

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021883Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: March 7, 2014

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Subject: Evaluation to determine if a REMS is necessary

Drug Name(s): Dalbavancin (Dalvance)

Therapeutic Class: Lipoglycopeptide antibacterial agent

Dosage and Route: 1000 mg intravenous on Day 1 and 500 mg intravenous on Day 8

Application Type/Number: NDA 21883

Applicant/sponsor: Durata Therapeutics, Inc.

OSE RCM #: 2013-2273

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity dalbavancin. On September 26, 2013, the Agency received a New Drug Application (NDA) from Durata Therapeutics for dalbavancin for the treatment of adult patients with acute bacterial skin and skin structure infections caused by susceptible strains of several gram-positive microorganisms, including methicillin-resistant *Staphylococcus aureus*. The applicant did not submit a proposed REMS or risk management plan.

1.1 BACKGROUND¹⁻⁴

Bacterial skin and soft tissue infections have variable presentations, etiologies, and clinical severities resulting from microbial invasion of the skin and underlying tissues. The infections are a common reason for patients to present to emergency rooms and outpatient practices, and the number of hospital admissions for these infections has been increasing. Although many bacterial species cause skin and soft tissue infections, gram-positive organisms such as *Staphylococcus*, *Enterococcus*, and *Streptococcus* are frequently isolated. Treatment of methicillin-resistant *Staphylococcus aureus* skin infections remains an important clinical problem.

For the purpose of drug development, the Agency defines an acute bacterial skin and skin structure infection (ABSSSI) as a bacterial infection of the skin with a lesion size area of at least 75 cm² as measured by the area of redness, edema, or induration. ABSSSIs include cellulitis, erysipelas, wound infections, and major cutaneous abscesses.

Dalbavancin is a semisynthetic lipoglycopeptide antibiotic with bactericidal activity against Gram-positive pathogens, including multi-drug resistant strains. The drug interrupts cell wall synthesis by blocking transglycosylation and transpeptidation of growing peptidoglycan chains. Dalbavancin has a long lipophilic side chain that extends its half-life (allowing for once-weekly dosing) and enhances anchoring of the drug to the cell membrane, improving its affinity for the C-terminal end of the growing peptidoglycan chain.

1.2 REGULATORY HISTORY

On December 21, 2004, the Agency received an NDA for the use of dalbavancin for the treatment of complicated skin and skin structure infections in adults. The dalbavancin application has gone through multiple review cycles since its original submission. An approvable letter was issued in September 2005 for deficiencies related to storage and stability data as well as deficient product labeling; a second approvable letter was issued in June 2006 due to the discovery of high bacterial

¹ Rajan S. Skin and soft-tissue infections: Classifying and treating a spectrum. *Cleve Clin J Med* 2012; 79:57-66.

² Moet GJ, et al. Contemporary causes of skin and soft tissue infections in North America, Latin America, and Europe: Report from the SENTRY Antimicrobial Surveillance Program (1998-2004). *Diagn Microbial Infect Dis* 2007; 57:7-13.

³ U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research (CDER). Guidance for Industry. Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. October 2013. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185.pdf>. Accessed February 11, 2014

⁴ Zhanel GG, et al. New lipoglycopeptides. A comparative review of dalbavancin, oritavancin, and telavancin. *Drugs* 2010; 70:859-886.

endotoxin levels in the active pharmaceutical ingredient and drug product; a third approvable letter was issued in December 2007 for violations of good manufacturing practices discovered upon inspection, deficient microbiologic storage data, and a lack of evidence from a second adequate well-controlled study to support the proposed indication. The application was withdrawn on September 15, 2008 by Pfizer Global Pharmaceuticals, the application holder at that time. Durata Therapeutics subsequently acquired the dalbavancin program and reinitiated clinical development. On September 26, 2013, the Agency received submission of the re-established NDA for dalbavancin for the treatment of adult patients with acute bacterial skin and skin structure infections caused by susceptible strains of the following gram-positive micro-organisms:

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

The review classification for the application is Priority. The applicant did not submit a proposed REMS or risk management plan. The Anti-Infective Drugs Advisory Committee is scheduled to discuss this NDA on March 31, 2014.

2 MATERIALS REVIEWED

- September 26, 2013, NDA 21883 submission. Sections reviewed include:
 - Section 1.14, Draft labeling
 - Section 2.5, Clinical Overview
 - Section 2.7.4, Summary of Clinical Safety
- January 8, 2014, slides from NDA 21883 Mid-Cycle Meeting
- March 7, 2014, Anti-Infective Drugs Advisory Committee Briefing Document

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

Two randomized, controlled, double-blind, multi-center Phase 3 clinical studies (DUR001-301 and DUR001-302) were completed in 2012 in support of the proposed indication. A third randomized, controlled, double-blind study (VER001-9) for the treatment of complicated skin and skin structure infections was completed in 2004, but had limitations in terms of study design and unreliable or missing measurements. Studies DUR001-301 and DUR001-302 closely followed the FDA's current ABSSSI guidance criteria³ and are considered the pivotal trials.

