

HIGHLIGHTS OF PRESCRIBING INFORMATION: These highlights do not include all the information needed to use DALBAVANCIN FOR INJECTION safely and effectively. See full prescribing information for DALBAVANCIN FOR INJECTION.

DALBAVANCIN for injection, for intravenous use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

Dalbavancin for injection is a lipoglycopeptide antibacterial indicated for the treatment of adult and pediatric patients with acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of Gram- positive microorganisms. (1.1)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of dalbavancin for injection and other antibacterial drugs, dalbavancin for injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. (1.2)

DOSAGE AND ADMINISTRATION

Dosage in Adult Patients (2.1, 2.3):	
Estimated Creatinine Clearance (CLcr)	Single Dose Regimen
30 mL/min and above or on regular hemodialysis	1,500 mg
Less than 30 mL/min and not on regular hemodialysis	1,125 mg

- Administer by intravenous infusion over 30 minutes (2.1, 2.4)
- See Full Prescribing Information for instructions on reconstitution of lyophilized powder and preparation of injection (2.4)

Dosage in Pediatric Patients with CLcr 30 mL/min/1.73m² and above (2.2)	
Age Range	Dosage (Single Dose Regimen)
Birth to less than 6 years	22.5 mg/kg (maximum of 1,500 mg)
6 to less than 18 years	18 mg/kg (maximum of 1,500 mg)

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FULL PRESCRIBING INFORMATION

1 INDICATION AND USAGE

- 1.1 Acute Bacterial Skin and Skin Structure Infections
- Dalbavancin for injection is indicated for the treatment of adult and pediatric patients with acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, *S. constellatus*) and *Enterococcus faecalis* (vancomycin susceptible isolates).

- 1.2 Usage
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of dalbavancin for injection and other antibacterial agents, dalbavancin for injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage Regimen in Adult Patients with CLcr 30 mL/min and Above
- The recommended dosage regimen of dalbavancin for injection in adult patients with CLcr 30 mL/min and above is 1,500 mg, administered as a single dose regimen. Administer dalbavancin for injection over 30 minutes by intravenous infusion. For adult patients with CLcr less than 30 mL/min, dosage adjustment is required [see *Dosage and Administration* (2.3) and *Clinical Pharmacology* (12.3)].
- 2.2 Recommended Dosage Regimen in Pediatric Patients with CLcr 30 mL/min/1.73m² and Above
- The recommended dosage regimen of dalbavancin for injection in pediatric patients with CLcr 30 mL/min/1.73m² and above is a single dose regimen based on the age and weight of the pediatric patient (Table 1). Administer dalbavancin for injection over 30 minutes by intravenous infusion.

There is insufficient information to recommend dosage adjustment for pediatric patients younger than 18 years with CLcr less than 30 mL/min/1.73m² [see *Use in Specific Populations* (8.4) and *Clinical Pharmacology* (12.3)].

- Dosage adjustment in pediatric patients with CLcr less than 30 mL/min has not been studied.

DOSAGE FORMS AND STRENGTHS

For injection: 500 mg of lyophilized powder in a single-dose vial for reconstitution (3)

CONTRAINDICATIONS

Known hypersensitivity to dalbavancin (4)

WARNINGS AND PRECAUTIONS

- Serious hypersensitivity (anaphylactic) and skin reactions have been reported in patients treated with dalbavancin for injection. If an allergic reaction occurs, discontinue treatment with dalbavancin for injection and institute appropriate therapy for the allergic reaction. Carefully monitor patients with known hypersensitivity to glycopeptides. (5.1)
- Rapid intravenous infusion of dalbavancin for injection can cause flushing of the upper body, urticaria, pruritus, rash, and/or back pain. Stopping or slowing the infusion may result in cessation of these reactions. (5.2)
- Alanine Aminotransferase (ALT) elevations with dalbavancin for injection treatment were reported in clinical trials. (5.3, 6.1)
- Clostridioides difficile*-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents, including dalbavancin for injection. Evaluate if diarrhea occurs. (5.4)

ADVERSE REACTIONS

The most common adverse reactions occurring in >4% of adult patients treated with dalbavancin for injection were nausea, headache, and diarrhea. The most common adverse reaction that occurred in >1% of pediatric patients was pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

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Table 1. Dosage of Dalbavancin for Injection in Pediatric Patients with CLcr 30 mL/min/1.73m² and above		
Age Range	Dosage (Single Dose Regimen)	
Birth to less than 6 years	22.5 mg/kg (maximum 1,500 mg)	
6 to less than 18 years	18 mg/kg (maximum 1,500 mg)	

*Estimate CLcr or glomerular filtration rate (GFR) using an age-appropriate equation accepted for pediatric patients (birth to less than 18 years old) to define renal function impairment.

