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RESEARCH**

APPLICATION NUMBER:

206334Orig1s000

SUMMARY REVIEW

Deputy Division Director Summary Memo

Date	(electronic stamp)
From	Katherine Laessig, MD
Subject	Deputy Division Director Summary Memo
NDA #	206-334
Applicant Name	The Medicines Company (MDCO)
Date of Submission	December 6, 2013
PDUFA Goal Date	August 6, 2014
Established (USAN) Name	Oritavancin diphosphate, tradename Orbactiv®
Dosage Forms / Strength	Oritavancin diphosphate sterile lyophilized powder, 400 mg/vial
Approved Indications	Treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of designated Gram-positive bacteria
Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package including:	Names of discipline reviewers
Medical Officer Review	Mayurika Ghosh
Statistical Review	Mushfiqur Rashid
Pharmacology Toxicology Review	Amy Nostrandt
Product Quality Reviews	Hitesh Shroff, Houda Mahayni, Vinayak Pawar
Microbiology Review	Avery Goodwin
Clinical Pharmacology and Pharmacometrics Reviews	Ryan Owen
CDTL Review	Yuliya Yasinskaya
Labeling Reviews	Carrie Newcomer, Rachna Kapoor, Justine Harris

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader

1.0 Background

MDCO has submitted NDA 206-334 in support of new molecular entity, oritavancin diphosphate (hereafter referred to as oritavancin). Oritavancin is formulated as a lyophilized powder for injection with a proposed dose and regimen of 1200 mg intravenously once. Oritavancin is a member of the lipoglycopeptide class of antibacterial drugs and acts via three mechanisms of action. First, it inhibits the transglycosylation step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors. It inhibits the transpeptidation step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall. Finally, oritavancin

disrupts the integrity of the bacterial membrane, leading to depolarization, permeabilization, and cell death. Oritavancin is active against certain Gram-positive bacteria, including staphylococci and streptococci.

The initial NDA for oritavancin was submitted in February 2008 by Targanta Therapeutics Corporation, later acquired by MDCO, for an indication of complicated skin and skin structure infections (cSSSI). However, the NDA received a complete response on December 8, 2008, for deficiencies including a lack of substantial evidence of efficacy, and concerns about a greater number of deaths and serious adverse events due to sepsis and related events, and a higher reported rate of adverse events of infections and infestations among oritavancin-treated subjects. After acquiring Targanta, MDCO initiated a new clinical development program for oritavancin for ABSSSI including a new Phase 2 dose-finding study, a thorough QT study, and two new Phase 3 trials. The original NDA (22-153) was withdrawn on September 6, 2013.

Under the provisions of the Generating Antibiotic Incentives Now provision of the Food and Drug Administration Safety and Innovation Act of 2012, oritavancin diphosphate was granted Qualified Infectious Disease Product (QIDP) designation and therefore this application was granted a priority review. QIDP designation qualifies oritavancin for an additional five years of marketing exclusivity.

This memo will summarize important findings and conclusions by review discipline. For further details, please refer to discipline specific reviews and the CDTL memo by Yuliya Yasinskaya, MD.

2.0 Product Quality

This NDA has been reviewed by multiple product quality reviewers. Dr. Hitesh Shroff conducted the review of the drug substance and drug product. Dr. Houda Mahanyi conducted the review of the biopharmaceutics, and Dr. Vinayak Pawar conducted the review of the product quality microbiology. They have concluded that the information provided by the applicant is sufficient to assure the identity, strength, purity, and quality of the drug and recommend approval. The Office of Compliance has made a final recommendation of acceptable for the manufacturing establishments filed in this NDA. Major conclusions from the product quality reviews are discussed below.

The drug substance contains oritavancin diphosphate as an active ingredient. It is a white to (b) (4) and is manufactured by (b) (4). Oritavancin diphosphate is semi-synthetic and the production of nucleus factor B involves a classical fermentation using a strain of the bacterium *Kibdelosporangium aridum*. (b) (4)

Oritavancin (b) (4) diphosphate has been prepared using (b) (4)

(b) (4) (b) (4)
The drug substance is characterized by mass spectroscopy, NMR spectroscopy methods and correlation with structurally related glycopeptides.

