DALVANCE: AN OPPORTUNITY FOR USE AT VARIOUS SITES OF CARE

One 30-minute infusion a week for two weeks provides a full course of therapy in treating adults with acute bacterial skin and skin structure infections (ABSSSI)—two-dose regimen: 1000 mg followed one week later by 500 mg.*

INDICATION
DALVANCE® (dalbavancin) for injection is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive microorganisms: Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains), Streptococcus pyogenes, Streptococcus agalactiae, and Streptococcus anginosus group (including S. anginosus, S. intermedius, S. constellatus).

IMPORTANT SAFETY INFORMATION
Contraindications
DALVANCE is contraindicated in patients with known hypersensitivity to dalbavancin.

Warnings and Precautions
HYPERSENSITIVITY REACTIONS
Serious hypersensitivity (anaphylactic) and skin reactions have been reported with glycopeptide antibacterial agents, including DALVANCE. Exercise caution in patients with known hypersensitivity to glycopeptides due to the possibility of cross-sensitivity. If an allergic reaction occurs, treatment with DALVANCE should be discontinued.

*In patients with renal impairment whose known creatinine clearance is less than 30 mL/min and who are not receiving regularly scheduled hemodialysis, the recommended two-dose regimen for DALVANCE is 750 mg followed one week later by 375 mg.

• In the Phase 3 clinical trials, approximately 25% of patients receiving DALVANCE and the comparator were treated in outpatient settings²

Please see additional Important Safety Information throughout. Please see full Prescribing Information.
THE ECONOMIC BURDEN OF HOSPITALIZATION IN ABSSSI

Example of allocation of U.S. costs by department for treating ABSSSI in an inpatient setting\(^1,3\)

Hospital costs and utilization were evaluated using a national hospital database for 2013 covering 190,969 hospital discharges with the principal diagnosis of ABSSSI after exclusion criteria were applied. Diagnoses and procedures were categorized according to ICD-9 and CPT codes current at the time. Average length of stay (LOS) was 5 days. The most frequent initial antibiotic treatments included vancomycin, piperacillin/tazobactam, clindamycin, linezolid, daptomycin, and tigecycline.

Allocation of Costs for ABSSSI Inpatient Care\(^1,3\)

<table>
<thead>
<tr>
<th>Resource</th>
<th>Cost per unit(^4)</th>
<th>5 days(^1) inpatient</th>
<th>7 days outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital bed</td>
<td>$1,853/day</td>
<td>$9,265</td>
<td>N/A</td>
</tr>
<tr>
<td>Vancomycin 1g bid(^2)</td>
<td>$11.58/day</td>
<td>$58</td>
<td>$81</td>
</tr>
<tr>
<td>Therapeutic drug monitoring—renal function and trough levels</td>
<td>$102/blood draw</td>
<td>$102</td>
<td>$102</td>
</tr>
<tr>
<td>PICC line placement</td>
<td>$786/placement</td>
<td>$786</td>
<td>N/A</td>
</tr>
<tr>
<td>PICC line complication management(^3)</td>
<td>$188/patient</td>
<td>$188</td>
<td>N/A</td>
</tr>
<tr>
<td>Total</td>
<td>$10,399</td>
<td>$183</td>
<td></td>
</tr>
</tbody>
</table>

*Illustrative costs do not include all costs associated with treatment of ABSSSI and do not represent overall cost of care.

\(^1\)Average length of stay for ABSSSI patients.
\(^2\)Cost of vancomycin updated July 2014.
\(^3\)Average cost per patient.

PICC=Peripherally inserted central catheter
Dalvance® (dalbavancin) for injection is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive microorganisms: Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains), Streptococcus pyogenes, Streptococcus agalactiae, and Streptococcus anginosus group (including S. anginosus, S. intermedius, S. constellatus).

Important Safety Information

Contraindications
Dalvance is contraindicated in patients with known hypersensitivity to dalbavancin.

