Dalbavancin (Dalvance) **February 2019** **Non-formulary (OP)**

Criteria for Formulary Consideration of Dalbavancin

Efficacy[1-5, 8, 11-14, 23-25]

Dalbavancin is a lipoglycopeptide antibiotic derived from teicoplanin, an analog of vancomycin. It possesses a similar spectrum of activity to vancomycin with potent activity against Gram-positive microorganisms, including *Streptococcus* spp., *Enterococcus* spp., and both methicillin-susceptible and -resistant *Staphylococcus aureus* (MSSA and MRSA). It also has activity against some vancomycin-intermediate *S. aureus* (VISA). However, it is not active against most vancomycin-resistant *Enterococcus* spp. and all Gram-negative pathogens. It is currently indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSIs). In two phase III trials that informed its approval, dalbavancin was shown to be non-inferior to intravenous (IV) vancomycin with optional switch to oral linezolid (8). Additionally, data has become available suggesting that it may also have a role in the treatment of other sources of infection, most notably osteomyelitis and endocarditis (11-14). Moreover, there is a phase II pilot study currently underway evaluating the safety and efficacy of dalbavancin in the treatment of Gram-positive osteoarticular infections (23).

Safety[1, 6-8, 10, 32]

The pivotal clinical trials for the use of dalbavancin in ABSSSI showed that it was generally well tolerated, demonstrating that the majority of adverse effects were designated as mild or moderate (6-8). The most common reported were rash, headache, nausea, vomiting, and diarrhea.

Uniqueness[2-5]

In comparison to the other antibacterial agents that also have activity against resistant Gram-positive pathogens such as vancomycin, daptomycin, linezolid, tedizolid, telavancin, and oritavancin, positive characteristics of dalbavancin include:

- Favorable adverse effect profile
  - Does not prolong prothrombin time (PT) or activated partial thromboplastin time (aPTT)
- Extended half-life
  - Once weekly dosing
- Short infusion time (30 minutes)
- No dosage-adjustment recommendation for hemodialysis
- Therapeutic drug monitoring is not routinely indicated

Cost[1-4]

ABSSSI		
Estimated CrCl[a]	**Single Dose Regimen[b]**	**Cost per Dose (AWP)**
≥ 30 mL/min or on regular hemodialysis	1500 mg	$5,524.92
< 30 mL/min and not on regular hemodialysis	1125 mg	$5,524.92

Estimated CrCl[a]	Two-Dose Regimen[b]	Cost per Dose (AWP)
≥ 30 mL/min or on regular hemodialysis	1000 mg followed one week later by 500 mg	$3,683.28 + $1,841.64
< 30 mL/min and not on regular hemodialysis	750 mg followed one week later by 375 mg	$3,683.28 + $1,841.64

[a] As calculated using the Cockcroft-Gault formula.
[b] Administer by intravenous infusion over 30 minutes.

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Introduction[1, 3, 4, 7-17, 19, 20]

Dalbavancin was originally approved in the United States in 2014 for the treatment of ABSSSIs caused by susceptible Gram-positive isolates (3). The pivotal trials that informed its approval demonstrated that a two-dose regimen of IV 1000 mg administered on day 1 followed by 500 mg on day 8 was non-inferior to standard-of-care (SOC) antibacterial agents such as vancomycin and linezolid (7-9). The pharmacokinetic (PK) and pharmacodynamic (PD) parameters of dalbavancin suggest that its time-dependent and prolonged and persistent antibacterial effects allow for larger doses to be given early in treatment and enhance its duration of action (19, 20). Because of these properties and its sustained half-life of ~14.4 days, the two-dose regimen was compared to a single-dose of IV 1500 mg given on day 1. The single-dose regimen was found to be as equally efficacious and safe as the two-dose and gained approval from the Food and Drug Administration (FDA) as another acceptable dosing strategy for ABSSSIs (3, 9).

In addition to the comparative dosing trial, dalbavancin has been studied for off-label uses in the treatment of osteomyelitis, infective endocarditis, prosthetic joint infections, and catheter-associated bacteremia (11-14). The most common indications for its use in three retrospective cohort studies were treatment failure to primary antimicrobial agents, reduction in hospital length of stay, the need for outpatient parenteral antimicrobial therapy, and reduction in costs for under- or uninsured patients who have limited funding for post-hospital care (11, 12, 14). Although all three studies reported varying dosing regimens, each study demonstrated that dalbavancin appeared to be safe and effective in treating these infections. Additionally, two of these studies found that dalbavancin treatment was associated with a decrease in hospital length of stay. The results of these studies indicate a potential cost-savings opportunity.