The drug substance specification includes appearance, identification, assay, impurities, water content, residual solvents, heavy metals and microbial contamination. The drug substance specification is deemed adequate to assure the identity, strength, purity, and quality of the drug substance.

The drug product, Orbactiv for injection, is a sterile, lyophilized white to off-white (b) (4) powder. It is supplied in a single use 50 mL USP/EP type I clear glass vial fitted with 20 mm gray (b) (4) rubber stoppers and sealed with 20 mm (b) (4) over seals. Each vial contains 449 mg of oritavancin diphosphate salt equivalent to 400 mg of oritavancin free base and (b) (4) of mannitol. A (b) (4) phosphoric acid solution is used to adjust the pH of the bulk solution (b) (4). The bulk solution is (b) (4)

The drug product is manufactured by (b) (4) (400 mg/vial) and (b) (4) is performed at (b) (4)

The proposed release specification of the finished product includes appearance, identification, assay of the active ingredient, impurities does uniformity, pH, particulate matter, sterility and microbial limits. The proposed specification is deemed adequate to assure the identity, strength, purity, and quality of the drug product.

Based on stability data from the registration and supportive batches of the drug product at long term (up to 36 months) and accelerated (6 months) conditions, the proposed 36 month expiration dating period, when stored at room temperature, is granted.

3.0 Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer, Amy Nostrandt, recommends approval. She noted that from the review of NDA 22-153, toxicities seen in the rat and dog were similar. Please refer to Dr. Wendelyn Schmidt's review of NDA 22-153 and Dr. Nostrandt's review of this NDA for further information.

In the dog, emesis, histamine release (manifested as facial reddening, welts, increased blood pressure), and stool changes were noted. In rats, death (moribund sacrifice) during the toxicity studies was much more common, partially due to injection site issues. Otherwise, both species

showed decreases in red blood cells, increases in BUN, AST/ALT, histiocytosis with eosinophilic/acidophilic granules in liver, kidney, spleen, injection site and lymph nodes. The histiocytosis did not resolve over the one to two month recovery period and correlates well with the persistent levels of oritavancin in the liver and carcass.

Four new studies were conducted. A study intended to qualify impurities utilized multiple batches of test article, all at a dose of 60 mg/kg. Lethality was seen in one test batch. Doses in that study were still only half the equivalent of the intended clinical dose, so this study was not sufficient to qualify all impurities in a manner relevant to clinical dosing. Two new fertility studies were conducted; these were again negative for adverse effects on fertility. A study to examine macrophage function concluded that effects on innate macrophage functions would be unlikely to occur following treatment with a single 1200 mg dose of oritavancin.

Dr. Nostrandt also noted that single doses administered by IV bolus or infusion over one hour were associated with lethality at doses lower than the proposed clinical dose. Safety of the proposed clinical dose and of the associated impurities has not been demonstrated in the clinical studies. Development proceeded on the basis of safety determined in clinical trials.

Key findings from Dr. Schmidt's review of NDA 22-153 include: 1) toxicities in the rat and dog were similar and included decreases in red blood cells, increases in BUN, AST/ALT, histiocytosis (macrophages) with eosinophilic/acidophilic granules in the liver, kidney, spleen, injection site, and lymph nodes which did not resolve over the 1-3 month recovery period and correlated well with the persistent levels of oritavancin in the liver and carcass, 2) in the dog only, emesis, histamine release (manifested as facial reddening, welts, increased blood pressure), and stool changes were noted, 3) in the rats, death (moribund sacrifice) during the toxicity studies was much more common, partly due to injection site issues, 4) oritavancin was negative in the genotoxicity studies conducted, and 5) oritavancin did not affect fertility in the rat, fetal development in the rat or rabbit, or pre- and post-natal development. Dr. Schmidt noted the persistent histiocytosis in multiple organs was troubling, however has no recommendations for additional nonclinical studies at this time.

