CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206334Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Yuliya Yasinskaya, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	206,334
Applicant	The Medicines Company (MDCO)
Date of Submission	December 6, 2013
PDUFA Goal Date	August 6, 2014
Proprietary Name / Established (USAN) names	ORBACTIV Oritavancin diphosphate for injection
Dosage forms / Strength	Sterile lyophilized powder, 400 mg oritavancin/vial
Proposed Indication(s)	Acute Bacterial Skin and Skin Structure Infections
Recommended:	*Approval*

1. Introduction

The Medicines Company (Applicant) has submitted NDA 206,334 for Orbactiv (oritavancin diphosphate) for Injection single 1200 mg dose after complete response and subsequent withdrawal of Targanta Therapeutic Corporation's NDA 22,153 for oritavancin 200 mg x5 day dosing regimen for the indication of treatment for complicated Skin and Skin Structure Infections (cSSSI). The Applicant, MDCO, is currently seeking approval of Orbactiv for the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI). To support the proposed indication, the Applicant has submitted the results of two new clinical trials of a single 1200 mg dose of oritavancin for ABSSSI. The safety and efficacy results of these two new trials will be the main focus of this review.

2. Background

Oritavancin is a lipoglycopeptide antibacterial, manufactured as a lyophilized powder for injection. Oritavancin has demonstrated in vitro antibacterial activity against certain Gram positive bacteria, with a mechanism of action similar to that of the glycopeptide, vancomycin. After reconstitution, oritavancin is administered by intravenous infusion over 3 hours.
The initial NDA submission for oritavancin was made in February 2008 by Targanta Therapeutics Corporation, later acquired by The Medicines Company (MDCO), and included trials to support an indication of cSSSI. However, during review of the original NDA, questions were raised as to the efficacy (in skin and skin structure infections other than abscesses, and those caused by MRSA) and safety [higher rates of discontinuation for efficacy failure and greater number of SAE in the Infection and Infestation System Organ Class (SOC) including sepsis and osteomyelitis] of oritavancin for the proposed indication and a complete response letter outlining the deficiencies was issued on December 8, 2008. Upon acquisition of Targanta on June 27, 2009, MDCO initiated a new clinical development program of oritavancin for ABSSSI that included a new Phase 2 dose finding, two new adequate and well controlled Phase 3 efficacy trials, and a thorough QT trial in close consultation with FDA. The

original NDA 22,153 was withdrawn on September 6, 2013. The efficacy and safety results from the new trials are the subject of this memorandum and are discussed below.

The NDA 206334 review team included:

a. Clinical – Mayurika Ghosh, M.D.
b. Chemistry and Manufacturing Controls (CMC) – Hitesh Shroff, Ph.D.
c. ONDQA Biopharmaceutics – Houda Mahayni, Ph.D.
d. Product Quality – Vinayak Pawar, Ph.D.
e. Nonclinical Pharmacology/Toxicology – Amy Nostrandt, DVM, Ph.D.
f. Clinical Pharmacology – Ryan Owen, Ph.D.
g. Pharmacometrics – Jeffry Florian, Ph.D.
h. Clinical Microbiology – Avery Goodwin, Ph.D.
i. Statistics – Mushfiqur Rashid, Ph.D.

3. CMC

Please refer to the respective CMC, ONDQA Biopharmaceutics, and quality microbiology reviews for details of product quality.
The CMC reviewer finds that CMC information in the NDA for Orbactiv is sufficient to assure the identity, strength, purity and quality of the drug product. No biowaiver was requested in the application as the product formulation used in the pivotal clinical trials and the proposed marketed formulation are identical.

- General product quality considerations
  The drug substance, oritavancin diphosphate, is synthesized in a (b) (4) production of nucleus factor B via fermentation (b) (4) using a strain of the bacterium *Kibdelosporangium aridum* followed by (b) (4) Oritavancin drug substance is supplied by (b) (4)