In the only published, randomized, comparator-controlled trial evaluating dalbavancin for the treatment of osteomyelitis, adult patients were included only if it was their first episode of osteomyelitis and they did not have prosthetic material at the site of infection. Patients were randomized in a 7:1 ratio to dalbavancin 1500 mg IV on day 1 and day 8 or to SOC for osteomyelitis based on investigator judgment. The most common SOC regimens consisted of IV vancomycin as monotherapy or IV vancomycin with a switch to IV linezolid or IV levofloxacin. Seventy-five patients were included in the final analysis. Clinical cure measured at day 42 demonstrated a 97% (65/67) response in the dalbavancin group and an 88% (7/8) in the SOC group. Two patients in the dalbavancin group were lost to follow-up before day 21, but both were found to have clinical improvement on day 8. Additionally, the mean hospital length of stay in the dalbavancin group was significantly shorter than in the SOC group (15.8 days vs 33.3 days, respectively; P<0.001) (13). The dosing regimen utilized in this trial was based off of population PK modeling from two phase I studies evaluating the distribution of dalbavancin into bone and articular tissue and an extended-duration dosing schedule (16).

Pharmacokinetics and Pharmacodynamics[1-4, 16, 17]

Dalbavancin Pharmacokinetic Parameters in Healthy Subjects[1]

Parameter	Single 1000 mg Dose	Single 1500 mg Dose
C_{max} (mg/L)	287 (13.9)[a]	423 (13.2)[d]
AUC_{0-24} (mg*h/L)	3185 (12.8)[a]	4837 (13.7)[d]
AUC_{0-Day7} (mg*h/L)	11160 (41.1)[b]	ND
AUC_{0-inf} (mg*h/L)	23443 (40.9)[b]	ND
Terminal $t_{1/2}$ (h)	346 (16.5)[b,c]	ND
CL (L/h)	0.0513 (46.8)[b]	ND

All values are presented as mean (% coefficient of variation)
[a] Data from 50 healthy subjects.
[b] Data from 12 healthy subjects.
[c] Based upon population pharmacokinetic analyses of data from patients, the effective half-life is approximately 8.5 days (204 hours).
[d] Data from 49 healthy subjects.
Abbreviations: ND, not determined; AUC, area under the curve; C_{max}, maximum concentration; CL, clearance; $t_{1/2}$, half-life.

Distribution (V_d)[2]	11.2 L (0.14 L/kg) to 13.8 L (0.18 L/kg)
Protein Binding	93% (primarily to albumin)
Metabolism	Minor metabolite (hydroxy-dalbavancin)
Excretion[4]	Urine (33% as unchanged drug, 12% as hydroxy metabolite through 42 days post-dose); feces (20% through 70 days post-dose)

Distribution into Bone and Articular Tissue

A phase I, open-label, PK study of bone, synovium, synovial fluid, skin, and plasma concentrations of dalbavancin enrolled 30 patients in six separate cohorts of five patients each undergoing elective orthopedic surgery. Patients received a 1000 mg infusion over 30 minutes 0.5, 1, 3, 7, 10 and 14 days prior to surgery where bone and joint samples were collected. Cortical bone mean concentrations at 0.5 and 14 days were 6.3 and 4.1 mcg/g, respectively. Synovial fluid mean concentrations at the same time points were 25.0 and 15.9 mcg/g, respectively (16). It is reasonable to expect these concentrations to be at or above the minimum inhibitory concentration (MIC_{90}) of *Staphylococcus aureus* (0.06 mcg/mL) for a prolonged treatment duration (17).

Pharmacology[2-4, 15, 26-31]

Mechanism of Action

Dalbavancin is a novel semisynthetic bactericidal lipoglycopeptide that impedes bacterial cell wall synthesis by binding to the D-alanyl-D-alanine terminus of the stem pentapeptides in emerging peptidoglycan, thereby inhibiting the formation of cross-links and causing cell death. It has a high affinity for bacterial peptidoglycan due to its long lipophilic side chain that enables it to dimerize and anchor in the bacterial cell membrane. This interaction accounts for its potent antibacterial activity. Dalbavancin has been shown to be bactericidal *in vitro* against *Staphylococcus aureus* and *Streptococcus pyogenes*.