Warnings and Precautions
HyperSensitivity Reactions
Serious hypersensitivity (anaphylactic) and skin reactions have been reported with glycopeptide antibacterial agents, including Dalvance. Exercise caution in patients with known hypersensitivity to glycopeptides due to the possibility of cross-sensitivity. If an allergic reaction occurs, treatment with Dalvance should be discontinued.

Infusion-related Reactions
Rapid intravenous infusion of Dalvance can cause reactions, including flushing of the upper body, urticaria, pruritus, and rash.

Hepatic Effects
ALT elevations with Dalvance treatment were reported in clinical trials.

Clostridium difficile-Associated Diarrhea
Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents, including Dalvance, with severity ranging from mild diarrhea to fatal colitis. Evaluate if diarrhea occurs.

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

Adverse Reactions
The most common adverse reactions in patients treated with Dalvance were nausea (5.5%), headache (4.7%), and diarrhea (4.4%).

Use in Specific Populations
- There have been no adequate and well-controlled studies with Dalvance in pregnant or nursing women. Dalvance should only be used if the potential benefit justifies the potential risk in these populations.
- In patients with renal impairment whose known creatinine clearance is less than 30 ml/min and who are not receiving regularly scheduled hemodialysis, the recommended two-dose regimen for Dalvance is 750 mg followed one week later by 375 mg. No dosage adjustment is recommended for patients receiving regularly scheduled hemodialysis, and Dalvance can be administered without regard to the timing of hemodialysis.
- Caution should be exercised when prescribing Dalvance to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) as no data are available to determine the appropriate dosing in these patients.

Please see full Prescribing Information.
References:


3. 2013 U.S. Premier Hospital database.

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use DALVANCE™ safely and effectively. See full prescribing information for DALVANCE.

**DALVANCE** (dalbavancin) for injection, for intravenous use

Initial U.S. Approval: 2014

**INDICATIONS AND USAGE**
DALVANCE is indicated for acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of Gram-positive microorganisms. (1)

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

**DOSAGE AND ADMINISTRATION**
- Two-dose regimen: 1000 mg followed one week later by 500 mg (2.1)
- Dosage adjustment for patients with creatinine clearance less than 30 mL/min and not receiving regularly scheduled hemodialysis: 750 mg followed one week later by 375 mg (2.2)
- Administer by intravenous infusion over 30 minutes (2.3)

**DOSAGE FORMS AND STRENGTHS**
For injection: 500 mg of lyophilized powder in a single-use vial for reconstitution (3)

**CONTRAINDICATIONS**
Hypersensitivity to dalbavancin (4)

**WARNINGS AND PRECAUTIONS**
- Serious hypersensitivity (anaphylactic) and skin reactions have been reported with glycopeptide antibacterial agents, including DALVANCE; exercise caution in patients with known hypersensitivity to glycopeptides. (5.1)
- Rapid intravenous infusion of glycopeptide antibacterial agents can cause reactions. (5.2)
- ALT elevations with DALVANCE treatment were reported in clinical trials. (5.3)
- Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents, including DALVANCE. Evaluate if diarrhea occurs. (5.4)

**ADVERSE REACTIONS**
The most common adverse reactions in patients treated with DALVANCE were nausea (5.5%), headache (4.7%), and diarrhea (4.4%).

To report SUSPECTED ADVERSE REACTIONS, contact Durata Therapeutics, Inc. at 1-855-387-2825 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**USE IN SPECIFIC POPULATIONS**
Dosage adjustment is required in patients whose creatinine clearance is less than 30 mL/min and who are not receiving regularly scheduled hemodialysis. (8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised May 2014
1 INDICATION AND USAGE

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

1.2 Usage
To reduce the development of drug-resistant bacteria and maintain the effectiveness of DALVANCE and other antibacterial agents, DALVANCE should be used only to treat 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
For treatment of adults with ABSSSI, the recommended two-dose regimen of DALVANCE is 1000 mg followed one week later by 500 mg. DALVANCE should be administered over 30 minutes by intravenous infusion. No dosage adjustment is required for patients receiving regularly scheduled hemodialysis, and DALVANCE can be administered without regard to the timing of hemodialysis. Reconstituted vials may be stored either refrigerated at 2 to 8 °C (36 to 46 °F), or at controlled room temperature 20 to 25 °C (68 to 77 °F). Do not freeze.