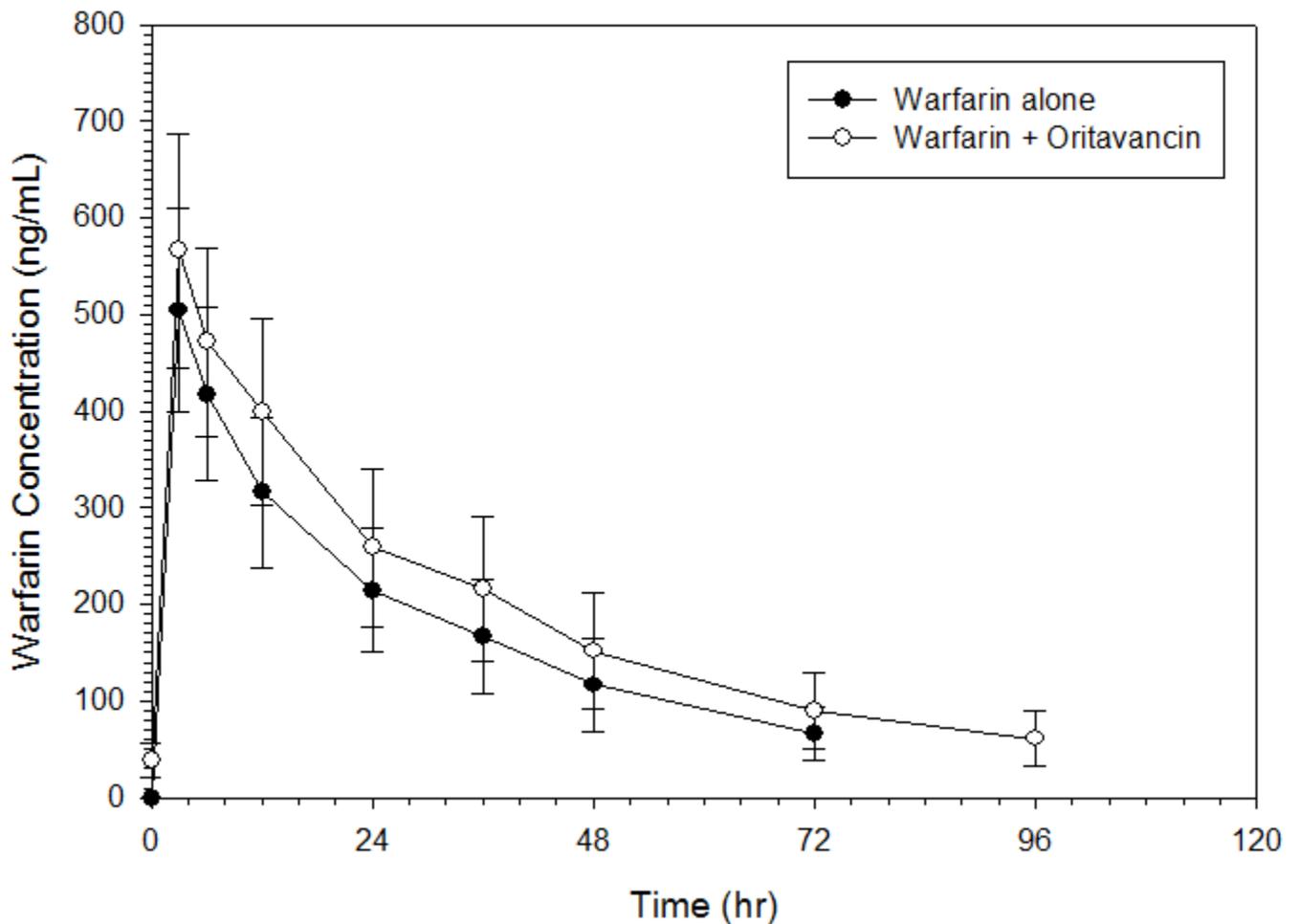
4.0 Summary of Clinical Pharmacology

The clinical pharmacology team finds that the information provided by the Applicant in support of this two NDA is acceptable and supports the proposed dose and duration for the treatment of ABSSSI. Following receipt of the complete response letter for NDA 22-153, the Applicant re-evaluated their dosing strategy and decided to conduct a phase 2 trial which evaluated a single 1200 mg dose of oritavancin to take advantage of oritavancin's long half-life and concentration-dependent antibacterial activity. The 1200 mg dose was selected for further development in two new, identically-designed phase 3 trials (SOLO I and SOLO II). Additionally, three other

clinical studies were submitted that included a thorough QTc study, a cocktail drug interaction study, and a phase 2 dose-ranging study. Please refer to the clinical pharmacology review of NDA 22-153 for previous findings. Some important points from this clinical pharmacology review include the following:

- Oritavancin PK are linear over the dose range studied. However, there are differences in oritavancin PK between healthy volunteers and patients such that the estimated half-life in patients is about twice as long as in healthy volunteers (245 h vs. 120 h). C_{max} , AUC, and CL are different as well with exposures being higher and clearance lower in health volunteers.
- Oritavancin is widely distributed into tissues, and penetrates into skin blister fluid, extracellular lung fluid, and alveolar macrophages. Oritavancin is approximately 85% bound across species. Oritavancin is not metabolized. Less than 5% is excreted unchanged in feces and urine up to 14 days after administration of a single dose. Body weight, age, BMI, BSA, race and renal function were not found to affect oritavancin PK at clinically relevant levels. An independent study of subjects with moderate hepatic impairment showed that a dose adjustment was not necessary. There is no information about the PK of oritavancin in subjects with severe hepatic impairment.
- In vitro evidence suggests that oritavancin may be a weak, non-specific inhibitor of several different CYP450 enzymes. The applicant conducted a cocktail drug interaction study (MDCO-ORI-12-03) to evaluate the impact of oritavancin on the PK of probe drugs in the Cooperstown 5+1 cocktail (caffeine, omeprazole, warfarin, vitamin K, dextromethorphan, and midazolam). The enzymatic activities of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, N-acetyltransferase-2 (NAT-2), and xanthine oxidase were also assessed. Only the activity of xanthine oxidase had the point estimate and lower and upper bounds of the 90% confidence interval fall within the traditional boundary of 80-125%. Thus, co-administration of oritavancin alters the activities of the other enzymes tested. However, the highest point estimate is 1.32 (for CYP2C9) and the lowest is 0.55 (CYP2D6), which indicates that the observed changes in enzymatic activity may not be of sufficient magnitude to be of clinical significance. The exception is for S-warfarin which is metabolized by CYP2C9 and had an increase of approximately 30%, which may be clinically significant in certain patients since warfarin has a narrow therapeutic window. Figure 1 shows warfarin plasma concentrations alone, as well as after co-administration of oritavancin from the cocktail study.

Figure 1: Mean warfarin plasma concentrations in the absence or presence of oritavancin



Source: Clinical Pharmacology Presentation by Dr. Ryan Owen

- The warfarin-oritavancin drug-drug interaction is compounded by the fact that although oritavancin does not affect coagulation, it has been shown to artificially prolong the activated partial thromboplastin time (aPTT) by binding to the phospholipid reagents. The aPTT test results will remain falsely elevated for approximately 48 hours after oritavancin administration. Based on in vitro studies, oritavancin may also interfere with the prothrombin time (PT) for 24 hours after administration of warfarin, and consequently the international normalized ratio (INR), which is calculated from the PT. The clinical significance of a 30% increase in warfarin exposure will depend, to some extent, on the patient's degree of baseline anticoagulation. A patient whose INR is, for

example, ≥ 5 , will be at a greater risk for a bleeding event, than a patient whose INR is ≤ 5 . The interference with the PT test for 24 hours would make it difficult for a healthcare provider to reliably monitor the PT if oritavancin is given concomitantly with warfarin. Although a PT may be reliable after that first 24 hour period, it may not entirely mitigate the risk of the increase in warfarin exposure. Given the availability of numerous other options for the treatment of ABSSSI due to Gram positive bacteria, the clinical team agrees that a Warning and Precaution should be included in the package insert directing healthcare providers to use oritavancin in patients on chronic warfarin therapy only when the benefit can be expected to outweigh the risk of increased bleeding. Also, the effect on coagulation parameters will be included in the Warnings and Precautions section as well. With respect to the interference with the aPTT, the heparin label states that: “Heparin sodium should not be used when suitable blood coagulation tests, e.g. the whole blood clotting time, partial thromboplastin time, cannot be performed at appropriate intervals”. Therefore, the oritavancin package insert will contraindicate the concomitant use of heparin and oritavancin because the inability to monitor the aPTT puts the patient at an unacceptable risk of bleeding. The Applicant has agreed to these Warnings and Contraindication, although the precise wording is under discussion. The Applicant is proposing to conduct a drug-drug interaction study in patients on chronic warfarin therapy who receive oritavancin for ABSSSI, a study in healthy volunteers to evaluate the effect of oritavancin on coagulation laboratory tests, and a dedicated warfarin-oritavancin drug interaction study in healthy volunteers. The review team is currently discussing the merits of these proposed studies.