- 2.3 Dosage Adjustments in Adult Patients with CLcr less than 30 mL/min
- In adult patients with renal impairment whose known CLcr is less than 30 mL/min and who are not receiving regularly scheduled hemodialysis, the recommended dosage regimen of dalbavancin for injection is 1,125 mg, administered as a single dose regimen.

No dosage adjustment is recommended for adult patients receiving regularly scheduled hemodialysis, and dalbavancin for injection can be administered without regard to the timing of hemodialysis [see *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)].

- 2.4 Preparation and Administration
- Dalbavancin for injection must be reconstituted with either Sterile Water for Injection, USP, or 5% Dextrose Injection, USP, and subsequently diluted only with 5% Dextrose Injection, USP, to a final concentration of 1 mg/mL to 5 mg/mL. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Reconstitution: dalbavancin for injection must be reconstituted under aseptic conditions, using 25 mL of either Sterile Water for Injection, USP, or 5% Dextrose Injection, USP, for each 500 mg vial. To avoid foaming, alternate between gentle swirling and inversion of the vial until its contents are completely dissolved. Do not shake. The reconstituted vial contains 20 mg/mL dalbavancin as a clear, colorless to yellow solution.

Reconstituted vials may be stored either refrigerated at 2°C to 8°C (36°F to 46°F), or at controlled room temperature 20°C to 25°C (68°F to 77°F). Do not freeze.

Dilution:

Adult Patients: Aseptically transfer the required dose of reconstituted dalbavancin for injection solution from the vial(s) to an intravenous bag or bottle containing 5% Dextrose Injection, USP. The diluted solution must have a final dalbavancin concentration of 1 mg/mL to 5 mg/mL. Discard any unused portion of the reconstituted solution.

Pediatric Patients: For pediatric patients, the dose of dalbavancin for injection will vary according to the age and weight of the child up to a maximum of 1,500 mg [see *Dosage and Administration* (2.2)]. Aseptically transfer the required dose of reconstituted dalbavancin for injection solution, based on the child’s weight, from the vial(s) to an intravenous bag or bottle containing 5% Dextrose Injection, USP. The diluted solution must have a final dalbavancin concentration of 1 mg/mL to 5 mg/mL. Discard any unused portion of the reconstituted solution.

Once diluted into an intravenous bag or bottle as described above, dalbavancin for injection 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.

Like all parenteral drug products, diluted dalbavancin for injection should be inspected visually for particulate matter prior to infusion. If particulate matter is identified, do not use.

Administration: After reconstitution and dilution, administer dalbavancin for injection via intravenous infusion, using a total infusion time of 30 minutes.

Do not co-infuse dalbavancin for injection with other medications or electrolytes. Saline-based infusion solutions may cause precipitation and should not be used. The compatibility of reconstituted dalbavancin for injection with intravenous medications, additives, or substances other than 5% Dextrose Injection, USP has not been established.

If a common intravenous line is being used to administer other drugs in addition to dalbavancin for injection, the line should be flushed before and after each dalbavancin for injection infusion with 5% Dextrose Injection, USP.

DOSAGE FORMS AND STRENGTHS

Dalbavancin for injection is supplied as a white/off-white to pale yellow lyophilized sterile powder for reconstitution in a single-dose clear glass vial containing dalbavancin hydrochloride equivalent to 500 mg of dalbavancin.

CONTRAINDICATIONS

Dalbavancin for injection is contraindicated in patients with known hypersensitivity to dalbavancin.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Serious hypersensitivity (anaphylactic) and skin reactions have been reported in patients treated with dalbavancin for injection. If an allergic reaction to dalbavancin for injection occurs, discontinue treatment with dalbavancin for injection and institute appropriate therapy for the allergic reaction. Before using dalbavancin for injection, inquire carefully about previous hypersensitivity reactions to other glycopeptides. Due to the possibility of cross-sensitivity, carefully monitor for signs of hypersensitivity during treatment with dalbavancin for injection in patients with a history of glycopeptide allergy [see *Patient Counseling Information* (17)].

Infusion-Related Reactions

Dalbavancin for injection is administered via intravenous infusion, using a total infusion time of 30 minutes to minimize the risk of infusion-related reactions. Rapid intravenous infusions of dalbavancin for injection can cause flushing of the upper body, urticaria, pruritus, rash, and/or back pain. Stopping or slowing the infusion may result in cessation of these reactions.