  The drug product, Orbactiv (oritavancin) for injection is a sterile, lyophilized white to off-white powder in a single use vial that contains 400 mg of oritavancin free base (449 mg of oritavancin diphosphate salt) and (b) (4) of mannitol. Phosphoric acid is used to adjust pH. The container closure system consists of a 50 ml USP/EP type I clear glass vial fitted with (b) (4) rubber stoppers and sealed with (b) (4) over seals.
  The vial should be reconstituted with 40 mL of Sterile Water for Injection (WFI) and further diluted with USP 5% Dextrose Injection (D5W) to a concentration of 1.2 mg/mL prior to administration to patients (the product must not be reconstituted or diluted with saline due to precipitation). Intravenous solution in the infusion bag should be used within 6 hours at room temperature (b) (4) or within 12 hours when refrigerated (2°-8°C). The combined storage time (reconstituted solution in the vial and diluted solution in the bag) and 3 hour infusion time should not exceed 6 hours at room temperature or 12 hours if refrigerated. Based on the stability data provided, the storage conditions for reconstituted and diluted solutions are acceptable from CMC perspective.
  Sterility of the drug product is achieved by (b) (4) The sterility and endotoxin levels were reviewed by the product quality microbiology reviewer and were found to be acceptable. The CMC information in the NDA,

including product quality microbiology, is sufficient to assure the identity, strength, purity and quality of the drug product.

As the formulation proposed for marketing is the same as the one used in the pivotal efficacy/safety clinical trials no biowaiver was needed. For details see CMC and biopharm filing review.

- Facilities review/inspection
  An overall "Acceptable" recommendation for the facilities involved in this application from the Office of Compliance has been documented in the CMC review.
- Other notable issues (resolved or outstanding)
  Long-term and accelerated stability studies support an expiration period of 36 months at room temperature.
  The storage conditions for the diluted and reconstituted product were deemed acceptable by the quality microbiology reviewer.
  No postmarketing studies were recommended by ONDQA.
- Review by the Division of Pharmaceutical Analysis Chemist, Larry Revelle recommended modifications to the methods of identification and labeling of the drug substance/product impurities and providing clear instructions regarding specific conditions for the preparation of the (b) (4) drug substance.

4. Nonclinical Pharmacology/Toxicology

Dr. Nostrandt considered the Orbactiv NDA approvable from pharmacology/toxicology perspective. She notes that although the safety pharmacology, fertility and reproductive toxicology studies conducted did not achieve oritavancin exposures seen at the proposed clinical dose and there are questions regarding potential differences in the Cmax, time course of exposure and tissue concentration between animal equivalent of a single 1200 mg human dose given by 3 hour infusion and the repeat 30 mg/kg bolus dose evaluated, new single high dose toxicology studies are unnecessary. The 1200 mg clinical dose is supported by clinical development program rather than by existing nonclinical pharmacology studies.

- General nonclinical pharmacology/toxicology considerations

  Most of the nonclinical studies had been reviewed prior or during the first oritavancin NDA 22-153 submission. Four new studies were conducted and included in the application under review: a study intended to qualify impurities utilized multiple batches of test article, two new fertility studies, and a study to examine macrophage function after a single 1200 mg oritavancin dose.
  The pharmacology/toxicology review of NDA 22-153 found that in safety pharmacology studies, minimal effect on CNS, cardiovascular, renal, or gastrointestinal systems were observed. The studies in rats and dogs showed similar toxicities: decreases in red blood cells, increases in BUN, AST/ALT, persistent (up to 2 month) histiocytosis with eosinophilic/acidophilic granules in liver, kidney, spleen, injection site, and lymph nodes that correlated well with the persistent levels of oritavancin in tissues. The following species specific toxicities were also noted: in dog, emesis, histamine release (manifested as facial reddening, welts, and increased blood pressure), and stool changes; in rat, moribund sacrifice. Although studies in dogs did not reveal

changes in ECGs, the hERG assay indicated a potential for QT prolongation (IC50 22μM).
No effects on fertility or innate macrophage function were found in the studies conducted. The study to qualify the impurities could not do so in a manner relevant to clinical dosing as the dose tested was equivalent to only 0.5x proposed clinical dose. In animal studies, single doses administered by IV bolus or infusion over 1 hour were associated with lethality at doses lower than the proposed clinical dose.

- Carcinogenicity

  Oritavancin was not mutagenic or clastogenic based on appropriate in vitro and in vivo studies. Carcinogenicity studies with oritavancin were considered unnecessary due to the short-term use indication.

- Reproductive toxicology

Oritavancin did not affect fertility or reproductive performance of male and female rats at doses of 0.25x the proposed clinical dose. There were no effects on fetal development in the rat and rabbit at doses up to 30 and 15 mg/kg, respectively, or pre and post-natal development in rats at doses up to 30 mg/kg. However, these daily doses are only 0.25x proposed human dose of 1200 mg. Higher doses were not evaluated in nonclinical developmental and reproductive toxicology studies and there are no adequate and well controlled trials in pregnant women; therefore, for the purposes of pregnancy labeling category C was recommended.

