

Brand Name: Dalvance

Generic Name: dalbavancin

Manufacturer¹: DURATA therapeutics

Drug Class^{1,2,3,4}: Antibiotic

Uses:

Labeled Uses¹:

Treatment of adult patients with acute bacterial skin and skin structure infections caused by susceptible isolates of the following Gram-positive microorganisms:

- Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains), Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus group (including S. anginosus, S. intermedius, S. constellatus)

Mechanism of Action:^{1,2,3,4}

This drug is a lipoglycopeptide which binds to the D-alanyl-D-alanine terminus of the stem pentapeptide in nascent cell wall. Through this above mechanism it prevents cross-linking and interferes with cell wall synthesis. Dalbavancin is bactericidal in vitro against Staphylococcus aureus and Streptococcus pyogenes.

Pharmacokinetics^{1,2,3,4}

Tmax	End of infusion time
Vd	7-13L
t1/2	346 hours
Clearance	.0513 l/h
Protein binding (albumin)	93% (primarily to albumin)
Bioavailability	100%

Metabolism^{1,2,3,4}:

A minor metabolite- hydroxy-dalbavancin has been observed in the urine of healthy subjects, however quantifiable plasma concentrations have not been observed.

Elimination^{1,2,3,4}:

- Urine (33% as unchanged drug, 12% as hydroxy metabolite)
- Feces (20%)

Efficacy:

Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW. Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection. N Engl J Med 2014; 370:2169-2179.

Study Design:

Double blind, double dummy, randomized controlled study

Description of Study:

Discover 1 and Discover 2 were international, multicenter, randomized trials conducted from 2011 through 2012 at 54 and 86 investigative sites, respectively. The studies had the same design. Patients with acute bacterial skin and skin-structure infection were stratified then randomly assigned to receive dalbavancin intravenously on days 1 and 8 or vancomycin intravenously for at least 3 days with the option to switch to oral linezolid to complete 10 to 14 days of therapy. The primary end point, early clinical response, required the cessation of spread of infection-related erythema and the absence of fever at 48 to 72 hours. Secondary end points at the end of therapy included clinical status and investigator's assessment of outcome

Results:

Analysis of the primary end point showed noninferiority of dalbavancin in both DISCOVER 1 and DISCOVER 2. In the pooled analysis, 525 of 659 patients (79.7%) in the dalbavancin group and 521 of 653 (79.8%) in the vancomycin–linezolid group had an early clinical response showing treatment success (95% confidence interval, –4.5 to 4.2). For patients infected with *Staph. aureus*, including MRSA clinical success was seen in 90.6% of the patients treated with dalbavancin and 93.8% of those treated with vancomycin–linezolid (no p-values given).

Limitations:

The study was sponsored by the manufacturer which could potentially introduce bias. Unblinding was more likely with dalbavancin group, thus some results such as side effects could have been affected. Another limitation was that not all results presented had a p value reported. Also, the study used vancomycin and linezolid together as a control and not each drug individually which makes the comparison of dalbavancin to each control drug individually challenging.

Conclusion:

The study utilized a good study design and despite the study’s limitations the results were significant and showed non inferiority of dalbavancin to vancomycin/linezolid in regards to treatment of skin infections.

Raad I, Darouiche R, Vazquez J, Lentnek A, Hachem R, Hanna H, et al. Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens. *Clin Infect Dis.* 2005 Feb 1;40(3):374-80.

Study Design:

Phase 2, open-label, randomized, controlled, multicenter study

Description of Study:

75 adult patients with catheter related blood stream infection received treatment with intravenous dalbavancin, administered as a single 1000-mg dose followed by a 500-mg dose 1 week later, or intravenous vancomycin, administered twice daily for 14 days. Gram-positive bacteria isolated in this study included coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus*, including methicillin-resistant *Staphylococci aureus* (MRSA). The primary outcome measure was overall efficacy at the follow-up visit (determined on the basis of combined clinically and microbiologically documented responses among patients with a bacterial pathogen identified at study entry). Secondary outcomes included individual evaluation of clinical and microbiological responses at end of therapy and end of cure.

Results:

Dalbavancin group had an overall success rate (87.0%; 95% confidence interval (CI) 73.2%–100.0%) that was significantly higher than the vancomycin group (50.0%; 95% CI, 31.5%–68.5%) and there was a significant association between treatment group and overall success rate (P=0.0355). Dalbavancin therapy was statistically superior to vancomycin therapy (P <0 .05) by virtue of the non-overlapping 95% CIs around the response rates. Adverse events and laboratory abnormalities were generally mild and were comparable for the 2 drugs.