Mechanism of Resistance

Three case reports were found regarding Gram-positive bacterial isolates displaying dalbavancin resistance. In two of the three, both patients were treated with vancomycin prior to receiving dalbavancin therapy (26, 27). One of the patients also received daptomycin after vancomycin but before dalbavancin treatment. Because of this, it is reasonable to at least partially attribute the reported resistance to the patients' previous glycopeptide or lipopeptide treatments due to dalbavancin being closely related to vancomycin and previous reports finding an increase in glycopeptide resistance related to the use of daptomycin. In the third case, the patient did not receive glycopeptide or lipopeptide pretreatment and developed dalbavancin resistance during approximately thirty weeks of dalbavancin therapy for cardiac device-related endocarditis. However, the isolate was susceptible to vancomycin and daptomycin. After whole genome sequencing revealed specific mutations in penicillin binding proteins and the DHH domain of GdpP that have not been previously described in the literature, the authors concluded that the isolate displayed a novel resistance mechanism (28).

Antimicrobial Susceptibility Testing

Susceptibility interpretations and breakpoints for dalbavancin against *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group, and vancomycin-susceptible *Enterococcus faecalis* are based on the Clinical and Laboratory Standards Institute (CLSI), the FDA guidelines, and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. These pathogens are reported to be susceptible to dalbavancin if the MIC is ≤0.25 mg/L. However, there is a lack of validated commercial dalbavancin susceptibility tests available. A study conducted by Jones et al. analyzed 64,815 isolates from 2011 to 2013 from a surveillance study collection in an effort to demonstrate that using vancomycin susceptibility to infer dalbavancin susceptibility is an appropriate practice until such reagents become readily available (31). Broth microdilution was utilized for susceptibility testing. The investigators found that vancomycin surrogate probability for dalbavancin-susceptible results was 99.97–100.0% at MIC ≤0.25 mg/L for indicated species. These findings support the utilization of vancomycin susceptibility as a surrogate marker to predict dalbavancin susceptibility. Insufficient evidence exists in providing breakpoint guidance for *Streptococcus pneumoniae* and vancomycin-resistant *Enterococcus* spp.

FDA Approved Indications[3, 8]

Dalbavancin gained approval by the FDA to treat ABSSSI caused by designated susceptible strains of Gram-positive microorganisms on May 23, 2014 after the DISCOVER 1 and DISCOVER 2 phase III trials demonstrated non-inferiority to IV vancomycin with optional switch to oral linezolid (8).

Clinical Trials[7-9, 11-14, 32]

Authors, Date	Methods	Endpoints	Results	Conclusions
Rappo et al, 2019	Randomized, open-label, single center, phase II, comparator-controlled trial of dalbavancin versus SOC in adults with a first episode of native **osteomyelitis** at a single site Randomized in a 7:1 ratio to receive: • Dalbavancin 1,500 mg IV on days 1 and 8 • SOC: IV vancomycin, linezolid, levofloxacin, and cefotaxime were all used in various patients	Clinical response at day 42	N=80 (clinically evaluated 75) All required surgical intervention No patients with vertebral osteomyelitis Clinical response at day 42: • Dalbavancin: 97% (65/67) o 2 patients were lost to follow-up before day 21 • SOC: 88% (7/8) Mean hospital length of stay: • Dalbavancin: 15.8 days • SOC: 33.3 days (P<0.001)	A two-dose regimen of dalbavancin is well-tolerated and effective for the treatment of osteomyelitis caused by Gram-positive pathogens. It also demonstrated a decreased hospital length of stay which can lead to cost savings.