5. Clinical Pharmacology/Biopharmaceutics

Drs. Ryan Owen (Clinical Pharmacology) and Jeffry Florian (Pharmacometrics) concluded that the Orbactiv NDA is acceptable from a clinical pharmacology perspective and recommend approval of 1200 mg oritavancin as a once-only intravenous dose for the treatment of ABSSSI.

- General clinical pharmacology/biopharmaceutics considerations

  Oritavancin is a lipoglycopeptide antibacterial drug, intended for administration as a single 1200 mg intravenous infusion over 3 hours for the treatment of ABSSSI in patients 18 years and older. The pharmacokinetic parameters of oritavancin in healthy subjects and patients are described in the clinical pharmacology review. Because of the long half-life (429 hours), oritavancin is administered as a single 1200 mg dose. Oritavancin is reversibly bound to plasma proteins; the mean protein binding is 85% and is independent of concentration. Penetration into skin blister fluid was 20%, based on AUC_{0-24} ratio after 800 mg dose.

- Drug-drug interactions

  Oritavancin was shown to be a weak inhibitor of CYP2C19 and CYP2C9 and a weak inducer of CYP2D6 and CYP3A4. The clinical implications of these interactions are likely to be minimal because the observed interactions are not large in magnitude, and

the duration of any interaction is likely to be brief as the concentration of oritavancin in plasma would be expected to fall below the observed IC50s within 48 hours after administration. However, warfarin (the CYP2C9 probe substrate) is known to have a narrow therapeutic range and an increase of 30% could be clinically significant. Dr. Owen agrees with the Applicant on including a warning for this potential interaction and recommends that patients should be monitored for signs of bleeding if taking both medications concomitantly.

- Pathway of elimination

  Oritavancin is slowly excreted unchanged in feces and urine with less than 1% and 5% of the dose recovered in feces and urine, respectively, after 2 weeks of collection.

- Critical intrinsic factors potentially affecting elimination: age, gender, hepatic insufficiency and renal impairment

  None of the following covariates were identified as clinically relevant during the population PK analysis: body weight, age, BMI, BSA, race, or baseline renal function. No dose adjustments are necessary for the above intrinsic factors.

  Due to the small number of patients with hepatic impairment in Phase 3 clinical trials, hepatic impairment was not included as a covariate in the population PK model. However, a study of subjects with moderate hepatic impairment revealed that oritavancin dose adjustment in these patients is not necessary. The pharmacokinetics of oritavancin in patients with severe renal or hepatic impairment have not been evaluated.

- Demographic interactions/special populations

  Oritavancin was not evaluated in pediatric patients. A Phase 1 PK, safety, and tolerability study in pediatric patients is currently on-going.

  Elderly: although there was a statistically significant relationship between the age and Vc, its effect on oritavancin Cmax and AUC changes were not clinically significant.

  Oritavancin was not evaluated in pregnant or nursing women. Of three pregnancies in oritavancin clinical trials, one each resulted in spontaneous abortion, elective termination and live birth of a healthy child.

- Thorough QT study

  The thorough QT study was reviewed by the QT interdisciplinary review team (IRT). A thorough QT study was randomized, double-blind, placebo-controlled, of parallel-design, where 150 subjects received oritavancin 1600 mg infusion, placebo, and moxifloxacin 400 mg. No significant QTc prolongation effects of oritavancin 1600 mg infusion were detected in this study. The largest upper bounds of the 2-sided 90% CI for the mean difference between oritavancin and placebo were below 10ms, with adequate assay sensitivity established (the largest lower bound of the 2-sided 90% CI

for the ΔΔQTcF moxifloxacin of >5ms and its ΔQTcF profile over time). For a complete assessment of the thorough QT study findings, refer to the QT Interdisciplinary Review Team review.

- Other notable issues

  The NDA applicant proposed a susceptibility breakpoint of ≤0.125 mcg/mL for *Staphylococcus aureus* and 0.5 mg/L for *Streptococcus pyogenes* (b) (4) Drs. Owen and Florian evaluated the applicant-conducted analyses and performed their own analyses of the clinical and nonclinical data. These analyses included:

  a) determining the probability of target attainment for achieving AUC_{0-72}/MIC relationships in patients corresponding to nonclinical PK/PD targets that were associated with bacteriostasis and 1-log kill
  b) univariate analyses based on categorical (two-group with a single cut off) and continuous AUC_{0-72}/MIC to predict clinical response for endpoints of early clinical efficacy at day 3, >20% lesion size reduction at day 3, and post-therapy evaluation.