2.2 Patients with Renal Impairment
In patients with renal impairment whose known creatinine clearance is less than 30 mL/min and who are not receiving regularly scheduled hemodialysis, the recommended two-dose regimen of DALVANCE is 750 mg followed one week later by 375 mg. No dosage adjustment is recommended for patients receiving regularly scheduled hemodialysis, and DALVANCE can be administered without regard to the timing of hemodialysis.

2.3 Preparation and Administration
DALVANCE (dalbavancin) for injection must be reconstituted with Sterile Water for Injection, USP, and subsequently diluted using 5% Dextrose Injection, USP, to a final concentration of 1 mg/mL to 5 mg/mL.

Reconstitution: DALVANCE must be reconstituted under aseptic conditions, using 25 mL of Sterile Water for 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 to 8 °C (36 to 46 °F), or at controlled room temperature 20 to 25 °C (68 to 77 °F). Do not freeze. Dilution: Aseptically transfer the required dose of reconstituted dalbavancin 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.

Once diluted into an intravenous bag or bottle as described above, DALVANCE may be stored either refrigerated at 2 to 8 °C (36 to 46 °F) or at a controlled room temperature of 20 to 25 °C (68 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 DALVANCE should be inspected visually for particulate matter prior to infusion. If particulate matter is identified, do not use. After reconstitution and dilution, DALVANCE is to be administered via intravenous infusion, using a total infusion time of 30 minutes. Do not co-infuse DALVANCE with other medications or electrolytes. Saline-based infusion solutions may cause precipitation and should not be used. The compatibility of reconstituted DALVANCE 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 DALVANCE, the line should be flushed before and after each DALVANCE infusion with 5% Dextrose Injection, USP.

3 DOSAGE FORMS AND STRENGTHS
DALVANCE is supplied in single-use, clear glass vials containing sterile powder (white/off-white to pale yellow) equivalent to 500 mg of anhydrous dalbavancin.

4 CONTRAINDICATIONS
DALVANCE is contraindicated in patients with known hypersensitivity to dalbavancin. No data are available on cross-reactivity between dalbavancin and other glycopeptides, including vancomycin.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions
Serious hypersensitivity (anaphylactic) and skin reactions have been reported in patients treated with DALVANCE. If an allergic reaction occurs, treatment with DALVANCE should be discontinued. Before using DALVANCE, inquire carefully about previous hypersensitivity reactions to glycopeptides, and due to the possibility of cross-sensitivity, exercise caution in patients with a history of glycopeptide allergy.

5.2 Infusion Related Reactions
DALVANCE is administered via intravenous infusion. Dosing intervals such as 72 hours over several days, may be used to minimize the risk of infusion-related reactions. 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.

5.3 Hepatic Effects
In Phase 2 and 3 clinical trials, more DALVANCE- than comparator-treated subjects (ALT, AST, bilirubin) were reported with similar frequency in the DALVANCE and comparator arms. Patients 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

5.4 Clostridium difficile-Associated Diarrhea
Clostridium difficile-associated diarrhea (CDAD) has been reported in users of nearly all systemic antibacterial drugs, including DALVANCE, 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 may 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.

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

6 ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of DALVANCE cannot be directly compared to rates in the clinical trials of other drugs and may not reflect rates observed in practice.
6.1 Adverse Reactions in Clinical Trials
Adverse reactions were evaluated for 1778 patients treated with DALVANCE and 1224 patients treated with comparator antibacterial drugs in seven Phase 2 and Phase 3 clinical trials. A causal relationship between study drug and adverse reactions was not always established. The median age of patients treated with DALVANCE was 47 years, ranging between 16 and 93 years old. Patients treated with DALVANCE were predominantly male (60%) and Caucasian (78%).