Almangour et al, 2019	Retrospective, multicenter cohort study evaluating the use of dalbavancin for the treatment of **osteomyelitis** caused by a Gram-positive pathogen. • 1,500 mg on days 1 and 8: 22.6% (7/31) • All other patients received 1,000 mg on day 1, and then 500 mg weekly for up to 5 weeks.	Clinical success at the end of treatment	N=31 Clinical success: • 90.3% (28/31) All three patients who failed treatment had foot infections that eventually required amputation. Cost savings: • Reduced hospital stays by 735 days • Estimated cost reduction: $649,954 Source control was not reported	Dalbavancin appears to be safe and effective in the treatment of osteomyelitis. It also presents cost-saving opportunities by reducing hospital length of stay.
Tobudic et al, 2018	Retrospective, single center cohort study evaluating the use of dalbavancin for the treatment of Gram-positive bacteremia with **infective endocarditis (IE)**. • Median duration of therapy: 6 weeks (range, 1-30 weeks) • Once-weekly regimens: 33.3% (9/27) • Twice-weekly regimens: 66.6% (18/27) o Dosage reduction required for one patient after experiencing acute kidney injury	• Clinical cure at 6-month follow-up OR • Failure: worsening of infection or new signs and symptoms of infection requiring change or addition of antibiotic therapy	N=27 Clinical cure: • Total: 92.6% (25/27) o Native valve IE: 100% (15/15) o Prosthetic valve IE: 85.7% (6/7) o Cardiac device-related IE: 80% (4/5) The one patient who failed to reach clinical cure in the cardiac device-related IE group did not have adequate source control. Pathogens β-lactam-sensitive: 92.6% (25/27) Second-line therapy: 88.9% (24/27)	Dalbavancin seems to be well-tolerated and effective as sequential antimicrobial therapy for IE caused by Gram-positive pathogens. Although only three patients received dalbavancin as initial therapy, all three met the primary outcome.
Bouza et al, 2018	Retrospective, multicenter cohort study evaluating all cases of infections treated with dalbavancin. • 1,000 mg on day 1 and 500 mg weekly thereafter up to 42 days: 58% (40/69) • 1,500 mg for one dose on day 1: 24.6% (17/69) • 1,500 mg on day 1 and continued every 14 days for up to >70 days 8.7% (6/69) • 1,000 mg for one dose on day 1: 4.3% (3/69) • 500 mg on day 1 and continued weekly thereafter up to 56 days: 2.9 % (2/69) • Dosage reduction for CrCl ≤ 30 mL/min for 56 days: 1.4% (1/69)	Report the use of dalbavancin in clinical practice, including its efficacy and tolerability.	N=69 Clinical success: • Total: 84.1% (58/69) o **ABSSSI**: 80% (12/15) o **Osteomyelitis**: 91.7% (11/12) o **Prosthetic joint infection**: 80% (16/20) o **IE**: 85.7% (12/14) o **Catheter-related bacteremia**: 75.1% (6/8) • **MRSA infection**: 93.8% (15/16) • **Enterococcal infection**: 70.0% (7/10) Second-line therapy: 97.1% (67/69) Source control considered adequate: 73.8% (31/42) Cost savings: • Reduced hospital stays by 1160 days • Estimated cost reduction: €211,481 or €3,064 per patient.	Dalbavancin appears to be a well-tolerated and effective drug for the treatment of off label Gram-positive infections. Its use may reduce hospital length of stay and decrease associated healthcare costs.
Dunne et al, 2016	Randomized, double blind, multicenter, noninferiority, phase III, controlled trial comparing two different dosing regimens of dalbavancin in adults with suspected or confirmed **ABSSSI** Randomized to receive: • 1,000 mg on day 1 and 500 mg on day 8 • 1,500 mg for one dose on day 1	Clinical response at 48-72 hours (≥20% decrease in lesion size from baseline)	N=698 (695 in safety analyses) Clinical response at 48-72 hours: • Two-dose regimen: 84.2% (294/349) • Single-dose regimen: 81.4% (284/349) Lower limit of the 95% CI was -8.5% (greater than the noninferiority margin of -10%) Drug related TEAE: • Two-dose regimen: 7.5% (26/346) • Single-dose regimen: 7.2% (25/349)	A single 1,500 mg dose of dalbavancin was not inferior to the traditional two-dose regimen in the treatment of ABSSSI and was shown to have a similar adverse event profile.