The reviewers accepted the applicant-proposed breakpoints.

6. Clinical Microbiology

Dr. Goodwin recommends approval of oritavancin for the treatment of ABSSSI caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible [MSSA] and methicillin–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).

- General considerations

  Oritavancin is a lipoglycopeptide antibacterial drug, structurally related to vancomycin. Oritavancin has three mechanisms of action:

  (i) inhibition of the transglycosylation (polymerization) step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors;
  (ii) inhibition of the transpeptidation (crosslinking) step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall (unique to oritavancin);
  (iii) disruption of bacterial membrane integrity, leading to depolarization, permeabilization, and cell death.

  These multiple mechanisms contribute to the concentration-dependent bactericidal activity of oritavancin. It is active against certain Gram-positive bacteria, including staphylococci and streptococci that are the causative pathogens in ABSSSI.
  The presence of Panton-Valentine leukocidin (pvl) did not appear to have an effect on the in vitro activity of oritavancin against staphylococci. Additionally, oritavancin appeared to perform well against isolates with a vancomycin MIC of 2 mcg/ml. When enterococci isolates were tested, higher MIC values were reported for isolates with VanA phenotype.

Oritavancin tested in combination with other antibacterial agents against individual representative bacterial strains demonstrated synergistic bactericidal activity in combination with gentamicin, linezolid and rifampin.
The applicant has proposed susceptibility interpretive criteria of ≤0.12 mcg/mL for *Staphylococcus aureus* and ≤0.5 mcg/mL for streptococci listed in the indication. The reviewer has concluded that there is sufficient information to support the applicant's proposal. The microbiology reviewer agrees with the proposed breakpoints, when considering the MIC distribution patterns from large surveillance studies, the observation of clinical response data with respect to the prescribed drug dose, and the PK/PD characteristics of the drug.

- Notable issues
  The review division has proposed postmarketing requirements (PMR) for a surveillance study to monitor for the development of in vitro resistance to oritavancin in the first five years of marketing, with annual interim reports to be submitted.

7. Clinical/Statistical- Efficacy

The reader is referred to the clinical and statistical reviews for detailed information about the clinical and statistical findings. Drs. Ghosh and Rashid concluded that adequate evidence of efficacy of oritavancin in ABSSSI had been provided. The clinical and statistical reviewers were in agreement regarding the primary efficacy conclusions and overall interpretation of the trial results, supporting the indication of oritavancin for ABSSSI.

The applicant conducted two clinical trials of ABSSSI, TMC-ORI-10-01 (SOLO 1) and TMC-ORI-10-02 (SOLO 2). They were identical phase 3 multicenter, randomized, double-blind, parallel-group, active-controlled trials where oritavancin given in a single 1200-mg intravenous dose was compared to intravenous vancomycin given as 1-g or 15-mg/kg dose every 12 hours for 7 to 10 days.

The trials were conducted in 2011-2013, as the FDA recommendations regarding the design of ABSSSI trials were evolving. The protocol of these identical trials was the subject of a Special Protocol Assessment, and agreement was reached on the trial design, including the primary endpoint. Subsequently, the Agency has published final guidance for acute bacterial skin and skin structure infection, though the trial was complete at the time this guidance was finalized. Despite this, the pivotal trials are consistent with the trial design recommended in the guidance, with the exception of the primary endpoint for the trial. The guidance-recommended primary endpoint (≥20% reduction in lesions size at 48-72 hours, compared to baseline) differs from the primary endpoint in these trials, but was evaluated as a secondary endpoint. The selection criteria for the trials were consistent with the guidance recommendations, as evidenced by the mean lesion size for oritavancin-treated patients of 405 cm^2 and 391 cm^2, in studies SOLO 1 and SOLO 2, respectively. Lesion type was also consistent with guidance: most lesions (29-51% of oritavancin patients) were categorized as cellulitis, and abscess was reported as the baseline lesion type in 29-33% of oritavancin-treated patients. The reader is referred to the clinical and statistical reviews for additional detailed information about the study design, patient demographics, and baseline characteristics.