Hepatic Effects

In Phase 2 and 3 clinical trials, more dalbavancin for injection than comparator-treated subjects with normal baseline transaminase levels had post-baseline alanine aminotransferase (ALT) elevation greater than 3 times the upper limit of normal (ULN). Overall, abnormalities in liver tests (ALT, AST, bilirubin) were reported with similar frequency in the dalbavancin for injection and comparator arms [see *Adverse Reactions* (6.1)].

Clostridioides difficile-Associated Diarrhea
Clostridioides difficile-associated diarrhea (CDAD) has been reported in users of nearly all systemic antibacterial drugs, including dalbavancin for injection, with severity ranging from mild diarrhea to fatal colitis. Treatment with antibacterial agents can alter the normal flora of the colon, and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* should be discontinued, if possible. Appropriate measures such as fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Development of Drug-Resistant Bacteria
Prescribing dalbavancin for injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

ADVERSE REACTIONS

The following clinically significant adverse reactions are also discussed elsewhere in the labeling:

- Hypersensitivity Reactions [see *Warnings and Precautions* (5.1)]
- Infusion Related Reactions [see *Warnings and Precautions* (5.2)]
- Hepatic Effects [see *Warnings and Precautions* (5.3)]
- Clostridioides difficile*-associated Diarrhea [see *Warnings and Precautions* (5.4)]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of dalbavancin for injection cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice.

Clinical Trials Experience in Adult Patients

Adverse reactions were evaluated for 2,473 patients treated with dalbavancin for injection: 1,778 patients were treated with dalbavancin for injection in seven Phase 2/3 trials comparing dalbavancin for injection to comparator antibacterial drugs and 695 patients were treated with dalbavancin for injection in one Phase 3 trial comparing dalbavancin for injection single dose and another dalbavancin dosing regimen. The median age of patients treated with dalbavancin for injection was 48 years, ranging between 16 and 93 years. Patients treated with dalbavancin for injection were predominantly male (59.5%) and White (81.2%).

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

Serious adverse reactions occurred in 121/2,473 (4.9%) of patients treated with any regimen of dalbavancin for injection. In the Phase 2/3 trials comparing dalbavancin for injection to comparator, serious adverse reactions occurred in 109/1,778 (6.1%) of patients in the dalbavancin for injection group and 80/1,224 (6.5%) of patients in the comparator group. In a Phase 3 trial comparing dalbavancin for injection single dose and another dalbavancin dosing regimen, serious adverse reactions occurred in 7/349 (2.0%) of patients in the dalbavancin for injection single dose group and 5/346 (1.4%) of patients in another dalbavancin dosing regimen group. Dalbavancin for injection was discontinued due to an adverse reaction in 64/2,473 (2.6%) patients treated with any regimen of dalbavancin for injection. In the Phase 2/3 trials comparing dalbavancin for injection to comparator, dalbavancin for injection was discontinued due to an adverse reaction in 53/1,778 (3.0%) of patients in the dalbavancin for injection group and 35/1,224 (2.9%) of patients in the comparator group. In a Phase 3 trial comparing dalbavancin for injection single dose and another dalbavancin dosing regimen, dalbavancin for injection was discontinued due to an adverse reaction in 6/349 (1.7%) of patients in the dalbavancin for injection single dose group and 5/346 (1.4%) of patients in another dalbavancin dosing regimen group.

Most Common Adverse Reactions

The most common adverse reactions in patients treated with dalbavancin for injection in Phase 2/3 trials were nausea (5.5%), headache (4.7%), and diarrhea (4.4%). The median duration of adverse reactions was 3.0 days in patients treated with dalbavancin for injection. In the Phase 2/3 trials comparing dalbavancin for injection to comparator, the median duration of adverse reactions was 3.0 days for patients in the dalbavancin for injection single dose and another dalbavancin dosing regimen group.

Table 2 lists selected adverse reactions occurring in 2% or more of patients treated with dalbavancin for injection in Phase 2/3 clinical trials.

Table 2. Selected Adverse Reactions Occurring in ≥ 2% of Patients Receiving Dalbavancin for Injection in Phase 2/3 Trials (Number (%) of Patients)

Adverse Reactions	Dalbavancin for Injection (N = 1,778)	Comparator* (N = 1,224)
Nausea	98 (5.5)	78 (6.4)
Diarrhea	79 (4.4)	72 (5.9)
Headache	83 (4.7)	59 (4.8)
Vomiting	50 (2.8)	37 (3)
Rash	48 (2.7)	30 (2.4)
Pruritus	38 (2.1)	41 (3.3)

*Comparators included linezolid, cefazolin, cephalixin, and vancomycin.

In the Phase 3 trial comparing the single dose and another dalbavancin dosing regimen, the adverse reaction that occurred in 2% or more of patients treated with dalbavancin for injection was nausea (3.4% in the dalbavancin for injection single dose group and 2% in another dalbavancin dosing regimen group).