Most Common Adverse Reactions
The most common adverse reactions in patients treated with DALVANCE were nausea (5.5%), headache (4.7%), and diarrhea (4.4%). The median duration of adverse reactions was 4.0 days in both treatment groups. Table 1 lists selected adverse reactions occurring in more than 2% of patients treated with DALVANCE in clinical trials.

Table 1. Selected Adverse Reactions in Phase 2/3 Trials (Number (%) of Patients)

<table>
<thead>
<tr>
<th>Condition</th>
<th>DALVANCE (N = 1778)</th>
<th>Comparator* (N = 1224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>98 (5.5)</td>
<td>78 (6.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>87 (4.9)</td>
<td>57 (4.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>75 (4.2)</td>
<td>72 (5.9)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>31 (1.8)</td>
<td>30 (2.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>46 (2.6)</td>
<td>30 (2.4)</td>
</tr>
<tr>
<td>Pain</td>
<td>28 (1.6)</td>
<td>41 (3.3)</td>
</tr>
</tbody>
</table>

The following selected adverse reactions were reported in DALVANCE 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, and other hematologic conditions. Gastrointestinal disorders: gastrointestinal hemorrhage, melena, hematochezia, abdominal pain.

8 USE IN SPECIFIC POPULATIONS
8.1 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. DALVANCE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.6 Renal Impairment
In patients with renal impairment whose known creatinine clearance is less than 30 mL/min and who are not receiving regularly scheduled hemodialysis, the recommended two-dose regimen for DALVANCE is 750 mg followed one week later by 375 mg. No dosage adjustment is recommended for patients receiving regularly scheduled hemodialysis, and DALVANCE can be administered without regard to the timing of hemodialysis [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment
No dosage adjustment of DALVANCE is recommended for patients with mild hepatic impairment (Child-Pugh Class A). Caution should be exercised when prescribing dalbavancin to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) as no data are available to determine the appropriate dosing in these patients [see Clinical Pharmacology (12.3)].

10 OVERDOSAGE
Specific information is not available on the treatment of overdose with DALVANCE, as dose-limiting toxicity has not been observed in clinical studies. In Phase 1 studies, healthy volunteers have been administered single doses of up to 1500 mg, and cumulative doses of up to 4500 mg over a period of up to 8 weeks, with no signs of toxicity nor laboratory results of clinical concern. Treatment of overdose with DALVANCE should consist of observation and general supportive measures. Although no information is available specifically regarding the use of hemodialysis to treat overdose, in a Phase 1 study in patients with renal impairment less than 6% of the recommended dalbavancin dose was removed [see Clinical Pharmacology (12.3)].
11 DESCRIPTION
DALVANCE (dalbavancin) for injection is a lipoglycopeptide synthesized from a fermentation product of Nonomuraea species.
Dalbavancin is a mixture of five closely related active homologs (A0, A1, B0, B1, and B2); the component B0 is the major component of dalbavancin. The homologues share the same core structure and differ in the fatty acid side chain of the N-acylaminoglucuronic acid moiety (R1) structure and/or the presence of an additional methyl group (R2) on the terminal amino group (shown in the figure and table below).

The Dalbavancin Structural Formula

DALVANCE is supplied in clear glass vials as a sterile, lyophilized, preservative-free, white to off-white to pale yellow solid. Each vial contains dalbavancin HCl equivalent to 500 mg of anhydrous dalbavancin as the free base, plus lactose monohydrate (129 mg) and mannitol (129 mg) as excipients. Sodium hydroxide or hydrochloric acid may be added to adjust the pH at the time of manufacture. The powder is to be reconstituted and further diluted for IV infusion [see Dosage and Administration (2.3) and How Supplied/Storage and Handling (16)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Dalbavancin is an antibacterial drug [see Clinical Pharmacology (12.4)].