The primary endpoint for the clinical trial was a composite endpoint of clinical response at 48 to 72 hours after the start of treatment in the modified Intent-to-Treat (mITT) population defined as cessation of spread of the skin lesion compared to baseline, no rescue antibacterial drugs, and temperature ≤37.6°C on repeated measurements between 48 and 72 hours. Patients who died, used non-trial antibacterial therapy, or had missing measurements (lesion size or temperature) or unplanned surgical procedures were classified as non-responders. The mITT population included all randomized patients who received at least one dose of the study drug. The results of the primary analysis are shown in the table below. Oritavancin meets the pre-specified criteria for non-inferiority (-10%) to the comparator in these two trials.

Table 1 Primary Analysis: Clinical Response Rates at 48-72 Hours after Initiation of Therapy

	Oritavancin n /N (%)	**Vancomycin** n /N (%)	Difference (95% CI)[1]
SOLO 1	391/475 (82.3)	378/479 (78.9)	3.4 (-1.6, 8.4)
SOLO 2	403/503 (80.1)	416/502 (82.9)	-2.7 (-7.5, 2.0)

[1] 95% CI based on the Normal approximation to Binomial distribution

As noted above, the current guidance for ABSSSI recommends a 20% or greater reduction in lesion size at 48-72 hours after the start of drug treatment as the primary endpoint for ABSSSI trials. The following table shows the analysis of patients meeting the criteria for 20% or greater reduction in lesion size at 48-72 hours in the clinical trials. As with the primary analysis, patients who died, used non-trial antibacterial therapy, or had missing measurements (lesion size) or unplanned surgical procedures were classified as non-responders. Oritavancin meets the criteria described in the ABSSSI guidance for non-inferiority to the comparator for this endpoint.

Table 2 Secondary Analysis: Reduction in Lesion Area of 20% or Greater at 48-72 Hours after Initiation of Therapy

	Oritavancin n /N(%)	**Vancomycin** n /N(%)	Difference (95% CI)[2]
SOLO 1	413/475 (86.9)	397/479 (82.9)	4.1 (-0.5, 8.6)
SOLO 2	432/503 (85.9)	404/502 (80.5)	2.2 (-2.6, 7.0)

[1] 95% CI based on the Normal approximation to Binomial distribution.

The clinical and statistical reviews include additional analyses of outcomes at the end of treatment visit (days 7-10, the end of comparator drug treatment) as well as the follow-up visit (day 14-24). The outcomes for the mITT population at the follow-up visit were included in proposed product labeling. Additional subgroup analyses by gender, infection type, baseline pathogen, and other baseline characteristics are also described in the reviews. The clinical review also included analyses evaluating the effect of exclusion of 8 subjects from the efficacy analyses for trial SOLO2 (GCP noncompliant site 240002 as identified by the applicant's audit). The statistical review provided concordance analyses between the early clinical response and the clinical outcome at the end of therapy and follow up visits as well as the additional analyses varying percent reduction in lesion size or evaluating specific components

of the outcome definitions for the end-of-treatment and follow-up visits. The reader is referred to the reviews for detailed information about the subgroup and sensitivity analyses.

- Other notable issues

There was agreement by the clinical and statistical reviewers regarding the primary and secondary analyses of efficacy in the ABSSSI trials. The trials did provide substantial evidence of efficacy for the treatment of ABSSSI.

8. Safety

The safety review was conducted by Dr. Mayurika Ghosh. She recommended approval of the NDA for oritavancin. She notes in her risk benefit assessment that the data submitted by the applicant demonstrated an acceptable safety profile of oritavancin while providing sufficient evidence for efficacy in the treatment of ABSSSI.

Although the safety database included >2,400 oritavancin-treated patients in Phase 2-3 clinical trials, Dr. Ghosh focused her safety review on the patients treated with oritavancin regimen proposed for marketing, a 1200 mg single dose administered as an intravenous infusion over 3 hours, due to substantial differences in the pharmacokinetics between the to-be-marketed regimen and the earlier multi-dose regimens.

Overall, there were 976 oritavancin-treated patients and 983 comparator patients in the pooled SOLO 1-2 trial safety database. As oritavancin has not been approved for US or foreign marketing, there are no domestic or foreign postmarketing data available.

The frequency of deaths in the SOLO clinical trial database was comparable in the two treatment arms: two (0.2%) deaths in oritavancin patients, and three (0.3%) deaths in comparator patients. The clinical review provides narratives of the deaths as well as summary information about deaths in the previous trials (review conducted by Dr. Nasim Moledina dated December 1, 2008). There were no specific findings to relate deaths in the oritavancin patients to study drug treatment.