- The Applicant’s population PK model was generally found to be acceptable. However, one of the covariate relationships that they identified was a relationship between height and clearance. In the Clinical Pharmacology analysis, height was replaced by more biologically plausible covariates such as BMI or BSA, since height is likely acting as a surrogate for weight. However, the alterations to the model did not result in differences in the parameter estimates which would be of clinical relevance.
- The Applicant conducted several analyses to support possible *S. aureus* breakpoints for oritavancin. They presented the probability of PK/PD target attainment for achieving the following: an AUC_{0-72}/MIC of 4,518, corresponding with a 1-log kill in the mouse neutropenic thigh model, the probability of achieving an AUC_{0-72}/MIC of 11,982 which corresponds to the AUC/MIC threshold identified for the univariate relationship for achieving a dichotomous efficacy endpoint at post-therapy evaluation (PTE). The Applicant also included the probability of achieving model-predicted clinical success by MIC . Note that all AUC/MIC targets are calculated with total AUC rather than free AUC since the protein binding of oritavancin is similar between humans and mice. The

Clinical Pharmacology reviewer conducted comparable analyses, as well as many others including at early clinical evaluation, for subjects with $\geq 20\%$ reduction in lesion size from baseline at 48-72 hours post-dose, and reduction in lesion size at PTE. In general, the Clinical Pharmacology reviewer's analysis was in alignment for oritavancin breakpoints for *S. aureus* of ≤ 0.12 mcg/mL.

- A thorough QT study was conducted in healthy adults with a single supratherapeutic dose of IV oritavancin of 1600 mg. No significant QTc prolongation effects were detected. For a complete assessment of the thorough QT study findings, please refer to the review by the Interdisciplinary Review Team.

5.0 Summary of Clinical Microbiology

The clinical microbiology reviewer, Avery Goodwin, states that based on the clinical microbiology data submitted by the Applicant, this NDA submission may be approved, with recommended revisions to the Microbiology subsection of the package insert. Major conclusions from his review are as follows:

- Oritavancin demonstrates in vitro activity against selected Gram-positive pathogens associated with ABSSSI. The MIC₉₀ against USA and European staphylococcal isolates was approximately 0.06 mcg/mL (range ≤ 0.002 -0.25 mcg/mL). Among European methicillin resistant *Staphylococcus aureus* (MRSA), the MICs ranged from ≤ 0.002 -0.5 mcg/mL while for US isolates, the MIC ranged from < 0.002 -0.25 mcg/mL. The presence of Panton Valentine leukocidin did not appear to have an effect on the in vitro activity of oritavancin. Against isolates with vancomycin MIC of 2 mcg/mL, the oritavancin MIC₉₀ was reported to be 0.12 mcg/mL (range ≤ 0.008 -0.25 mcg/mL). Against all coagulase negative staphylococcal isolates tested, the oritavancin MIC₉₀ was reported to be 0.12 mcg/mL with a range of 0.004-0.25 mcg/mL. The highest MIC observed was 0.25 mcg/mL and was encountered primarily among isolates of *S. epidermidis*. For streptococcus, the MIC₉₀ for *S. pneumoniae* was 0.15 mcg/mL while for beta-hemolytic streptococci, it was 0.25 mcg/mL. Against viridans streptococci, the MIC₉₀ was 0.06 for US isolates. Against the 148 isolates of the *S. anginosus* group, the MIC₉₀ was 0.0015 mcg/mL. The MIC₉₀ against *S. dysgalactiae* was 0.25 mcg/mL. Against all *E. faecalis* isolates, the MIC₉₀ was 0.06 mcg/mL. Against *E. faecium*, the MIC₉₀ was 0.12 mcg/mL. Higher MIC values were reported for isolates with the Vana phenotype.
- Mechanisms of resistance were not studied. Resistance to oritavancin was examined by serial passage studies in staphylococci and enterococci. A 4 to 8-fold increase in oritavancin MIC was observed for staphylococcal isolates of different drug resistance

phenotypes and a 4-64 fold increase in oritavancin MIC was reported for different enterococcal isolates.