Limitations:

The study had a potential for bias because the study was open label, the authors work for the manufacturer and the study was sponsored by the manufacturer. Also, the small number of study subjects makes it harder to extrapolate the results to the population.

Conclusion:

The study’s design was weak because it was open label. Even though the results were statistically significant it is not possible to make a definitive conclusion because of the study’s limitations. Further research is warranted to establish superiority or non-inferiority of dalbavancin to vancomycin.

Jauregui L, Babazadeh S, Seltzer E, Goldberg L, Krievins D, Frederick M, et al. Randomized, Double-Blind Comparison of Once-Weekly Dalbavancin versus Twice-Daily Linezolid Therapy for the Treatment of Complicated Skin and Skin Structure Infections. *Clin Infect Dis.* 2005 Nov 15;41(10):1407-1415.

Study Design:

Double blind, controlled, randomized

Description of Study:

This was a phase 3 non inferiority study that included adult patients with complicated skin and skin structure infections (including infections known or suspected to involve MRSA). The subjects were randomized (ratio, 2 : 1) to receive dalbavancin (1000 mg given intravenously on day 1 and 500 mg given intravenously on day 8) or linezolid (600 mg given intravenously or intravenously/orally every 12 h for 14 days). The efficacy was assessed by determining clinical and microbiological responses at the end of therapy and at the test-of-cure visit. Relapses were identified by additional follow-up ~1 month later. Relapse was defined as receipt of antibacterials for the skin and skin structure infections after the test-of-cure visit.

Results:

Dalbavancin and linezolid demonstrated comparable clinical efficacy at the test-of-cure visit: 88.9% and 91.2% success (The lower limit of the 95% CI (-7.28%) was within the limit for demonstration of non-inferiority (-12.5%)). The rate of clinical success at the end of therapy was >90% in both arms. Less than 1.0% of patients in either treatment arm experienced relapse after the test-of-cure visit. Both treatments yielded successful microbiological response in excess of 85% among microbiologically evaluable patients at end of therapy and at the test-of-cure visit for all pathogens combined.

Limitations:

The study had potential for bias because 2 of the authors work for the manufacturer. The Results couldn't be assessed for statistical significance because no p values or other measure of assessment was provided to the reader.

Conclusion:

Overall the study utilized a good study design being controlled, blinded, and double dummy. The biggest downside of the study was lack of p-values or some other measure to assess statistical significance of the results. Also, the study had an uneven distribution between the two groups making the evidence found during the study weaker. Future research is warranted to better determine the non-inferiority or superiority of the two therapies.

Contraindications^{1,2,3,4}:

Hypersensitivity to dalbavancin

Precautions^{1,2,3,4}:

Gastrointestinal:

- Use may result in fungal or bacterial superinfection, including *Clostridium difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months post antibiotic treatment. Patient should be evaluated for clostridium difficile-associated diarrhea (CDAD) if suspected and appropriate treatment (eg, discontinuation of dalbavancin use, antibiotic treatment of C difficile, surgical evaluation, fluid and electrolyte management, protein supplementation) should be implemented if suspected or confirmed.

Hepatic:

- ALT elevation greater than 3 times ULN has been reported

Immunologic:

- Serious hypersensitivity (anaphylactic) and skin reactions have been reported; discontinue use if an allergic reaction occurs. Use caution when dalbavancin is given to patients with a history of hypersensitivity to glycopeptides (cross-sensitivity is possible).

Other:

- Rapid intravenous infusions of Dalvance can cause reactions that resemble Red-Man syndrome, including flushing of the upper body, urticaria, pruritus, and/or rash. stopping or slowing the infusion

may result in cessation of these reactions. Administer in a dilute solution over at least 30 minutes to avoid the above reaction.

Adverse Effects^{1,2,3,4}:

Most common

- Nausea: 6%
- Headache: 5%
- Diarrhea: 4%

Others by body system

- Cardiovascular: Flushing, phlebitis (<2%)
- Central nervous system: dizziness (<2%)
- Dermatologic: Skin rash, pruritus, urticaria (<2-3%)
- Endocrine & Metabolic: Hypoglycemia (<2%)
- Gastrointestinal: vomiting, abdominal pain, gastrointestinal hemorrhage, hematochezia, melena, oral candidiasis, pseudomembranous colitis (<2-3%)
- Hematologic & oncologic: Acute posthemorrhagic anemia (<2%), anemia (<2%), eosinophilia (<2%), hematoma (spontaneous; <2%), increased INR (<2%), leukopenia (<2%), neutropenia (<2%), petechia (<2%), thrombocythemia (<2%), thrombocytopenia (<2%), wound hemorrhage (<2%)
- Hepatic: Hepatotoxicity (<2%)
- Hepatic: Increased serum alkaline phosphatase, increased serum transaminases (<2%)
- Hypersensitivity: Anaphylactoid reaction (<2%)
- Infection: Vulvovaginal infection (<2%)
- Respiratory: Bronchospasm (<2%)
- Miscellaneous: Infusion related reaction (<2%)
- Alanine Aminotransferase (ALT) Elevations