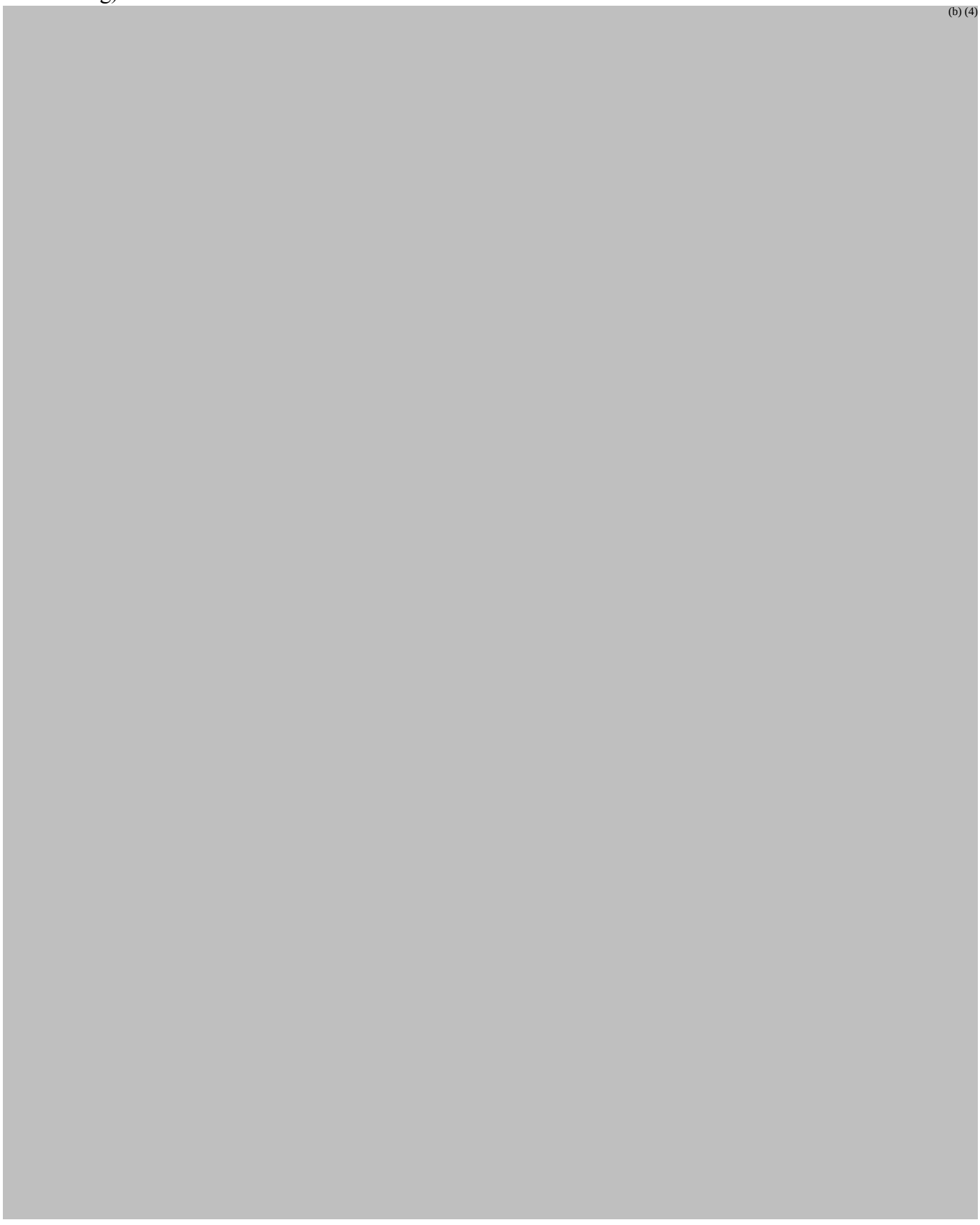
In the two SOLO clinical trials, non-fatal serious adverse reactions were reported in 57 (5.8%) oritavancin patients and 58 (5.9%) comparator patients. The system organ class (SOC) with the highest number of non-fatal serious adverse reactions was the Infections and Infestations SOC. There were 40 (4.1%) patients in oritavancin and 31 (3.1%) patients in vancomycin arm in this SOC, with most reactions related to the skin infections. However, due to numerical imbalance of the rate of adverse reactions in the Infection and Infestation SOC, particularly as it relates on the occurrence of osteomyelitis and abscesses, the clinical reviewer assessed the CRFs and case narratives for these patients in detail.