- In vitro studies of oritavancin in combination with an array of antibacterial drugs showed synergistic bactericidal activity with gentamicin, moxifloxacin, or rifampicin against isolates of methicillin susceptible *Staphylococcus aureus* (MSSA), with gentamicin or linezolid against isolates of heterogeneous vancomycin intermediate *S. aureus* (hVISA), vancomycin intermediate *S. aureus* (VISA), and vancomycin resistant *S. aureus* (VRSA), and with rifampicin against isolates of VRSA.
- The addition of 0.002% polysorbate 80 lowered the oritavancin MIC₉₀ by 16 to 32-fold for enterococci and staphylococci as tested by broth microdilution. However, the MIC₉₀ did not change in the presence of 0.002% polysorbate 80 for streptococci.
- The efficacy of oritavancin has been investigated in a number of animal models of infection including staphylococcal and enterococcal bloodstream infection in mice, endocarditis models of staphylococcal and enterococcal infections in rabbits and rats, mouse and rat *S. pneumoniae* infection models, biofilm *S. aureus* infection models in mice, meningitis models of *S. pneumoniae* infection in rabbits, and *Bacillus anthracis* mouse infection models.
- Based on the data provided by the applicant for the MIC distribution patterns for large surveillance studies, the observation of clinical response data from the Phase 3 trials at the to-be-marketed dose, and the PK/PD characteristics of the drug, Dr. Goodwin agrees with the susceptibility test interpretive criteria proposed by the Applicant. For *S. aureus* including MRSA, the breakpoint is ≤ 0.12 mcg/mL, for all the indicated streptococcal spp. the breakpoint is ≤ 0.25 mcg/mL, and for *E. faecalis*, the breakpoint is ≤ 0.12 mcg/mL.

6.0 Summary of Clinical Efficacy

The biometrics reviewer, the primary medical reviewer, and the CDTL conclude that the applicant has demonstrated substantial evidence of the efficacy of oritavancin for the treatment of ABSSSI, as the results of the two Phase 3 trials demonstrate the oritavancin is noninferior to the comparator, vancomycin. Therefore, they recommend approval. I concur with their assessment.

This NDA contains the results of two Phase 3 trials, SOLO I and SOLO II. Both were global, multicenter, randomized, double blind, active-controlled, parallel group clinical trials in patients with ABSSSI suspected or confirmed to be caused by Gram-positive bacteria. The objective of the trials was to establish the noninferiority of a single IV dose 1200 mg of oritavancin compared to 7-10 days of intravenous vancomycin (either 1 g IV q 12h or 15 mg/kg IV q 12 h). The

protocols were designed in accordance with 2010 Agency guidance at the time, and used a primary endpoint of cessation of spread of the primary skin lesion, absence of fever ($\leq 37.6^{\circ}\text{C}$), and no rescue antibacterial drug therapy 48-72 hours after initiation of oritavancin or vancomycin. The primary analysis population included all randomized patients who were treated (modified intent-to-treat/mITT). Secondary endpoints included $\geq 20\%$ reduction in lesion size from baseline at 48-72 h (currently recommended as the primary endpoint for ABSSSI trials in the final Agency guidance), investigator-assessed clinical cure at the post treatment evaluation (PTE) visit from end of therapy (EOT), and sustained clinical response at PTE

In SOLO I, 968 patients were randomized 1:1 to oritavancin or vancomycin at 46 trial sites in nine countries. In SOLO II, 1019 subjects were randomized 1:1 to oritavancin or vancomycin at 32 trial sites in ten countries. For both trials, the two arms were balanced with respect to baseline demographics, fever, type of infection, anatomical site of infection, prior medications (including antibacterial drugs) and/or procedures such as incision and drainage (I&D), and baseline symptoms of the primary ABSSSI.

Table 1 illustrates the results for the primary endpoint and selected secondary endpoints from SOLO I while Table 2 depicts the findings for SOLO II.