The following selected adverse reactions were reported in dalbavancin for injection treated patients at a rate of less than 2% in these clinical trials:

Blood and lymphatic system disorders: anemia, hemorrhagic anemia, leucopenia, neutropenia, thrombocytopenia, petechiae, eosinophilia, thrombocytosis

Gastrointestinal disorders: gastrointestinal hemorrhage, melena, hematochezia, abdominal pain

General disorders and administration site conditions: infusion-related reactions

Hepatobiliary disorders: hepatotoxicity

Immune system disorders: anaphylactic reaction

Infections and infestations: *Clostridioides difficile* colitis, oral candidiasis, vulvovaginal mycotic infection

Investigations: hepatic transaminases increased, blood alkaline phosphatase increased, international normalized ratio increased, blood lactate dehydrogenase increased, gamma-glutamyl transferase increased

Metabolism and nutrition disorders: hypoglycemia

Nervous system disorders: dizziness

Respiratory, thoracic and mediastinal disorders: bronchospasm

Skin and subcutaneous tissue disorders: rash, pruritus, urticaria

Vascular disorders: flushing, phlebitis, wound hemorrhage, spontaneous hematoma

Alanine Aminotransferase (ALT) Elevations

Among patients with normal baseline ALT levels treated with dalbavancin for injection 17 (0.8%) had post baseline ALT elevations greater than 3 times the upper limit of normal (ULN) including five subjects with post-baseline ALT values greater than 10 times ULN.

Among patients with normal baseline ALT levels treated with non-dalbavancin for injection comparators 2 (0.2%) had post-baseline ALT elevations greater than 3 times the upper limit of normal. Fifteen of the 17 patients treated with dalbavancin for injection and one comparator patient had underlying conditions which could affect liver enzymes, including chronic viral hepatitis, history of alcohol abuse and metabolic syndrome. In addition, one dalbavancin for injection-treated subject in a Phase 1 trial had post-baseline ALT elevations greater than 20 times ULN. ALT elevations were

reversible in all subjects with follow-up assessments. No comparator-treated subject with normal baseline transaminases had post-baseline ALT elevation greater than 10 times ULN.

Clinical Trials Experience in Pediatric Patients

Adverse reactions were evaluated in one Phase 3 pediatric clinical trial which included 161 pediatric patients from birth to less than 18 years of age with ABSSSI treated with dalbavancin for injection (83 patients treated with a single dose and 78 patients treated with another dalbavancin dosing regimen) and 30 patients treated with comparator agents for a treatment period up to 14 days. The median age of pediatric patients treated with dalbavancin for injection was 9 years, ranging from birth to <18 years. The majority of patients were male (62.3%) and White (89.0%).

The safety findings of dalbavancin for injection in pediatric patients were similar to those observed in adults.

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

Serious adverse reactions (SARs) occurred in 3/161 (1.9%) of patients treated with dalbavancin for injection, all in the single-dose arm. There were no adverse reactions leading to dalbavancin for injection discontinuation.

Most Common Adverse Reactions

Most common adverse reaction occurring in more than 1% of pediatric patients 2/161 (1.2%) was pyrexia.

Other Adverse Reactions

The following selected adverse reactions were reported in dalbavancin for injection-treated patients at a rate of less than 1% in this pediatric clinical trial:

Gastrointestinal disorders: diarrhea

Nervous system disorders: dizziness

Skin and subcutaneous tissue disorders: pruritus

Post Marketing Experience

The following adverse reaction has been identified during post-approval use of dalbavancin. Because the reaction is reported voluntarily from a population of uncertain size, it is not possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

General disorders and administration site conditions: Back pain as an infusion-related reaction [See *Warnings and Precautions* (5.2)].

DRUG INTERACTIONS

Drug-Laboratory Test Interactions

Drug-laboratory test interactions have not been reported. Dalbavancin for injection at therapeutic concentrations does not artificially prolong prothrombin time (PT) or activated partial thromboplastin time (aPTT).

Drug-Drug Interactions

No clinical drug-drug interaction studies have been conducted with dalbavancin for injection. There is minimal potential for drug-drug interactions between dalbavancin for injection and cytochrome P450 (CYP450), substrates, inhibitors, or inducers [see *Clinical Pharmacology* (12.3)].

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with dalbavancin for injection use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse developmental outcomes.

No treatment-related malformations or embryo-fetal toxicity were observed in pregnant rats or rabbits at clinically relevant exposures of dalbavancin. Treatment of pregnant rats with dalbavancin at 3.5 times the human dose on an exposure basis during early embryonic development and from implantation to the end of lactation resulted in delayed fetal maturation and increased fetal loss, respectively [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

No evidence of embryo or fetal toxicity was found in the rat or rabbit at a dose of 15 mg/kg/day (1.2 and 0.7 times the human dose on an exposure basis, respectively). Delayed fetal maturation was observed in the rat at a dose of 45 mg/kg/day (3.5 times the human dose on an exposure basis).