The study treatment was discontinued due to adverse reactions in 33 (3.4%) oritavancin patients and 32 (3.3%) comparator patients. The Infusion site reactions leading to study drug discontinuation were slightly more frequent in the oritavancin arm (5 subjects) than in the vancomycin arm (2 subjects). The majority of TEAEs leading to study drug discontinuation were in the Infections and Infestations System Organ Class (1.6% in oritavancin arm versus 1.9% in vancomycin arm).

The most common adverse reactions for oritavancin-treated patients were nausea (9.9%), headache (7.1%), vomiting (4.6%), diarrhea (3.7%), abscess limb (2.8%), increased alanine aminotransferase (2.8%), dizziness (2.7%), infusion site phlebitis (2.5%), and tachycardia (2.5%).

Special safety concerns for oritavancin (described in Warnings and Precautions in proposed labeling) include:

(b) (4)



(b) (4)

The clinical review details other investigations of adverse reactions. This includes investigations of tachycardia, hematological effects, and nervous system disorders. The reader is referred to the clinical review for detailed information.

- Notable safety issues

✓ Infection: the original NDA submission for oritavancin discussed the signal of increased infections on oritavancin arm including sepsis, septic shock and osteomyelitis. There were 40 (4%) cases of infection in the oritavancin arm versus 31 (3%) cases in the vancomycin arm. The majority of these adverse events were reported as the underlying ABSSSI: cellulitis and skin abscess. They were considered as efficacy failures at the appropriate time points of assessment by the applicant. There was no excess of adverse events of sepsis and septic shock was on oritavancin arm (0.3%) as compared to vancomycin arm (0.7%) in SOLO trials. In addition, nonclinical assessment of macrophage killing of ABSSSI and other infectious pathogens revealed that oritavancin has no effect on macrophage killing efficiency.

✓ Dr. Ghosh has identified hepatic safety as an issue with oritavancin. There was a nonclinical signal: oritavancin accumulates in macrophages including those of the liver, and hepatocellular necrosis with long-term exposure was documented in animal studies. In the SOLO trials there were 27 (2.8%) and 16 (1.6%) subjects with elevated ALT in the oritavancin and vancomycin arm, respectively, reported as adverse events. Elevated AST was reported as an adverse event in 18 (1.8%) oritavancin subjects and 16 (1.6%) subjects on vancomycin arm. Elevation of LFTs (ALT/AST>3, TB>1.5, and ALP> normal) any time during the study was seen in two subjects in the oritavancin arm and none in the vancomycin arm while on study treatment. There were 18 subjects in the oritavancin arm and 14 subjects in the vancomycin arm where ALT rose from baseline to 3-5xULN and three subjects in the oritavancin arm versus one subject in the vancomycin arm where TB rose from normal to 1.5-2xULN. None of these subject met Hy's law criteria. In the hepatic impairment study, there were two (10%) subjects with clinically significant elevations of transaminases.

This reviewer does not see a strong case for hepatic toxicity of oritavancin in the submission under review. Reporting laboratory test abnormalities as adverse events is generally not uniform across the study sites and often is subject to preferred term splitting (transaminitis, elevation of ALT/AST, elevation of transaminases, LFT abnormality, etc). Additionally, comparing only the incidence of postbaseline value abnormalities does not take into account presence of abnormal LFTs at baseline. As LFTs were collected at prespecified time points during the study, the best way to assess the potential hepatotoxicity of a new drug relative to a non-hepatotoxic drug in an absence of Hy's law cases is to compare the number of patients with LFT elevations from baseline.

The table below describes the number of patients with postbaseline elevations of LFTs relative to their respective baseline category

Table 3 LFT shifts (elevations) from baseline pooled SOLO trials

SOLO pool				
Baseline Category	**Oritavancin N = 976 elevated/tested**	**%**	**Vancomycin N = 983 elevated/tested**	**%**
ALT				
<ULN	179/765	23.4	185/771	24.0
1-<3xULN	19/171	11.1	11/170	6.5
3-5xULN	3/14	21.4	5/13	38.5
5-<10xULN	0	0.0	½	50.0
10-<20xULN	0	0.0	0	0.0
Total	201/953	21.1	202/956	21.1
AST				
<ULN	176/781	22.5	177/798	22.2
1-<3xULN	16/163	9.8	15/154	9.7
3-5xULN	1/9	11.1	5/5	100.0
5-<10xULN	0/2	0.0	0/1	0.0
10-<20xULN	0	0.0	0/1	0.0
Total	193/955	20.2	197/595	20.5
T Bili				
<ULN	17/890	1.9	22/900	2.4
1-<1.5xULN	0/31	0.0	2/33	0.0
1.5-2xULN	0/13	0.0	0/10	0.0
>=2xULN	0/9	0.0	0/8	0.0
Total	17/943	1.8	24/951	2.5