Drug Interactions^{1,2,3,4}:

- BCG: Antibiotics may diminish the therapeutic effect of BCG. Avoid combination.
- Sodium Picosulfate: Antibiotics may diminish the therapeutic effect of Sodium Picosulfate. Consider therapy modification.
- Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated vaccine is affected. Vaccination with live attenuated typhoid vaccine should be avoided in patients being treated with systemic antibacterial agents.

Dosing:^{1,2,3,4}

- Adult Dosing
 - 1000 mg followed one week later by 500 mg
- Pediatrics (≥4 years of age)
 - The safety and efficacy have not been established
- Geriatrics
 - Refer to adult dosing
- Renal impairment
 - CrCl ≥30 mL/minute: No dosage adjustment necessary
 - CrCl <30 mL/minute: 750 mg as a single dose initially, followed by 375 mg as a single dose 1 week later
 - ESRD patients receiving regularly scheduled intermittent hemodialysis (IHD): No dosage adjustment necessary; administer without regard to hemodialysis
- Hepatic impairment
 - Mild hepatic impairment (Child-Pugh class A): No dosage adjustment necessary

- Moderate or severe hepatic impairment (Child-Pugh class B or C): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); use with caution

Administration: I.V.^{1,2,3,4}

- Infuse over 30 minutes
- If a common I.V. line is being used to administer other drugs in addition to dalbavancin the line should be flushed with D₅W before and after each infusion.

Preparations:^{1,2,3,4}

- IV- Solution Reconstituted 500 mg

Preparation for Administration:^{1,2,3,4}

- Must be reconstituted under aseptic conditions
- 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
- Dilute for infusion in D₅W (final solution concentration 1 to 5 mg/mL)

Storage/Stability:^{1,2,3,4}

- Store intact vials at 25°C (77°F)
 - Excursions are permitted between 15°C and 30°C (59°F and 86°F)
- Reconstituted vials and diluted solution may be stored refrigerated at 2°C to 8°C (36°F to 46°F) or at room temperature 20°C to 25°C (68°F to 77°F)
 - Do not freeze
 - The total time from reconstitution to dilution to administration should be ≤48 hours
- Stable in D₅W
- Incompatible: NS or any saline-based solution

Use in special circumstances^{1, 2, 3, 4:}

- Pregnancy category C
 - There have been no adequate and well-controlled studies with dalbavancin in pregnant women.
 - Dalvance should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
 - No evidence of embryo or fetal toxicity was found in the rat or rabbit at a dose of 15 mg/kg/day
 - Delayed fetal maturation was observed in the rat at a dose of 45 mg/kg/day
 - 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
- Lactation
 - Dalbavancin is excreted in the milk of lactating rats.
 - It is not known whether dalbavancin or its metabolite is excreted in human milk
 - Caution should be exercised when Dalvance is administered to a nursing woman

Conclusion:

Dalbavancin is an alternative for patients that don't want daily drug administrations or have contraindications to the current standard of care, however, the cost makes its place in therapy limited and uncertain. The Discover studies were well designed and showed non-inferiority of dalbavancin to linezolid/vancomycin combination, however non inferiority studies didn't discuss Dalbavancin's place in therapy. Another problem with this novel therapy is the extremely long half-life of 346 hours. If a patient experiences any unwanted/harmful effects from the drug, it would be difficult to rectify the situation. Though dalbavacin does provide an alternative to the

current treatment of choice, its place in therapy is still not well established and should be reserved for patients unable to receive vancomycin and/or linezolid.

Recommended References:

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5. Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW. Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection. *N Engl J Med* 2014; 370:2169-2179.
6. Raad I, Darouiche R, Vazquez J, Lentnek A, Hachem R, Hanna H, et al. Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens. *Clin Infect Dis*. 2005 Feb 1;40(3):374-80.
7. Jauregui L, Babazadeh S, Seltzer E, Goldberg L, Krievins D, Frederick M, et al. Randomized, Double-Blind Comparison of Once-Weekly Dalbavancin versus Twice-Daily Linezolid Therapy for the Treatment of Complicated Skin and Skin Structure Infections. *Clin Infect Dis*. 2005 Nov 15;41(10):1407-1415.

Prepared by: Dina Tsybina, Doctor of Pharmacy Candidate