In a rat prenatal and postnatal development study, increased embryo lethality and increased offspring deaths during the first week post-partum were observed at a dose of 45 mg/kg/day (3.5 times the human dose on an exposure basis).

Lactation

Risk Summary

There are no data on the presence of dalbavancin or its metabolite in human milk, the effects on the breast-fed child, or the effects on milk production. Dalbavancin is excreted in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for dalbavancin for injection and any potential adverse effects on the breast-fed child from dalbavancin for injection or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of dalbavancin for injection for the treatment of ABSSSI has been established in pediatric patients aged birth to less than 18 years. Use of dalbavancin for injection for this indication is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged birth to less than 18 years [see *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3), and *Clinical Studies* (14.1)].

There is insufficient information to recommend dosage adjustment for pediatric patients with ABSSSI and CLcr less than 30 mL/min/1.73m² [see *Dosage and Administration* (2.2)].

Geriatric Use

Of the 2,473 patients treated with dalbavancin for injection in Phase 2 and 3 clinical trials, 403 patients (16.3%) were 65 years of age or older. The efficacy and tolerability of dalbavancin for injection were similar to comparator regardless of age. The pharmacokinetics of dalbavancin for injection was not significantly altered with age; therefore, no dosage adjustment is necessary based on age alone.

Dalbavancin for injection is substantially excreted by the kidney, and 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 dose selection in this age group.

Renal Impairment

In patients with renal impairment whose known CLcr is less than 30 mL/min and who are not receiving regularly scheduled hemodialysis, the recommended regimen for dalbavancin for injection is 1,125 mg, administered as a single dose. No dosage adjustment is recommended for patients receiving regularly scheduled hemodialysis, and dalbavancin for injection can be administered without regard

12.3 Pharmacokinetics
General Pharmacokinetic Properties
Dalbavancin pharmacokinetic parameters have been characterized in healthy subjects, patients, and specific populations. Pharmacokinetic parameters following administration of single intravenous 1,000 mg and 1,500 mg doses were as shown in Table 4. The pharmacokinetics of dalbavancin can be described using a three-compartment model.

Table 4. Dalbavancin Pharmacokinetic Parameters in Healthy Subjects			
Parameter	Single 1,000 mg Dose	Single 1,500 mg Dose	
C _{max} (mg/L)	287 (13.9) ¹	423 (13.2) ⁴	
AUC ₀₋₂₄ (mg•h/L)	3,185 (12.8) ¹	4,837 (13.7) ⁴	
AUC _{0-Day7} (mg•h/L)	11,160 (41.1) ²	ND	
AUC _{0-inf} (mg•h/L)	23,443 (40.9) ²	ND	
Terminal t _{1/2} (h)	346 (16.5) ^{2,3}	ND	
CL (L/h)	0.0513 (46.8) ²	ND	

All values are presented as mean (% coefficient of variation)
¹ Data from 50 healthy subjects.
² Data from 12 healthy subjects.
³ Based upon population pharmacokinetic analyses of data from patients, the effective half-life is approximately 8.5 days (204 hours).
⁴ Data from 49 healthy subjects.
Abbreviation: ND = not determined

CLr 30 mL/min/1.73 m² and above. There is insufficient information to assess the exposure of dalbavancin for injection in the pediatric patients with CLcr less than 30 mL/min/1.73 m². No clinically important differences in drug exposure between pediatric age groups (including preterm neonates) and adults are expected following administration of the age-dependent recommended single dose of dalbavancin for injection. The median plasma AUC from 0 to 120 hours (AUC_{0-120h}) of dalbavancin in pediatric patient age groups from term neonates at birth to less than 18 years is expected to be comparable to that in adult patients (AUC_{0-120h}: 10,400 mg•h/L). The expected median plasma AUC_{0-120h} of dalbavancin in preterm neonates at birth (gestational age 26 weeks to <37 weeks) was approximately 62% of that in adult patients. The expected median maximum plasma concentrations (C_{max}) of dalbavancin for pediatric patient age groups ranged between approximately 53% to 73% of that in adult patients (C_{max}: 412 mg/L). However, in all pediatric age groups, the percentage of patients attaining PK/PD targets related to *in vivo* drug activity were above 90% or higher for MICs up to 0.25 mg/L.