No differences between arms were noted in the percentage of subjects (individual baseline category or overall) who experienced elevations from baseline for ALT, AST or Total bilirubin.

9. Advisory Committee Meeting

Advisory Committee was not held for the current oritavancin NDA.

10. Pediatrics

The NDA applicant requested a deferral of required pediatric studies, because adult trials of ABSSSI were completed and the product is ready for approval. The applicant has proposed PK and safety studies of pediatric patients from birth to 18 years of age with ABSSSI. The application was discussed with the Pediatric Review Committee (PeRC) on June 11, 2014. The PeRC agreed with deferral of pediatric studies for the entire pediatric population. Postmarketing requirements for pediatric PK and safety studies have been proposed.

11. Other Relevant Regulatory Issues

A clinical inspection summary (CIS) by Dr. Janice Pohlman was archived to the NDA file on June 6, 2014. In this document, the overall data from the high enrolling US (3) and foreign (1) sites for the pivotal trials were found acceptable. VAI letters were issued to the primary investigators at the sites due to protocol non-adherences in some cases. The primary investigators in the US have responded satisfactorily in addressing the issues identified by FDA inspectors. Dr. Porwal's response was still pending at the time of the review completion. The inspectors also concluded that the sponsor, MDCO, has maintained satisfactory oversight of the trials. The regulatory violations were deemed minor by the inspectors without significant effect on data integrity or subject safety.
Financial disclosure information is included in an appendix to the clinical review. There were no reportable financial disclosures for the investigators in the clinical trials.

12. Labeling

The proprietary name review was conducted by Dr. Rachna Kapoor. The proposed proprietary name, ORBACTIV, was considered acceptable. Justine Harris, RPh conducted the labeling review for the Division of Medication Errors and Prevention Analyses (DMEPA). Dr. Carrie Newcomer conducted the Office of Prescription Drug Promotion (OPDP) labeling review. The recommendations from these reviews were incorporated in the labeling recommendations to the applicant. The remaining unresolved labeling issues were described in previous sections of this memo.
Dr. Suzanne Robottom conducted the Risk Evaluation and Mitigation Strategy (REMS) review for the Division of Risk Management. The review concurred that a REMS was not necessary based on the available data.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of the NDA for ORBACTIV for the treatment of ABSSSI.

- Risk Benefit Assessment

The applicant has provided substantial evidence of safety and effectiveness of oritavancin for the treatment of acute bacterial skin and skin structure infections. The benefits of treatment outweigh the known risks as demonstrated in clinical trials. All the reviewers recommended approval of the application from their perspectives.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

A REMS was not considered necessary based on the available data for oritavancin. See DRISK review by Dr. Suzanne Robottom for details.

- Recommendation for other Postmarketing Requirements and Commitments

The postmarketing requirements included a microbiology study, a US surveillance study, to monitor for the development of in vitro resistance to oritavancin. This study is necessary to determine whether widespread use of oritavancin will quickly generate resistance and can only be performed after NDA approval.

The recommended postmarketing requirements include two pediatric studies to evaluate both PK and safety in the pediatric population.

Table 4 Required PREA studies

Study 1: An Open label, Dose-finding, Pharmacokinetics, Safety and Tolerability Study (TMC-ORI-11-01)	
Protocol Submission Date:	December 16, 2013
Estimated Study Initiation Date:	No later than March 2014
Estimated Final Report Submission Date:	No later than September 2017
Study 2: A Multicenter, Single-Blind, Randomized, Safety and Tolerability Study (TMC-ORI-11-02)	
Estimated Protocol Submission Date:	No later than September 2017
Estimated Study Initiation Date:	No later than December 2017
Estimated Final Report Submission Date:	No later than December 2020

The division is formulating a postmarketing study to investigate the effect of oritavancin on clinical care of patients receiving chronic warfarin therapy.

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/s/

YULIYA I YASINSKAYA
07/09/2014