Both of the pivotal studies were designed to test the non-inferiority of dalbavancin compared with vancomycin (followed by linezolid) using a lower limit of -10%. In Study DUR001-301, a total of 573 patients were randomized 1:1 to dalbavancin (n=288), or vancomycin followed by an optional switch to oral linezolid (n=285). In Study DUR001-302, a total of 739 patients were randomized 1:1 to dalbavancin (n=371) or the vancomycin/linezolid regimen (n=368). Patients randomized to dalbavancin received 1000 mg intravenous on Day 1 and 500 mg on Day 8. Patients in the comparator arm received vancomycin 1000 mg or 15 mg/kg intravenous every 12 hours with an optional switch to oral linezolid 600 mg every 12 hours after three days. The duration of treatment was 10-14 days. The primary efficacy endpoint was early clinical response based on cessation of spread of the lesion and absence of fever at 48 to 72 hours post-study drug

initiation. The Agency evaluated an additional efficacy endpoint of 20% reduction in lesion size at 48 to 72 hours, as well as other sensitivity and secondary endpoints.

The primary efficacy endpoint for Study 301 and Study 302 showed dalbavancin responder rates were within the non-inferiority margin compared with vancomycin/linezolid. The percent treatment differences and 95% confidence intervals for cessation of spread of the lesion and absence of fever were 1.5% (-4.6, 7.9) and -1.5% (-7.4, 4.6) for the respective studies. Similar treatment differences were observed in evaluating the 20% reduction in lesion size endpoint, with Study 301 showing a difference of -1.0% (-5.7, 4.0) and Study 302 showing a difference of 1.7% (-3.2, 6.7). The clinical success rate at the end of treatment (Day 14-15), an additional secondary endpoint determined by several criteria, found dalbavancin was inferior to vancomycin/linezolid in one of the studies; the treatment difference was -5.4% (-11.5, 0.6) in Study 301 and 3.4% (-1.5, 8.3) in Study 302. Additional sensitivity analyses of clinical status at the end of treatment showed dalbavancin was inferior to vancomycin/linezolid in Study 301, but not Study 302, for responders with 80% or larger reductions in lesion size.

3.2 SAFETY CONCERNS

Unless otherwise specified, the frequency and incidence of the adverse events described below are with reference to the integrated safety population of Study 301 and Study 302.

3.2.1 Serious Adverse Events

Nonfatal serious adverse events (SAEs) of any nature were reported in 17/652 (2.6%) patients in the dalbavancin arm compared with 29/651 (4.4%) patients in the comparator arm. The most frequently reported SAEs came under the category of infections and infestations. There were more adverse events with an outcome of death in patients who received vancomycin/linezolid (n=8) than in patients treated with dalbavancin (n=1); the death in the dalbavancin group was a 78 year old female who died from sepsis due to retroperitoneal abscess on Day 32 of the study. The death was considered not related to the study drug.

3.2.2 Hypersensitivity and Infusion Reactions

Hypersensitivity reactions occurred at a lower incidence in the dalbavancin arm, 43/652 (6.6%) patients, compared with 52/651 (8%) patients in the vancomycin/linezolid arm. However, one anaphylactoid reaction occurred in a 22 year old male upon receiving the first dose of dalbavancin. The infusion was stopped and the patient was treated and recovered; this patient had also received an infusion of aztreonam immediately prior to dalbavancin.

Infusion-site reactions occurred in 12/652 (1.8%) patients randomized to dalbavancin and 14/651 (2.1%) patients in the comparator group. There were no serious infusion-site adverse events in either group. No cases of Red Man syndrome were reported in any dalbavancin-treated patient in Study 301 or Study 302.

3.2.3 Hepatic toxicity

Patients on treatment with dalbavancin experienced a higher incidence of alanine aminotransferase (ALT) elevations compared with the vancomycin/linezolid group. ALT elevations between three to five times the upper limit of normal (ULN) occurred in 26/652 (4%) patients who received

dalbavancin compared with 15/651 (2.3%) patients who received vancomycin/linezolid. Nine patients in the dalbavancin group experienced ALT elevations greater than five times the ULN compared with none in the comparator arm. Most of the patients with significant transaminase elevations had a history of viral hepatitis or alcohol abuse that may have predisposed them to liver injury. One dalbavancin-treated patient, with a history of hepatitis C and other confounders, experienced elevations of ALT (> 10x ULN) and total bilirubin (> 4x ULN) on Study Day 14; the events resolved by Study Day 27.

3.2.4 Bleeding Events

There was an imbalance in bleeding adverse events reported in the two studies. Thirteen events in 12 patients were observed in the dalbavancin arm compared with three events in three patients in the vancomycin/linezolid arms. A decrease in platelet counts was not observed while patients were on treatment. One dalbavancin-treated patient experienced a serious gastrointestinal bleed that was considered unrelated to dalbavancin by the investigator; the patient received treatment and recovered. An imbalance in bleeding events was also found in the safety population comprised of all Phase 2 and Phase 3 trials; 36 (2%) dalbavancin-treated patients experienced a bleeding event compared with 19 (1.6%) patients in the comparator arm.