Drug Interactions
Nonclinical studies demonstrated that dalbavancin is not a substrate, inhibitor, or inducer of CYP450 isoenzymes. In a population pharmacokinetic analysis, dalbavancin pharmacokinetics were not affected by co-administration with known CYP450 substrates, inducers or inhibitors, nor by individual medications including acetaminophen, aztreonam, fentanyl, metronidazole, furosemide, proton pump inhibitors (omeprazole, esomeprazole, pantoprazole, lansoprazole), midazolam, and simvastatin.

12.4 Microbiology
Mechanism of Action
Dalbavancin, a semisynthetic lipoglycopeptide, interferes with cell wall synthesis by binding to the D-alanyl-D-alanine terminus of the stem pentapeptide in nascent cell wall peptidoglycan, thus preventing cross-linking. Dalbavancin is bactericidal *in vitro* against *Staphylococcus aureus* and *Streptococcus pyogenes* at concentrations similar to those sustained throughout treatment in humans treated according to the recommended dosage regimen.

Resistance
The development of bacterial isolates resistant to dalbavancin has not been observed, either *in vitro*, in studies using serial passage, or in animal infection experiments.

Interaction with Other Antimicrobials
When tested *in vitro*, dalbavancin demonstrated synergistic interactions with oxacillin and did not demonstrate antagonistic or synergistic interactions with any of the following antibacterial agents of various classes: gentamicin, vancomycin, levofloxacin, clindamycin, quinupristin/dalfopristin, linezolid, aztreonam, rifampin or daptomycin. The clinical significance of these *in vitro* findings is unknown.

Antimicrobial Activity
Dalbavancin has been shown to be active against the following microorganisms, both *in vitro* and in clinical infections [see *Indications and Usage (1)*].

- Aerobic bacteria
 - Gram-positive bacteria
 - Staphylococcus aureus* (including methicillin-resistant isolates)
 - Streptococcus pyogenes*
 - Streptococcus agalactiae*
 - Streptococcus dysgalactiae*
 - Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, *S. constellatus*)
 - Enterococcus faecalis* (vancomycin-susceptible isolates only)

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for dalbavancin against isolates of similar genus or organism group. However, the efficacy of dalbavancin in treating clinical infections caused by these bacteria has not been established in adequate well-controlled clinical trials.

- Aerobic bacteria
 - Gram-positive bacteria
 - Enterococcus faecium* (vancomycin-susceptible isolates only)

Susceptibility Testing
For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: <https://www.fda.gov/STIC>.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Long-term studies in animals to determine the carcinogenic potential of dalbavancin have not been conducted.

Mutagenesis
Dalbavancin was not genotoxic in a bacterial reverse mutation (Ames) assay, a mammalian HGPRT gene mutation assay, an *in vitro* chromosome aberration assay in Chinese Hamster Ovary cells, or an *in vivo* mouse micronucleus assay.

Impairment of Fertility
Impaired fertility in the rat was not observed at a dose of 15 mg/kg/day (1.2 times the human dose on an exposure basis). Reductions in male and female fertility and increased embryo resorptions occurred at a dose of 45 mg/kg/day (3.5 times the human dose on an exposure basis), at which signs of parental toxicity were also observed.

13.2 Animal Toxicology and/or Pharmacology
Increases in serum levels of liver enzymes (ALT, AST), associated with microscopic findings in the liver were noted in toxicology studies in rats and dogs where dalbavancin was administered daily for 28 to 90 days. Hepatocellular necrosis was observed in dogs dosed at ≥10 mg/kg/day for longer than 2 months, i.e., at approximately 5 to 7 times the expected human dose on an exposure basis. Histiocytic vacuolation and hepatocyte necrosis were observed in rats dosed daily at 40 and 80 mg/kg/day, respectively, for 4 weeks, (approximately 3 and 6 times the expected human dose on an exposure basis, respectively). In addition, renal toxicity characterized by increases in serum BUN and creatinine and microscopic kidney findings was observed in rats and dogs at doses 5 to 7 times the expected human dose on an exposure basis. The relationship between these findings in the animal toxicology studies after 28 and 90 consecutive days of dosing to the indicated clinical dosing of 2 doses 7 days apart are unclear.

14 Clinical Studies of Dalbavancin for Injection in Adult Patients with Acute Bacterial Skin and Skin Structure Infections
Dalbavancin for Injection 1,500 mg Single Dose Regimen
Adult patients with ABSSSI were enrolled in a Phase 3, double-blind, clinical trial. The ITT population included 698 patients who were randomized to dalbavancin for injection treatment with either a single 1,500 mg dose or another dalbavancin dosing regimen (Trial 3). Patients with creatinine clearance less than 30 mL/min had their dose adjusted (Section 2.2). Approximately 5% of patients also received a protocol-specified empiric course of treatment with intravenous aztreonam for coverage of Gram-negative pathogens. The specific infections and other patient characteristics in this trial were similar to those described above for previous ABSSSI trials.

