalbavancin 1,000 mg

followed 1 week later by dalbavancin 500 mg. After reconstitution and dilution, dalbavancin is to be administered via IV infusion over 30 minutes.¹

In patients with renal impairment with a CrCl less than 30 mL/min not receiving regularly scheduled hemodialysis, the recommended 2-dose regimen is dalbavancin 750 mg followed 1 week later by dalbavancin 375 mg.¹ For patients receiving regularly scheduled hemodialysis, no dosage adjustment is recommended, and dalbavancin can be administered without regard to the timing of hemodialysis.¹

Prior to IV administration, dalbavancin must be reconstituted with sterile water for injection and subsequently diluted only with 5% dextrose injection to a final concentration of 1 to 5 mg/mL.¹ Dalbavancin 500 mg vials must be reconstituted with 25 mL of sterile water for injection. The reconstituted vial contains dalbavancin 20 mg/mL. Reconstituted dalbavancin solution from the vial(s) must be transferred to an IV bag or bottle containing 5% dextrose injection. The diluted solution must have a final dalbavancin concentration of 1 to 5 mg/mL.¹

Dalbavancin solutions should not be co-infused with other medications or electrolytes. The compatibility of reconstituted dalbavancin with IV medications, additives, or substances other than 5% dextrose injection has not been established. Saline-based infusion solutions may cause precipitation. If a common IV line is being used to administer other drugs in addition to dalbavancin, the line should be flushed before and after each dalbavancin infusion with 5% dextrose injection.¹

The total time from reconstitution to dilution to administration should not exceed 48 hours.¹

PRODUCT AVAILABILITY

Dalbavancin was approved for marketing in the United States on May 23, 2014.¹³ Unreconstituted dalbavancin is supplied in a single-use, clear glass vial, as a sterile, lyophilized, preservative-free, white to off-white to pale yellow powder equivalent to anhydrous dalbavancin 500 mg. Vials are supplied as a single unit.¹

Unreconstituted dalbavancin vials are stored at controlled room temperature at 25°C (77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F). Reconstituted dalbavancin vials may be stored either refrigerated at 2°C to 8°C (36°F to 46°F) or at 20°C to 25°C (68°F to 77°F). Do not freeze. Once dalbavancin is diluted into an IV bag or bottle containing 5% dextrose injection, the solution may be stored either refrigerated at 2°C to 8°C (36°F to 46°F) or at a controlled

room temperature of 20°C to 25°C (68°F to 77°F). Do not freeze. The total time from reconstitution to dilution to administration should not exceed 48 hours.¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for dalbavancin.¹³

CONCLUSION

Dalbavancin is a semisynthetic lipoglycopeptide antibacterial indicated for ABSSSI caused by certain susceptible bacterial strains. Dalbavancin has a pharmacokinetic profile that allows for once-weekly dosing; therefore, only 2 dalbavancin IV infusions, separated by 1 week, are required for the treatment of bacterial infection. In 2 clinical trials with 1,289 adults with ABSSSI (Discover 1 and Discover 2), dalbavancin was as effective as vancomycin/linezolid for the treatment of ABSSSI. Common adverse effects associated with dalbavancin were nausea, headache, diarrhea, and elevations in liver enzyme tests.

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