CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206334Orig1s000

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:	May 12, 2014
Reviewer(s):	Suzanne Robottom, Pharm.D. Division of Risk Management (DRISK)
Team Leader:	Cynthia LaCivita, Pharm.D. DRISK
Subject:	Evaluation to determine if a REMS is necessary
Division Director:	Claudia Manzo, Pharm.D. DRISK
Drug Name(s):	Orbactiv (oritavancin)
Therapeutic Class:	lipoglycopeptide antibiotic
Dosage and Route:	single 1200 mg intravenous infusion over 3 hours
Application Type/Number:	NDA 206334
Applicant/sponsor:	The Medicines Company
OSE RCM #:	2014-40

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 oritavancin. The Agency received the new drug application (NDA) from The Medicines Company for oritavancin on December 6, 2013. The proposed indication is "for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSIs) caused or suspected to be caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible [MSSA] and –resistant [MRSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

Oritavancin is dosed as a single, 1200 mg intravenous infusion over three hours. According to the proposed package insert (PI), the half-life is 245 hours (b) (4)

The Medicines Company submitted a "risk management plan"; not a REMS.

1.1 BACKGROUND

According to the Centers for Disease Control and Prevention, studies show that about one in three people carry staphylococcus in their nose, usually without any illness. Two in 100 people carry MRSA. Most staphylococcus infections, including MRSA present as a bump or infected area on the skin and "recent data suggest that MRSA as a cause of skin infection in the general community remains a high probability."[1]

The Infectious Disease Society of America (IDSA) last published practice guidelines for the "diagnosis and management of skin and soft-tissue infections" in 2005. This guideline lists the following options for MRSA skin and soft-tissue infections:

- Vancomycin
- Linezolid
- Clindamycin
- Daptomycin
- Doxycycline[2], minocycline[3]
- Trimethoprim sulfamethoxazole[2]

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[1] http://www.cdc.gov/mrsa/ - accessed April 24, 2014.

[2] Not approved for treatment of skin or skin structure infections.

[3] The Minocycline labeling states, "Minocycline is indicated for skin and skin structure infections caused by staphylococcus aureus (note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection)."

Since 2005, the following drugs were approved for the treatment of skin and skin structure infections including infections caused by MRSA:

- Tigecycline – approved 2005; indicated for complicated skin and skin structure infections
- Telavancin – approved 2009; indicated for complicated skin and skin structure infections
- Ceftaroline fosamil – approved 2010; indicated for acute skin and skin structure infections

In January 2011, IDSA published their first practice guideline for the treatment of MRSA infections in adults and children.

- For **outpatients** with skin and soft tissue infections in the era of community acquired MRSA, the recommended oral empirical antibiotic treatment options are: clindamycin, trimethoprim sulfamethoxazole, doxycycline/minocycline, and linezolid.
- For **hospitalized patients** with skin and soft tissue infections in the era of community acquired MRSA, the recommended empirical antibiotic treatment options are: vancomycin (IV), linezolid (IV or oral), daptomycin (IV), telavancin (IV), and clindamycin (IV or oral).

Oritavancin acts at the same site of peptidoglycan biosynthesis as vancomycin, another glycopeptide but requires only a single, 3 hour infusion.

1.2 REGULATORY HISTORY

The previous NDA (NDA 22153 held by Targanta Therapeutics Corporation) for oritavancin for injection with a dose of 200 mg IV for adults weighing < 110 kg, and a dose of 300 mg for adults weighing > 110 kg. The NDA was reviewed by the Agency, presented to the Anti-Infective Drugs Advisory Committee on November 19, 2008, and issued a Complete Response letter on December 8, 2008 citing both safety and efficacy concerns; requiring an additional adequate and well-controlled study to evaluate the safety and efficacy of ortiavancin for cSSSI.

The December 8, 2008 Office Director Decisional Memo notes the following:

> Two main studies were completed to evaluate the safety and efficacy of oritavancin for complicated skin and skin structure infections (cSSSI).
>
> - Study ARRD was a double-blind, randomized, multi-center trial that compared oritavancin 1.5 mg/kg/day, oritavancin 3.0 mg/kg/day, and vancomycin/cephalexin in cSSSI. Study ARRD was powered to show non-inferiority with a margin of -15% and failed to meet a non-inferiority margin of -10%.
> - Study ARRI was a double-blind, randomized, multi-center study comparing oritavancin 200 mg to vancomycin. The results of this study were well within a lower bound of -10% for the 95% confidence interval. Study ARRI does

provide evidence of the activity of oritavancin, but does not provide substantial evidence alone or with the data from study ARRD to support the safety and efficacy of oritavancin for cSSSI.