3.2.5 Renal toxicity

Renal failure was reported in one patient in the dalbavancin arm compared with four patients in the vancomycin/linezolid arm. There was a lower incidence of post-baseline creatinine elevations in the dalbavancin-treated patients (7.2%) than in patients in the comparator arm (9.1%).

3.2.6 Teratogenicity

Reproductive toxicity studies in rats and rabbits did not show evidence of teratogenicity at 15 mg/kg/day, or 1.2 times the human dose on an exposure basis.

3.2.7 Postmarketing Requirements

Safety-related postmarketing requirements have not been determined at the time of this review.

4 DISCUSSION

Dalbavancin is a lipoglycopeptide antibiotic with bactericidal activity against gram-positive pathogens, including multi-drug resistant strains. The drug is proposed for use in the treatment of acute bacterial skin and skin structure infections caused by several gram-positive organisms, including methicillin-resistant *Staphylococcus aureus*. In the two pivotal clinical studies for the proposed indication, dalbavancin's efficacy was found to be non-inferior to a vancomycin/linezolid regimen, based on early clinical response 48-72 hours after initiation of treatment. However, analysis of certain secondary endpoints and sensitivity measures did not find consistent results between the two studies.

The most important safety concerns associated with dalbavancin appear to be hypersensitivity and infusion reactions, and possible hepatic toxicity. Hypersensitivity and infusion reactions are well-known risks associated with glycopeptide antibiotics, and the current dalbavancin draft labeling includes warnings for both adverse events. Most patients with dalbavancin-associated transaminase elevations had baseline risk factors for hepatic injury. One case of possible drug-

induced liver injury demonstrated an ALT elevation more than ten times the ULN as well as elevated bilirubin levels, but this case was confounded by the patient's history of hepatitis C, a baseline elevation of alkaline phosphatase, and the use of concomitant medication associated with liver injury. Although there were more bleeding events associated with dalbavancin in the pivotal studies, only one of these events resulted in a serious outcome. When the safety population from all Phase 2 and 3 studies is evaluated, the incidence of bleeding events associated with dalbavancin is similar to that associated with the comparator treatments.

The pharmacologic class of lipoglycopeptides approved for use in the U.S. includes telavancin, which is approved with a REMS for the treatment of complicated skin and skin structure infections as well as for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP). The telavancin REMS addresses the risk of increased mortality in patients with renal impairment while receiving treatment for HABP/VABP. The REMS also addresses the potential risk of teratogenicity, which was observed in three animal species during non-clinical testing. See the Appendix for a high-level comparison of the safety profiles of dalbavancin and telavancin.

Dalbavancin does not share the same risks associated with telavancin that necessitated a REMS for its approval. Dalbavancin did not show evidence of teratogenicity in non-clinical testing. The proposed indication for use does not include treatment of nosocomial pneumonia, thus the potential mortality risks associated with telavancin for that indication do not apply. The risk of hepatic toxicity is considered in the context that dalbavancin is an acute therapy and that most patients who experienced ALT elevations in the clinical studies had baseline risk factors for liver injury. Labeling for [REDACTED] ^{(b) (4)} is under consideration by the Division of Anti-Infective Products. The dalbavancin application is still under review and it has not been concluded that the benefits outweigh the risks for the proposed indication. At this time, DRISK does not recommend a REMS for the management of the risks associated with dalbavancin.

5 CONCLUSION

DRISK concurs with the Division of Anti-Infective Products that, based on the available data and the potential benefits and risks of treatment, a REMS requirement for dalbavancin cannot be established at this time. DRISK will continue to follow this NDA and if new safety information or analyses become available, the decision can be re-evaluated.

APPENDIX

Table 1: Abbreviated comparison of lipoglycopeptide antibacterial agents

	Telavancin	Dalbavancin (Proposed)
Indication(s)	<ul style="list-style-type: none"> ▪ Complicated skin and skin structure infections (CSSSI) ▪ Hospital-acquired and ventilator-associated bacterial pneumonia caused by susceptible <i>S. aureus</i> 	<ul style="list-style-type: none"> ▪ Acute bacterial skin and skin structure infections caused by susceptible gram-positive microorganisms
Boxed Warnings	<ul style="list-style-type: none"> ▪ Increased mortality in renal impairment ▪ Nephrotoxicity ▪ Potential teratogenicity 	None
Warnings and Precautions	<ul style="list-style-type: none"> ▪ Increased mortality in renal impairment ▪ Decreased clinical response in renal impairment for the treatment of CSSI ▪ Nephrotoxicity ▪ Potential teratogenicity ▪ Hypersensitivity and infusion-related reactions ▪ <i>C. difficile</i>-associated diarrhea ▪ Development of drug-resistant bacteria ▪ QTc prolongation ▪ Interference with certain coagulation tests 	<ul style="list-style-type: none"> ▪ Hypersensitivity and infusion-related reactions ▪ <i>C. difficile</i>-associated diarrhea ▪ Development of drug-resistant bacteria ▪ (b) (4) (under consideration)
Risk Management	<p>REMS with communication plan</p> <ul style="list-style-type: none"> ▪ Addresses risks of increased mortality in renal impairment and potential teratogenicity 	Prescribing information

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/s/

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03/07/2014

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