Table 1: SOLO I-Summaries of the efficacy analyses for the mITT population

Endpoints	Oritavancin (N=475) n (%)	Vancomycin (N=479) n (%)	Difference (%) (95% CI*)
Early clinical response	391(82.3)	378(78.9)	3.4 (-1.6, 8.4)
Investigator assessed clinical cure at PTE	378 (79.6)	383 (80.0)	-0.4(-5.5, 4.7)
Lesion size reduction $\geq 20\%$ at ECE	413 (86.9)	397 (82.9)	4.1 (-0.5, 8.6)
Sustained clinical response at PTE	313 (65.9)	322 (67.2)	-1.3 (-7.3,4.7)

Source: Biometrics review

*Based on the normal approximation to Binomial distribution

Table 2: SOLO II-Summaries of the efficacy analyses for the mITT population

Endpoints	Oritavancin (N=503) n (%)	Vancomycin (N=502) n (%)	Difference (95% CI*)
Early clinical response	403(80.1)	416(82.9)	-2.7(-7.5, 2.0)
Investigator assessed clinical cure at PTE	416 (82.7)	404(80.5)	2.2 (-2.6, 7.0)
Lesion size reduction \geq 20% at ECE	432(85.9)	428(85.3)	0.6 (-3.7, 5.0)
Sustained clinical response at PTE	313 (65.9)	322 (67.2)	-1.3 (-7.3,4.7)

Source: Biometrics review

*Based on the normal approximation to Binomial distribution

The lower bound of the 95% confidence interval (CI) for the difference in early clinical response rates for oritavancin compared to vancomycin in SOLO I is -1.6 and in SOLO II is -7.5, which is greater than the prespecified noninferiority margin of -10%, indicating that oritavancin is noninferior to vancomycin for the treatment of ABSSSI. In addition, the lower bounds of the 95% CIs of the secondary analyses of $\geq 20\%$ reduction in lesion size are also greater than -10%, demonstrating that the conclusion would be the same whether the cessation of lesion spread plus afebrile status definition or the $\geq 20\%$ reduction in lesion size definition is used. In addition, the results at the PTE visits are in good alignment with the early clinical response rates.

7.0 Summary of Clinical Safety

The medical officer and the CDTL conclude that adequate evidence of safety has been provided to support the use of oritavancin for the treatment of adults with ABSSSI and that the benefit/risk profile is favorable. I concur with their assessment.

The overall safety database consisted of 3017 oritavancin-treated subjects from 22 clinical trials, including four Phase 3 trials, four Phase 2 studies, and 14 Phase 1 studies. A total of 1075

ABSSSI subjects were treated with the 1200 mg single dose regimen. The safety review focused primarily on the pooled Phase 3 SOLO trials. The mean duration of exposure to oritavancin was eight days.

In the pooled SOLO trials, there were five deaths (two in the oritavancin group and three in the vancomycin group). There were another five deaths in one of the Phase 2 studies. None of these deaths appeared to be related to study drug. The incidence of treatment emergent adverse events (TEAEs) in the Phase 3 trials was 55% in the oritavancin group and 57% in the vancomycin group. More TEAEs in the Infections and Infestations System Organ Class (SOC) were reported in subjects receiving oritavancin compared to subjects receiving vancomycin (40 cases vs. 31 cases, respectively). This was noted in the previous NDA that received a complete response. Review of these cases revealed four subjects with oritavancin who had osteomyelitis, possibly due to poor efficacy or failure to diagnose at baseline. An additional four oritavancin-treated subjects developed pneumonia but these subjects appeared to have risk factors for pneumonia including history of COPD, and history of aspiration pneumonia. Because the finding of disproportionate numbers of oritavancin-treated subjects with an adverse event of osteomyelitis was noted in the previous NDA package, the Applicant has proposed to include a Warning and Precaution about not using oritavancin in patients diagnosed with osteomyelitis and the clinical review team agrees.