Boucher et al, 2014 (DISCOVER 1)	Randomized, double blind, multicenter, noninferiority, phase III, controlled trial of dalbavancin versus vancomycin/linezolid in adults with a diagnosis of **ABSSSI** who were thought to require at least 3 days of IV therapy Randomized to receive: • Dalbavancin 1,000 mg IV on day 1 and 500 mg on day 8 • Vancomycin ± Linezolid 600 mg IV every 12 hours for 10 to 14 days	Clinical response at 48-72 hours (afebrile with cessation of erythema spread)	N=573 Clinical response at 48-72 hours: • Dalbavancin: 83.3% (240/288) • Vancomycin/linezolid: 81.8% (233/285) Lower limit of the 95% CI was -4.6% (greater than the noninferiority margin of -10%)	Dalbavancin was well-tolerated and not inferior to a twice daily SOC antibiotic regimen for the treatment of ABSSSI. This was a pivotal study that informed the approval of dalbavancin for this indication.
Boucher et al, 2014 (DISCOVER 2)	Randomized, double blind, multicenter, noninferiority, phase III, controlled trial of dalbavancin versus vancomycin/linezolid in adults with a diagnosis of **ABSSSI** who were thought to require at least 3 days of IV therapy Randomized to receive: • Dalbavancin 1,000 mg IV on day 1 and 500 mg on day 8 • Vancomycin ± Linezolid 600 mg IV every 12 hours for 10 to 14 days	Clinical response at 48-72 hours (afebrile with cessation of erythema spread)	N=739 Clinical response at 48-72 hours: • Dalbavancin: 76.8% (285/371) • Vancomycin/linezolid: 78.3% (288/368) Lower limit of the 95% CI was -7.4% (greater than the noninferiority margin of -10%)	Dalbavancin was well-tolerated and not inferior to a twice daily SOC antibiotic regimen for the treatment of ABSSSI. This was a pivotal study that informed the approval of dalbavancin for this indication.
Jauregui et al, 2005	Randomized, double blind, multicenter, noninferiority, phase III, controlled trial of dalbavancin versus linezolid in adults with suspected or confirmed **SSSI** due to gram-positive pathogens that warranted initial parenteral therapy Randomized in a 2:1 ratio to receive: • Dalbavancin 1,000 mg IV on day 1 and 500 mg on day 8 • Linezolid 600 mg IV every 12 hours for 14 days	Clinical success at the TOC visit (14 ± 2 days after completion of treatment)	N=854 (clinically evaluated 660 at TOC visit) Clinical success at TOC visit: • Dalbavancin: 88.9% (386/434) • Linezolid: 91.2% (206/226) Lower limit of the 95% CI was -7.28% (greater than the noninferiority margin of -12.5%) Adverse events: • Dalbavancin: 25.4% (145/571) • Linezolid: 32.2% (91/283) Organisms isolated: • *S. aureus*: 89.5% (492/550) • MRSA: 50.5% (278/550)	Dalbavancin was well-tolerated and not inferior to linezolid for the treatment of complicated SSSI, including infections involving MRSA. This study suggested it could be an alternative to SOC regimens for the treatment of SSSIs due to Gram-positive pathogens.
Raad et al, 2005	Randomized, open-label, multicenter, phase II, controlled trial of dalbavancin versus vancomycin in adults with bacteremia with possibly or definitely associated **Catheter-related bloodstream infections (CR-BSIs)** due to gram-positive pathogens. Randomized to receive the following two therapies for 14 days: • Dalbavancin 1,000 mg IV on day 1 and 500 mg on day 8 • Vancomycin 1000 mg IV every twice daily with the dose to be adjusted based on serum levels, per investigator routine	Overall efficacy at the TOC visit (21 ± 3 days after completion of treatment)	N=75 (8 patients were not included in analyses after protocol was changed) Only microbiologically confirmed patients were included in efficacy analyses (N=51) Overall efficacy at TOC visit: • Dalbavancin: 87% (20/23) • Vancomycin: 50% (14/28) Catheter retained at baseline: • Dalbavancin: 75% (6/8) • Vancomycin: 40% (4/10) Catheter removed at or before baseline: • Dalbavancin: 93.3% (14/15) • Vancomycin: 55.6% (10/18) Common adverse events: • Dalbavancin: diarrhea, constipation • Vancomycin: renal impairment Common organisms isolated: • Coagulase-negative staphylococci (CoNS) • *S. aureus*, including MRSA • *Enterococcus faecalis*	Dalbavancin seems to be well-tolerated and effective for CR-BSIs caused by CoNS, MSSA, and MRSA.

Abbreviations: IV, intravenous; ABSSSI, acute bacterial skin and skin structure infection; SOC, standard of care; SSSI, skin and skin structure infection; TOC, test-of-cure; CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*

Warnings and Precautions, Specific Populations, and Adverse Effects[2-4, 10, 18, 19, 21, 22]

Warnings and Precautions

- *Hypersensitivity Reactions*

There are reports of anaphylactic and skin reactions experienced by patients who received dalbavancin. If this occurs, treatment should be discontinued immediately. Because cross-sensitivity with dalbavancin and other glycopeptides has not been established, caution should be employed when administering antibacterials in the same or related class (including vancomycin or daptomycin).

- *Infusion-Related Reactions*

Dalbavancin is administered as an IV infusion delivered over 30 minutes in order to prevent infusion-related reactions. If given too quickly, “Red-Man Syndrome” can occur causing flushing of the upper body, urticaria, pruritus, rash, and/or back pain. Slowing the infusion rate or discontinuing the drug may result in termination of the reaction.