The primary endpoint in this ABSSSI trial was the clinical response rate where responders were defined as patients who had at least a 20% decrease from baseline in lesion area 48 to 72 hours after randomization without receiving any rescue antibacterial therapy. The secondary endpoint was the clinical success rate at a follow-up visit occurring between Days 26 and 30, with clinical success defined as having at least a 90% decrease from baseline in lesion size, a temperature of 37.6°C or lower, and meeting pre-specified criteria for local signs: purulent discharge and drainage absent or mild and improved from baseline (for patients with wound infections), heat/warmth and fluctuance absent, swelling/induration and tenderness to palpation absent or mild. Table 9 summarizes results for these two endpoints in the ITT population. Note that there are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at the follow-up visit. Therefore, comparisons between treatment groups based on clinical success rates at this visit cannot be utilized to establish non-inferiority.

Table 9. Primary and Secondary Efficacy Results in ABSSSI Patients (Trial 3) ^{1,2}			
	Dalbavancin for Injection, n/N (%)		
	Single Dose (1,500 mg)	Another Dalbavancin Dosing Regimen	Difference (95% CI) ³
Clinical Responders at 48-72 Hours (ITT)	284/349 (81.4)	294/349 (84.2)	-2.9 (-8.5, 2.8)
Clinical Success at Day 26-30 (ITT)	295/349 (84.5)	297/349 (85.1)	-0.6 (-6.0, 4.8)
Clinical Success at Day 26-30 (CE)	250/271 (92.3)	247/267 (92.5)	-0.3 (-4.9, 4.4)

¹ There were 3 patients in another dalbavancin dosing regimen group who did not receive treatment and were counted as non-responders.
² Patients who died or used non-study antibacterial therapy or had missing measurements were classified as non-responders.
³ The 95% Confidence Interval (CI) is computed using the Miettinen and Nurminen approach. Abbreviations: ITT=intent to treat; CE=clinically evaluable

Table 10 shows outcomes in patients with an identified baseline pathogen from Trial 3 in the microbiological ITT (microITT) population. The outcomes shown in the table are clinical response rates at 48 to 72 hours and clinical success rates at follow-up (Day 26 to 30), as defined above.

Table 10. Outcomes by Baseline Pathogen (Trial 3; MicroITT)				
Pathogen	Early Clinical Response at 48-72 hours		Clinical Success at Day 26 to 30	
	≥ 20% reduction in lesion size			
	Single dose (1,500 mg) n/N (%)	Another Dalbavancin Dosing Regimen n/N (%)	Single dose (1,500 mg) n/N (%)	Another Dalbavancin Dosing Regimen n/N (%)
<i>Staphylococcus aureus</i>	123/139 (88.5)	133/156 (85.3)	124/139 (89.2)	140/156 (89.7)
Methicillin-susceptible	92/103 (89.3)	89/96 (89.6)	93/103 (90.3)	86/96 (89.6)
Methicillin-resistant	31/36 (86.1)	48/61 (78.7)	31/36 (86.1)	55/61 (90.2)
<i>Streptococcus agalactiae</i>	6/6 (100.0)	4/6 (66.7)	5/6 (83.3)	5/6 (83.3)
<i>Streptococcus anginosus</i> group	31/33 (93.9)	19/19 (100.0)	29/33 (87.9)	17/19 (89.5)
<i>Streptococcus pyogenes</i>	14/14 (100.0)	18/22 (81.8)	13/14 (92.9)	19/22 (86.4)
<i>Enterococcus faecalis</i>	4/4 (100.0)	8/10 (80.0)	4/4 (100.0)	9/10 (90.0)

In Trial 3, all patients had blood cultures obtained at baseline. A total of 40 ABSSSI patients who received dalbavancin for injection had bacteremia at baseline caused by one or more of the following bacteria: 26 *S. aureus* (21 MSSA and 5 MRSA), 6 *S. agalactiae*, 7 *S. pyogenes*, 2 *S. anginosus* group, and 1 *E. faecalis*. In patients who received dalbavancin for injection, a total of 34/40 (85%) were clinical responders at 48-72 hours and 32/40 (80%) were clinical successes at Day 26 to 30.