There were findings from the pivotal trials that raise questions about the efficacy and/or safety of oritavancin for cSSSI within the limited data available. These findings include (1) the higher rate of study discontinuation for lack of efficacy among oritavancin treated subjects, (2) the greater number of oritavancin-treated subjects who died or had an SAE of sepsis, septic shock, and related events, and (3) more oritavancin-treated subjects who experienced AEs of osteomyelitis and sepsis.

The NDA was withdrawn on March 22, 2013.

2 MATERIALS REVIEWED

- QT-IRT Consult Response for NDA 206334. Signed in DARRTS by Kozeli D on March 3, 2014.
- December 6, 2013. NDA 206334.
- Moledina N. Clinical Review for NDA 22-153. Signed by Moledina N and Alexander J on December 1, 2008.
- Worthy K. Review of proposed risk management plan for Nuvocid. Signed by Dempsey M and Karwoski C on October 28, 2008.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

Please refer to Dr. Mayurika Ghosh's review for the full clinical review of efficacy and safety.

The NDA is based on the results of two Phase 3, randomized, double-blind, non-inferiority studies (SOLO I and SOLO II) comparing a single dose of oritavancin to a 7 to 10 day course of vancomycin. The primary endpoint for both trials was early clinical response (responder rate) defined as cessation of spread or reduction in size of baseline lesion, absence of fever, and no rescue antibacterial drug 48 to 72 hours after initiation of therapy. The following table provides the efficacy results:

	Oritavancin n /N(%)	**Vancomycin** n /N(%)	Difference (95% CI)
SOLO I	390/473 **(82)**	379/481 **(78.9)**	3.1 (-1.6, 8.4)
SOLO II	403/503 **(80)**	416/502 **(83)**	-3 (-7.5, 2.0)

3.2 SAFETY CONCERNS

3.2.1 Review of NDA 22-153 (2008)

During review of NDA 22153 in 2008, the OSE review dated October 28, 2008 identified the primary safety concern associated with oritavancin as injection site reactions. The 2008 review states:

> *Based on the information provided by the sponsor, discussion with medical officer, Dr. Moledina in DAIOP, review of the proposed label and that of vancomycin (the comparator drug in clinical studies), it does not appear that injection site phlebitis is substantially more frequent or severe with oritavancin in comparison to vancomycin. These risks, the interference with the aPTT assay, and other class risks can be managed through labeling and routine pharmacovigilance practices, consistent with the plan proposed by the sponsor.*

Further, under "Risk Benefit Assessment," Dr. Moledina's clinical review signed December 1,2008, stated:

> *Based upon the data submitted for review of safety and effectiveness of oritavancin for patients with complicated skin and skin structure infections, there were concerns about i.v. administration leading to injection site phlebitis, but the applicant addressed this issue by conducting a tolerance study with results that were acceptable. No further assessment is necessary at this time.*

3.2.2 Review of NDA 206334 (current submission)

In the December 6, 2013 submission, the Applicant identified the following "**identified risks**":

- **Hypersensitivity**: The incidence of hypersensitivity was lower in the oritavancin group (7.7%) than the vancomycin group (14.1%) in the SOLO pool. Serious events of hypersensitivity occurred in 0.4% of patients in both the oritavancin and vancomycin groups. The incidence of hypersensitivity leading to study drug discontinuation was lower in the oritavancin group (0.5%) compared to the vancomycin group (1.4%) in the SOLO pool.

- **Concomitant use with warfarin**: The proposed PI states, "Results from a drug-drug interaction study in healthy volunteers showed that oritavancin is a weak inhibitor of CYP2C9 (approximately (b) (4)% increase in the mean AUC of warfarin) (b) (4)

- **Coagulation test interference**: The Applicant states that, "in the oritavancin development program, there was no in vitro or in vivo evidence that oritavancin affects the coagulation system. In addition, there was no evidence that oritavancin had an effect on coagulation when bleeding was assessed directly by template bleeding time." The proposed PI states, "ORBACTIV has been shown to artificially prolong the activated partial thromboplastin time (aPTT) by binding to the phospholipid reagents commonly found in laboratory coagulation tests.

(b) (4)

The Applicant identified the following "**potential risks**":

- **Pseudomembranous colitis/*Clostridium difficile* associated diarrhea (CDAD)**: No events related to pseudomembranous colitis/CDAD were reported in the SOLO pool.

  The incidence of pseudomembranous colitis/CDAD was similar in the oritavancin and vancomycin/comparator groups in the ARRD/I (oritavancin, 0.3%; vancomycin, 0.3%).