- *Hepatic Impairment*

Dalbavancin was shown to increase normal baseline transaminase levels greater than 3 times the upper limit of normal in the seven phase II and phase III randomized trials. However, the comparator agents demonstrated a similar incidence. Because no data exists for patients with moderate to severe hepatic impairment (Child-Pugh Class B & C), there are no dosage adjustment recommendations for this patient population. Caution should be employed when administering dalbavancin to this patient population.

- *Renal Impairment*

Phase I open-label clinical trials evaluated the PK parameters of dalbavancin in 28 patients with varying levels renal impairment. In patients with mild renal impairment (CrCl 50-79 mL/min) receiving either a 500 mg or 1000 mg dose of dalbavancin, the mean plasma clearance was reduced by 11%. In patients with moderate renal impairment (CrCl 30-49 mL/min), the mean plasma clearance was reduced by 35%. In patients with severe renal impairment (CrCl < 30 mL/min), the mean plasma clearance was reduced by 47%. In patients with end-stage renal disease undergoing three-hour hemodialysis sessions, less than 6% of an administered dose is removed. Because of these studies, no dosage adjustment is necessary in patients with CrCl ≥ 30 mL/min or on regular hemodialysis. However, the recommended single-dose regimen is 1125 mg on day 1 and the two-dose regimen is 750 mg on day 1 followed by 375 mg on day 8 in patients with CrCl < 30 mL/min.

- *Clostridium difficile-Associated Diarrhea*

Antibacterial agents may facilitate the overgrowth of *Clostridium difficile* by altering the normal flora of the colon. Nearly all systemic antibacterials have been associated with *Clostridium difficile*-associated diarrhea (CDAD) at varying severities and has been reported to occur after their administration, including dalbavancin.

- *Development of Drug-Resistant Bacteria*

Patients who receive dalbavancin without a proven or strongly suspected bacterial infection are at an increased risk of developing drug-resistant bacteria due to selective pressure. It may also promote the overgrowth of non-susceptible microorganisms.

Specific Populations

- *Pediatric Use*

Safety and efficacy of dalbavancin in patients under the age of 18 years has not been definitively established (3). However, two open-label, multicenter, phase I trials investigated the PK and safety of a single dose of dalbavancin in pediatric patients. The first evaluated dalbavancin in 10 children between the ages of 12 and 17 years. Five of the 10 children who weighed at least 60 kg received a single dose of 1000 mg and the other 5 who weighed <60 kg received a dose of 15 mg/kg. Both groups of children displayed similar mean plasma exposures, but 9 out of the 10 still had detectable levels at 55 days after administration. Their reported terminal half-life was 9 days which is less than the half-life of 14.4 days in adults (21). The second study evaluated dalbavancin in children 3 months to 11 years of age. Subjects were enrolled in 3 age cohorts of 6 to 11 years of age, 2 to <6 years of age, and 3 months to <2 years of age. Eleven subjects were enrolled in each cohort. Those ≥5 years of age received 15 mg/kg (not to exceed 1000 mg), <5 years of age received 25 mg/kg, and <2 years of age received 10 mg/kg (maximum of 1000 mg). The investigators also included the patients from the previous study in their PK analysis. Utilizing simulations from a 3-compartment, linear PK model, they found that subjects 6 to <18 years of age receiving a dose of 12mg/kg (1000 mg maximum) on day 1 and 6 mg/kg (500 mg maximum) on day 8, and subjects 3 months to <6 years of age receiving 15 mg/kg (1000 mg maximum) on day 1 and 7.5 mg/kg (500 mg maximum) on day 8, would reach similar exposure levels to that in adults. For the single-dose regimen, subjects 6 to <18 years of age receiving a dose of 18 mg/kg (1500 mg maximum), and subjects 3 months to <6 years of age receiving 22.5 mg/kg (1500 mg maximum), would reach similar exposure levels to that in adults. Overall, dalbavancin was generally well-tolerated, but 19 children experienced a combined total of 36 treatment-emergent adverse events (TEAEs). Only 5 were assessed as possibly or probably related to treatment and were consistent with previously reported adverse events (AEs) in adults (22).

- *Pregnancy*

Dalbavancin has not been well-studied in pregnant women. Human dosages given to pregnant rats or rabbits (15 mg/kg/day, 1.2 and 0.7 times the human dose on an exposure basis, respectively) have not demonstrated evidence of embryo or fetal toxicity. However, pregnant rats who received a dose of 45 mg/kg/day (3.5 times the human dose on an exposure basis) experienced delayed fetal maturation.