For subjects in both treatment groups, the most common reason for drug discontinuation was also Infections and Infestations (1.6% for the oritavancin group and 1.9% for the vancomycin group). Twenty-one subjects in the oritavancin arm and 19 in the vancomycin arm had a serious adverse event (SAE) leading to treatment discontinuation. The most common TEAEs in both the oritavancin and vancomycin treated groups were nausea (17.7% vs. 18.3%), headache (12.6% vs. 11.7%), vomiting (8.2% for both groups), diarrhea (6.6% vs. 5.7%), cellulitis (6.8% vs. 5.7%), constipation (6% vs. 6.7%), and infusion site extravasation (6% vs. 5.9%). There were 24 subjects (4.4%) in the oritavancin group and 11 subjects (1.9%) in the vancomycin group with an AE of tachycardia. However, there was no relationship established between administration of oritavancin and the occurrence of tachycardia. Although elevated ALT was reported as an AE in 27 oritavancin-treated subjects compared to 16 vancomycin treated subjects, analysis of the laboratory data demonstrated that 18 subjects in the oritavancin arm compared to 14 subjects in the vancomycin arm had ALT elevations from baseline to 3-5 X ULN and three subjects vs. one subject in the oritavancin and vancomycin arms, respectively, who had an elevation in total bilirubin from normal to 1.5-2 X ULN. There were no subjects who met Hy's Law criteria. Therefore, there does not appear to be a signal for hepatic events.

8.0 Advisory Committee Meeting

There were no safety, efficacy, or other issues identified requiring advisory committee input, so no advisory committee meeting was convened.

9.0 Pediatrics

The Applicant's proposed pediatric plan was presented to the Pediatric Research Committee and the following PREA requirements were found acceptable:

1. Conduct an open label, dose finding, pharmacokinetics, safety and tolerability study of Orbactiv (oritavancin diphosphate) single dose infusion in pediatric subjects less than 18 years of age with suspected or confirmed bacterial infections.
2. Conduct a multicenter, evaluator-blind, randomized study to evaluate the safety and tolerability of single-dose IV Orbactiv (oritavancin diphosphate) versus vancomycin for the treatment of pediatric subjects less than 18 years of age with acute bacterial skin and skin structure infections.

10.0 Other Regulatory Issues

Data from four sites (three in the U.S. and one foreign) were found acceptable, based on clinical site investigations and the clinical inspection summary from the Office of Scientific Investigations by Dr. Janice Pohlman. The inspectors also concluded that the Applicant had maintained satisfactory oversight of the trials.

The carton and container labeling have been reviewed by ONDQA and the DMEPA and recommendations incorporated. The proprietary name Orbactiv has been found acceptable by DMEPA.

11.0 Benefit/Risk Assessment and Recommendations

I concur with the findings and the recommendations of the review team that sufficient evidence of safety and efficacy has been submitted to support the approval of oritavancin lyophilized powder for injection for the treatment of adults with ABSSSI, caused by susceptible isolates of the designated bacteria. In addition, the benefit/risk assessment for oritavancin is favorable as it has been shown to be safe for its use as labeled in the package insert based on a safety database of over 1000 subjects from the most recent two Phase 3 trials as well as an additional 2000 subjects from the overall development program, and has demonstrated noninferiority to vancomycin, a drug commonly used for the treatment of skin infections. The single dose regimen

may provide a benefit to patients for whom compliance is an issue with oral formulations, or who are not able to take oral medications, and reduces the need for prolonged intravenous access in all patients.

As noted above, the Applicant has proposed pediatric studies to be completed to address requirements of PREA. In addition, they have agreed to a postmarketing requirement to evaluate for the development of resistance to oritavancin, as follows:

Conduct US surveillance studies for five years from the date of marketing Orbactiv to determine if resistance to oritavancin has developed in those organisms specific to the indication in the label for ABSSSI.

To generate additional information regarding the drug-drug interaction with oritavancin and warfarin, effects of oritavancin alone on or co-administered with warfarin on coagulation parameters, and effects *in vitro* on additional coagulation tests, the Applicant has agreed to the following three PMRs and one PMC:

Conduct an open label study evaluating the safety of a single 1200 mg IV dose of oritavancin in patients on concomitant chronic warfarin therapy being treated for ABSSSI.

Conduct an open-label study to assess the clinical significance of the drug-drug interaction between a single 1200 mg IV dose of oritavancin and warfarin in healthy volunteers.

Conduct a single-center, open-label study to evaluate the effects of a single 1200mg IV dose of oritavancin on the results of multiple coagulation tests in healthy volunteers.

Conduct a study to evaluate the effects of oritavancin on phospholipid and non-phospholipid based coagulation tests *in vitro*.

Katherine A. Laessig, MD

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/s/

KATHERINE A LAESSIG
08/06/2014