12.2 Pharmacodynamics
The antibacterial activity of dalbavancin appears to best correlate with the ratio of area under the concentration-time curve to minimal inhibitory concentration (AUC/MIC) for Staphylococcus aureus based on animal models of infection. An exposure-response analysis of a single study in patients with complicated skin and skin structure infections supports the two-dose regimen [see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)].

Cardiac Electrophysiology: In a randomized, positive- and placebo-controlled, thorough QT/QTc study, 200 healthy subjects received dalbavancin 1000 mg IV, dalbavancin 1500 mg IV, oral maxofloxacin 400 mg, or placebo. Neither dalbavancin 1000 mg nor dalbavancin 1500 mg (supratherapeutic dose) had any clinically relevant adverse effect on cardiac repolarization.

12.3 Pharmacokinetics
Dalbavancin pharmacokinetic parameters have been characterized in healthy subjects, patients, and specific populations. Pharmacokinetic parameters following administration of a single intravenous 1000 mg dose were as shown in Table 3. The pharmacokinetics of dalbavancin can be described using a three-compartment model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single 1000 mg Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/L)</td>
<td>287 (13.9)</td>
</tr>
<tr>
<td>T1/2(t)</td>
<td>146 hours</td>
</tr>
<tr>
<td>AUC0-144 (µg•h/L)</td>
<td>2165 (17.9)</td>
</tr>
<tr>
<td>AUC0-5500 (µg•h/L)</td>
<td>11500 (61.0)</td>
</tr>
<tr>
<td>AUC0-10000 (µg•h/L)</td>
<td>23443 (68.9)</td>
</tr>
<tr>
<td>Terminal t1/2 (h)</td>
<td>346 (16.5)</td>
</tr>
<tr>
<td>CL/f (mL/h)</td>
<td>348 (40.6)</td>
</tr>
<tr>
<td>CL/F (mL/h/kg)</td>
<td>0.015 (44.9)</td>
</tr>
</tbody>
</table>

Table 3. Dalbavancin Pharmacokinetic Parameters in Healthy Subjects

Metabolism: In vitro studies using human microsomal enzymes and hepatocytes indicate that dalbavancin is not a substrate, inhibitor, or inducer of CYP450 isoenzymes. A minor metabolite of dalbavancin (hydroxy-dalbavancin) has been observed in the urine of healthy subjects. Quantifiable concentrations of the hydroxy-dalbavancin metabolite have not been observed in human plasma (lower limit of quantitation = 0.4 µg/mL) [see Drug Interactions (7.2)].

Excretion: Following administration of a single 1000 mg dose in healthy subjects, 20% of the dose was excreted in feces through 70 days post dose. An average of 33% of the administered dalbavancin dose was excreted in urine as unchanged dalbavancin and approximately 12% of the administered dose was excreted in urine as the metabolite hydroxy-dalbavancin through 42 days post dose.

Specific Populations

Renal Impairment: The pharmacokinetics of dalbavancin were evaluated in 28 subjects with varying degrees of renal impairment and in 15 matched control subjects with normal renal function. Following a single dose of 500 mg or 1000 mg dalbavancin, the mean plasma clearance (CLcr) was reduced 11%, 35%, and 47% in subjects with mild (CLcr, 50 to 79 mL/min), moderate (CLcr, 30 to 49 mL/min), and severe (CLcr less than 30 mL/min), renal impairment, respectively, compared to subjects with normal renal function. The clinical significance of the decrease in mean plasma CLcr and the associated increase in AUC0-∞ noted in these pharmacokinetic studies of dalbavancin in subjects with severe renal impairment has not been established [see Dosage and Administration (2.2) and Use in Specific Populations (8.6)].
No dosage adjustment is necessary for patients with CL\textsubscript{cr} greater than 30 mL/min or patients receiving hemodialysis. The recommended two-dose regimen for dalbavancin in patients with severe renal impairment who are not receiving regularly scheduled hemodialysis is 750 mg followed one week later by 375 mg.