- *Lactation*

It is unknown if dalbavancin or its metabolite is excreted in human milk. However, it has been shown to be excreted in the milk of lactating rats. Because dalbavancin has poor oral bioavailability, it is not likely to reach the bloodstream of the infant or cause any adverse effects in breastfed infants (18). Despite this, an alternate drug may be preferred due to the lack of published data.

- *Geriatric Use*

Safety and efficacy of dalbavancin in patients over the age of 64 was not shown to be significantly decreased in clinical trials.

Adverse Effects

Dalbavancin is contraindicated in patients who are hypersensitive to the drug or to any ingredient in the formulation. The table below is adapted from Dunne et al and shows the most frequently reported AEs in adults from all 7 phase II and III randomized trials in the dalbavancin clinical development program that informed its approval for the treatment of ABSSSIs (10). There were 3,002 participants enrolled with 1,778 receiving dalbavancin and 1,224 receiving a comparator agent of linezolid, cefazolin, cephalexin, or vancomycin. This pooled analysis revealed that patients receiving dalbavancin experienced significantly less TEAE rates (799/1778; 44.9%) compared to those receiving comparator agents (573/1224; 46.8%, P = 0.012). However, this difference may not be considered clinically significant.

	Dalbavancin (N=1778)	**Comparator* (N=1224)**
	N (%)	**N (%)**
Treatment-emergent adverse events^	799 (44.9)	573 (46.8)
Nausea	98 (5.5)	78 (6.4)
Headache	83 (4.7)	59 (4.8)
Diarrhea	79 (4.4)	72 (5.9)
Constipation	52 (2.9)	30 (2.5)
Vomiting	50 (2.8)	37 (3.0)
Rash	38 (2.1)	22 (1.8)
Urinary tract infection	36 (2.0)	16 (1.3)
Pruritis	32 (1.8)	35 (2.9)
Insomnia	27 (1.5)	30 (2.5)
Treatment-related and treatment-emergent adverse events		
Nausea	49 (2.8)	40 (3.3)
Diarrhea	45 (2.5)	45 (3.7)
Pruritis^	11 (0.6)	23 (1.9)
Treatment-related serious adverse event	3 (0.2)	9 (0.7)
Leukopenia	1 (0.1)	0
Anaphylactoid reaction	1 (0.1)	0
Cellulitis	1 (0.1)	1 (0.1)
Renal failure acute	0	2 (0.2)
Gastrointestinal disorder	0	1 (0.1)
Face edema	0	1 (0.1)
Pancytopenia	0	1 (0.1)
Thrombocytopenia	0	1 (0.1)
Nephropathy toxic	0	1 (0.1)
Pancreatitis acute	0	1 (0.1)

*Comparators included linezolid, cefazolin, cephalexin, and vancomycin.
^P < 0.05

Interactions[1, 3]

Agent	Effect	Risk
Bacillus Calmette-Guerin (BCG) Intravesical	Antibiotics may decrease the efficacy of BCG (Intravesical).	Avoid combination
Cholera Vaccine	Antibiotics may decrease the efficacy of Cholera Vaccine.	Avoid combination
Sodium Picosulfate	Antibiotics may decrease the efficacy of Sodium Picosulfate.	Consider using an alternative product for bowel cleansing prior to a colonoscopy in patients who have recently used or are concurrently using an antibiotic.
Typhoid Vaccine (Vivotif)	Antibiotics may decrease the efficacy of the oral, live attenuated Typhoid Vaccine (Vivotif), Ty21a strain.	Use of this vaccine should be postponed until at least 3 days after cessation of antibacterial agents, and when possible, antibacterials should not be started within 3 days of the last vaccine dose.
BCG Vaccine (Immunization)	Antibiotics may decrease the efficacy of BCG Vaccine (Immunization).	Monitor therapy

Drug-Laboratory Test Interactions
There are no drug-laboratory test interactions that have been reported. Dalbavancin does not artificially prolong prothrombin time (PT) or activated partial thromboplastin time (aPTT).

Drug-Drug Interactions
Because dalbavancin is not a substrate, inhibitor, or inducer of CYP450 isoenzymes, there is low potential risk for drug-drug interactions.