- **Osteomyelitis**: According the Applicant, "the percentage of patients with osteomyelitis was higher in the in the oritavancin group (0.6%) than the vancomycin group (0.1%) in the SOLO pool." Discontinuations of study drug due to osteomyelitis occurred in 0.3% and 0.1% of the oritavancin and vancomycin groups, respectively, in the SOLO pool.

  Reviewer Comment: The FDA-revised proposed labeling includes a (b) (4) *that* (b) (4)

- **Development of drug-resistant bacteria**: The applicant does not identify a particular resistance vulnerability with oritavancin.

During the March 4, 2014 internal midcycle meeting, the following aspects of the oritavancin safety profile were discussed:

- **Deaths**: There were five deaths (2 patients treated with oritvancin, 3 treated with vancomycin), all were considered unrelated to treatment.

- **Pregnancy**: The sponsor proposes Pregnancy Category (b) (4) There were five pregnancies during the clinical development. Of these, there were two miscarriages, one elective termination, one healthy birth, and one pregnancy is ongoing.

  Reviewer Comment: According to the 2008 clinical review, oritavancin "did not affect fertility in the rat (doses up to 30 mg/kg), fetal development in the rat and rabbit (doses up to 30 and 15 mg/kg respectively), or pre and post-natal development (doses up to 30 mg/kg)."

  The current dose (1200 mg) is higher than previous NDA but would range from 26 mg/kg or less for adults.

- The **most common TEAE** observed SOLO I and II for oritavancin and vancomycin, respectively, were nausea (17.73% and 18.26%), headache (12.61% and 11.7%), vomiting (8.23% and 8.16%) and cellulitis (6.76% and 5.67%). The following adverse events were noted in slide 16 of the clinical presentation:

Body system or Organ Class	Oritavancin	Vancomycin
CELLULITIS	37 (6.76%)	32 (5.67%)
ABSCESS LIMB	27 (4.94%)	13 (2.30%)
INFECTION	12 (2.19%)	2 (0.35%)
ABSCESS	11 (2.01%)	6 (1.06%)
SUBCUTANEOUS ABSCESS	15 (2.74%)	11 (1.95%)

The clinical reviewer noted that cases of infection were reviewed and found well balanced in both arms and mostly related to lack of efficacy.

- **Infusion site phlebitis** was reported in 4.39% of the oritavancin treatment group versus 2.66% in the vancomycin treatment group.

- **Hepatotoxicity** was reviewed based on reports of increased ALT and AST in the oritavancin treatment group.

Body system or Organ class	Oritavancin	Vancomycin
ALANINE AMINOTRANSFERASE INCREASED	27 (2.8%)	16 (1.6%)
ASPARTATE AMINOTRANSFERASE INCREASED	18 (1.8%)	16 (1.6%)

Reviewer Comment: The final clinical review states that while the frequency of LFT elevation from baseline in both arms was balanced, there was one subject in the oritavancin arm versus none in the vancomycin arm where ALT levels rose to >10xULN from a normal baseline. Three cases with significant idiosyncratic ALT elevations fell into the Hy's law quadrant; however, upon further examination none met Hy's law criteria.

The FDA-revised proposed labeling includes [redacted] (b) (4) *as a Warning (5.3) stating,* [redacted] (b) (4)

The QT-IRT review completed by the Division of Cardiovascular and Renal Products uncovered no concerning cardiac safety signals.

3.3 Proposed Risk Management Plan

The Applicant proposes that labeling and routine pharmacovigilance are adequate to address the identified and potential risks. In addition, the Applicant proposes to conduct a "surveillance study after introduction of Orbactiv (oritavancin) to the market to determine if decreased susceptibility to Orbactiv (oritavancin) is occurring … ."

4 DISCUSSION

Adverse events of special concern include osteomyelitis and infection; both of which are likely more related to efficacy failure and/or appropriate diagnosis and use than a safety risk. The clinical review also notes hepatic effects but no cases met Hy's law criteria.

We note that televancin (Vibativ, a lipoglycopeptide) is approved for cSSSIs and is approved with a REMS consisting of a Medication Guide and Communication Plan to address the risks of:

- increased risk of mortality associated with VIBATIV in patients with pre-existing creatinine clearance of ≤50 mL/min being treated for hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP); and
- avoid unintended exposure of pregnant women to Vibativ

Neither of these risks are associated with oritavancin. While more cases of osteomyelitis were observed in the oritavancin arm, an imbalance of death between the treatment groups was not observed.

Based on the available safety information, DRISK does not recommend a REMS for management of the risks associated with oritavancin.

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, at this time a REMS is not necessary for oritavancin. If new safety information becomes available this recommendation can be reevaluated.

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/s/

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