Dalbavancin pharmacokinetic parameters in subjects with end-stage renal disease receiving regularly scheduled hemodialysis (three times/week) are similar to those observed in subjects with mild to moderate renal impairment, and less than 6% of an administered dose is removed after three hours of hemodialysis. Therefore, no dosage adjustment is recommended for patients receiving regularly scheduled hemodialysis, and dalbavancin may be administered without regard to the timing of hemodialysis in such patients [see Dosage and Administration (2.1) and Overdosage (10)].

**Hepatic Impairment:** The pharmacokinetics of dalbavancin were evaluated in 17 subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B or C) and compared to those in nine matched healthy subjects with normal hepatic function. The mean AUC\textsubscript{0-336 hrs} was unchanged in subjects with mild hepatic impairment compared to subjects with normal hepatic function; however, the mean AUC\textsubscript{0-336 hrs} decreased 28% and 31% in subjects with moderate and severe hepatic function respectively, compared to subjects with normal hepatic function. The clinical significance of the decreased AUC\textsubscript{0-336 hrs} in subjects with moderate and severe hepatic function is unknown. No dosage adjustment is recommended for patients with mild hepatic impairment. Caution should be exercised when prescribing dalbavancin to patients with moderate or severe hepatic impairment as no data are available to determine the appropriate dosing.

**Gender:** Clinically significant gender-related differences in dalbavancin pharmacokinetics have not been observed either in healthy subjects or in patients with infections. No dosage adjustment is recommended based on gender.

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

**Gram-positive bacteria**

- *Staphylococcus aureus* (including methicillin-resistant isolates)
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus anginosus group* (including *S. anginosus*, *S. intermedius*, *S. constellatus*)

The following in vitro data are available, but their clinical significance is unknown. In addition, at least 90% of organisms in the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the dalbavancin susceptible breakpoint of 0.12 mcg/mL. However, the safety and efficacy of dalbavancin in treating clinical infections due to these bacteria have not been established in adequate well-controlled clinical trials.

**Gram-positive bacteria**

- *Enterococcus faecium* (vancomycin-susceptible isolates only)
- *Enterococcus faecalis* (vancomycin-susceptible isolates only)

**Susceptibility Test Methods**

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug for treatment.

**Dilution Techniques**

Quantitative methods are used to determine minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method. When determining dalbavancin MICs, polysorbate-80 (P-80), should be added at a final concentration of 0.02% to freshly prepared or frozen microtiter trays. The MIC values should be interpreted according to the criteria provided in Table 4.

**Diffusion Techniques**

Dalbavancin disks for diffusion susceptibility testing are not available. Disk diffusion is not a reliable method for determining the in vitro activity of dalbavancin.

**Table 4. Susceptibility Test Interpretive Criteria for Dalbavancin**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>MIC (mcg/mL)a</th>
<th>Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (including methicillin-resistant isolates)</td>
<td>≤ 0.12</td>
<td>--</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>≤ 0.12</td>
<td>--</td>
</tr>
<tr>
<td><em>Streptococcus anginosus</em></td>
<td>≤ 0.12</td>
<td>--</td>
</tr>
</tbody>
</table>

*a The current absence of data on resistant isolates precludes defining any category other than “Susceptible.” If isolate yield MIC results other than susceptible, they should be submitted to a reference laboratory for additional testing.

A report of “Susceptible” indicates that the antibacterial agent is likely to inhibit growth of the pathogen. If the antibacterial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen.

**Quality Control**

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard dalbavancin powder should provide the following range of MIC values noted in Table 5.

**Table 5. Acceptable MIC Quality Control Ranges for Dalbavancin**

<table>
<thead>
<tr>
<th>Quality Control Strain</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> ATCC® 29213</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em> ATCC® 49619</td>
<td>0.008-0.03</td>
</tr>
<tr>
<td><em>Streptococcus anginosus</em> ATCC® 8045012</td>
<td>0.015-0.12</td>
</tr>
</tbody>
</table>

*ATCC® = American Type Culture Collection.