Dosage and Administration[3, 9]

ABSSSI		
Estimated CrCl	**Single Dose Regimen**	**Two-Dose Regimen**
≥ 30 mL/min or on regular hemodialysis	1500 mg	1000 mg followed one week later by 500 mg
< 30 mL/min and not on regular hemodialysis	1125 mg	750 mg followed one week later by 375 mg

Monitoring Parameters[1, 3]
Prior to administration, appropriate culture and sensitivity tests should be obtained. Additionally, patient's allergy history should be evaluated. Baseline laboratory tests assessing renal (blood urea nitrogen, serum creatinine) and liver function (aspartate transaminase, alanine aminotransferase, bilirubin) should also be obtained. Patients should be monitored for any infusion-related reactions and superinfections, such as CDAD during therapy.

How Supplied/Cost[2, 4]
Dalbavancin is supplied in 500 mg single-use vials that require reconstitution with either sterile water for injection or 5% dextrose injection to a concentration of 20 mg/mL. Inactive ingredients include mannitol, lactose and either sodium chloride or hydrochloric acid to adjust pH.

Dalbavancin

Route of Administration	Strength and Dosage Form	Cost per Vial (Outpatient)	Cost per Vial (Inpatient)
Intravenous (IV)	500 mg of Lyophilized Powder for Solution per 48 mL Vial	$649.95	$931.50

Utilization
- Two non-formulary orders have been placed for dalbavancin between July and December of 2018 in the inpatient setting at Nebraska Medicine.
- Five patients received 9 doses of dalbavancin as an outpatient in FY2018/2019.
- Anticipated frequency of use annually: 10-30 patients

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Appendix: Summary of Safety Issues and Implications for Pharmacy Operations

Characteristic	Summary
Medication Information	
Drug generic name (brand name)	Dalbavancin (Dalvance)
Drug manufacturer	Allergan USA, Inc.
Schedule of medication	None
Anticipated use per month, anticipated patient population	10-30 patients per year
Route of administration	Intravenous
Preparation	Lyophilized Powder that requires reconstitution with either sterile water for injection or 5% dextrose injection
Stability	Stored at controlled room temperature 25ºC (77ºF)
Recommended storage conditions for medication, and how to manage excursions outside these conditions	Excursions permitted to 15 to 30ºC (59 to 86ºF)
Does the manufacturer require patients to meet specific criteria for treatment with this medication? If so, where may healthcare providers find these criteria?	No
Operations Information	
Is filtration required during preparation or administration of the IV medication?	No ☒ Yes ☐ N/A ☐
Can medication doses be sent to patient care units via pneumatic tube system? See IC24.	No ☐ Yes ☒ N/A ☐
Does the manufacturer have a restricted or special distribution program? If so, how may healthcare providers contact the program?	No ☒ Yes ☐
Safety/Policy Information	
Will this impact a dynamic alternative alert?	No ☒ Yes ☐
Is the medication (brand name, generic name, product packaging) similar to any other medications on the Institute for Safe Medication Practices (ISMP) Sound-Alike-Look-Alike (SALA) list or confused names list? If not, is the medication expected to be added to the list? https://www.ismp.org/tools/tallmanletters.pdf http://www.ismp.org/Tools/confuseddrugnames.pdf	No ☒ Yes ☐
Does the product package insert currently have any black box warning? For what?	No ☒ Yes ☐
Is this medication a hazardous agent?	No ☒ Yes ☐
Is the medication a vesicant or irritant?	No ☒ Yes ☐
Is this a high-alert medication that requires an indication? See MM02.	No ☒ Yes ☐
Are there contraindications or significant warnings against medication use?	No ☒ Yes ☐
Is special monitoring recommended when starting therapy with this medication (eg. Telemetry, BP, etc)?	No ☒ Yes ☐
Is there a Risk Evaluation and Management Strategy (REMS) program for the medication? If so, where may healthcare providers find these criteria?	No ☒ Yes ☐
Does the medication require precautions for disposal? What kind? See EC20 Disposal of Pharmaceutical Products; EC11 Chemo Drugs-Safety Precautions for Administration	No ☒ Yes ☐
Does this medication need to be considered for auto-wasting on the MAR or another avenue for documenting waste?	No ☒ Yes ☐

Will the medication be restricted: MS68 Levels of Care	
• To a specific level of care (LOC)?	No ☒ Yes ☐ Unknown ☐
• To a specific location?	No ☒ Yes ☐ Unknown ☐
• To specific services/ providers?	No ☐ Yes ☒ Unknown ☐
• To providers credentialed in deep sedation or general anesthesia?	No ☒ Yes ☐ Unknown ☐
• To patients who are on the medication prior to admit?	No ☒ Yes ☐ Unknown ☐

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