Clinical Study of Dalbavancin for Injection in Pediatric Patients with Acute Bacterial Skin and Skin Structure Infections

The pediatric trial was a multicenter, open-label, randomized, actively controlled trial (NCT02814916, Trial 4) conducted in pediatric patients 3 months of age to less than 18 years with ABSSSI, not known or expected to be caused exclusively by Gram-negative organisms. Patients were randomized in a 3:3:1 ratio to receive either dalbavancin single-dose regimen, another dalbavancin dosing regimen, or comparator. The comparator regimens included IV vancomycin for methicillinresistant Gram-positive infections, or IV oxacillin or flucloxacillin for methicillinsusceptible Gram-positive infections. Patients in the comparator arm received IV treatment for a minimum of 72 hours before an optional switch to oral therapy to complete a total of 10-14 days of antibacterial drug therapy. Additional 5 patients from birth to < 3 months of age were enrolled and assigned to the dalbavancin for injection single-dose regimen.

A study population of 191 pediatric patients received study medication (dalbavancin single dose regimen n=83, another dalbavancin dosing regimen n=78, comparator n=30); 62% of the patients were male and 89% were white, and 83% were from Eastern Europe. The pediatric age groups who received dalbavancin for injection were as follows:

12 to < 18 years (n=58), 6 to < 12 years (n=49), 2 to < 6 years (n=35), 3 months to < 2 years (n=14), and birth < 3 months (n=5). Patients had diagnoses of major cutaneous abscess (53%), cellulitis (29%), or surgical site/traumatic wound infection (18%). The predominant pathogen at baseline was *Staphylococcus aureus* (84%).

The primary objective was to evaluate the safety and tolerability of dalbavancin for injection. The trial was not powered for a comparative inferential efficacy analysis. Efficacy was assessed in the modified intent-to-treat population (n=183) which included all randomized patients who received any dose of study drug and had a diagnosis of ABSSSI caused by Gram-positive organism(s). Patients with ABSSSI only caused by Gram-negative organisms were excluded. The five patients in the age group birth to < 3 months of age were not included in efficacy analyses since they were enrolled with expanded inclusion criteria and only received the single dose dalbavancin for injection regimen. An early clinical response at 48-72 hours was defined as ≥ 20% reduction in lesion size compared to baseline and no receipt of rescue antibacterial therapy. The proportion of patients with early clinical response, was 97.3% (73/75) in the dalbavancin for injection single-dose arm, 93.6% (73/78) in another dalbavancin dosing regimen arm, and 86.7% (26/30) in the comparator arm. The difference in responder rates between the dalbavancin single-dose and comparator arms was 10.7%, with an exact 97.5% confidence interval (CI) of (-1.7%, 31.6%). The difference in responder rates between another dalbavancin dosing regimen and comparator arms was 6.9%, with an exact 97.5% CI of (-6.4%, 27.7%).

Clinical cure was defined as resolution of the clinical signs and symptoms of infection, when compared to baseline, and no additional antibacterial treatment for the disease under study. In patients, 3 months of age or older in the mITT population, the clinical cure rate at the test of cure (TOC) visit (28 ± 2 days) was 94.7% (71/75) in the dalbavancin for injection single-dose arm, 92.3% (72/78) in another dalbavancin dosing regimen arm and 100% (30/30) in the comparator arm. The difference in cure rates between the dalbavancin single- dose and comparator arms was -5.3%, with an exact 97.5% CI of (-15.1%, 10.5%). The difference in cure rates between another dalbavancin dosing regimen and comparator arms was -7.7%, with an exact 97.5% CI of (-17.9%, 8.3%).

16 HOW SUPPLIED/STORAGE AND HANDLING
Dalbavancin for injection is supplied as a white/off-white to pale yellow sterile lyophilized powder in a single-dose glass vial containing dalbavancin hydrochloride equivalent to 500 mg dalbavancin:

Product Code	Unit of Sale	Strength
221012	NDC 65219-120-12 Individually packaged	500 mg per single-dose vial

Dalbavancin for injection should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Storage of the reconstituted and diluted solutions of dalbavancin for injection are described elsewhere in the prescribing information [see *Dosage and Administration (2.4)*].

The container closure is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION
Allergic Reactions
Advise patients that allergic reactions, including serious allergic reactions, could occur with dalbavancin for injection, and that serious allergic reactions require immediate treatment. Patients should inform their healthcare provider about any previous hypersensitivity reactions to dalbavancin for injection, or other glycopeptides [see *Warnings and Precautions (5.1)*].

Diarrhea
Advise patients that diarrhea is a common problem caused by antibacterial drugs, including dalbavancin for injection, and usually resolves when the drug is discontinued. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, patients should contact their healthcare provider [see *Warnings and Precautions (5.4)*].

Development of Drug-Resistant Bacteria
Patients should be counseled that antibacterial drugs including dalbavancin for injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When dalbavancin for injection is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by dalbavancin for injection or other antibacterial drugs in the future [see *Warnings and Precautions (5.5)*].

Manufactured by:

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