*a This organism may be used for validation of susceptibility test results when testing *Staphylococcus species other than *S. pneumoniae.

** mech
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to determine the carcinogenic potential of dalbavancin have not been conducted.

Dalbavancin was not genotoxic in a mammalian HGPSRT gene mutation assay, an in vitro chromosome aberration assay in Chinese Hamster Ovary cells, or an in vivo mouse micronucleus assay. 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 and 28 and 90 consecutive days of dosing to the indicated clinical dosing of 2 doses 7 days apart are unclear.

14 CLINICAL STUDIES

Acute Bacterial Skin and Skin Structure Infections: Adult patients with ABSSSI were enrolled in two Phase 3, randomized, double-blind, double-dummy clinical trials of similar design (Trial 1 and Trial 2). The Intent-to-Treat (ITT) population included 1,312 randomized patients. Patients were treated for two weeks with either a two-dose regimen of intravenous DALVANCE (1000 mg followed one week later by 500 mg) or intravenous vancomycin (1000 mg or 15 mg/kg every 12 hours, with the option to switch to oral linezolid after 3 days). DALVANCE-treated patients with creatinine clearance of less than 30 mL/min received 750 mg followed one week later by 375 mg. 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 in these trials included cellulitis (approximately 50% of patients across treatment groups), major abscesses (approximately 30%), and wound infection (approximately 20%). The median lesion area at baseline was 341 cm². In addition to local signs and symptoms of infection, patients were also required to have at least one systemic sign of disease at baseline, defined as temperature 38°C or higher (approximately 85% of patients), white blood cell count greater than 12,000 cells/mm³ (approximately 40%), or 10% or more band forms on white blood cell differential (approximately 23%). Across both trials, 59% of patients were from Eastern Europe and 36% of patients were from North America. Approximately 89% of patients were Caucasian and 58% were males. The mean age was 50 years and the mean body weight was 80 kg. The mean BMI was 28.8 kg/m². The mean duration of therapy was 14 days (10.5 to 17.5 days).

1 Early Clinical Response at 48-72 hours after initiation of therapy, and had 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, heat/warmth & fluctuance absent, swelling/induration & tenderness to palpation absent or mild. Table 8 summarizes the clinical success rates assessed at follow-up visit occurring between Days 26 to 30. Clinical Success at this visit was defined as absence or mild improvement from baseline for lesion size (both length and width measurements), 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, heat/warmth & fluctuance absent, swelling/induration & tenderness to palpation absent or mild. Table 8 summarizes clinical success rates at a follow-up visit for the ITT and clinically evaluable population in these two ABSSSI trials. Note that there are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at the follow-up visits. Therefore, comparisons of DALVANCE to vancomycin/linezolid based on clinical success rates at these visits cannot be utilized to establish non-inferiority.

Table 6. Clinical Response Rates in ABSSSI Trials at 48-72 Hours after Initiation of Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Early Clinical Response Rate (%)</th>
<th>Clinical Success Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DALVANCE</td>
<td>Vancomycin/Linezolid</td>
<td></td>
</tr>
<tr>
<td>Trial 1</td>
<td>243/288 (84.3%)</td>
<td>235/285 (82.1%)</td>
</tr>
<tr>
<td>Trial 2</td>
<td>205/211 (97.0%)</td>
<td>200/208 (97.0%)</td>
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</tbody>
</table>
15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

DALVANCE (dalbavancin) for injection is supplied in the following packaging configuration:

500 mg/vial: package of 1 (NDC 57970-100-01)

Unreconstituted DALVANCE (dalbavancin) for injection should be stored at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Patients should be counseled that antibacterial drugs including DALVANCE should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When DALVANCE 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 treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by DALVANCE and other antibacterial drugs in the future.

Patients should be advised that diarrhea is a common problem caused by antibacterial drugs 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.

Rx only

Manufactured for:
Durata Therapeutics U.S. Limited
Chicago, IL 60606


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