Brand Name: Orbactiv

Generic Name: oritavancin

Manufacturer[1,2,3,4,5]: The Medicines Company

Drug Class[1,2,3,4,5]: Semisynthetic Lipoglycopeptide Antibacterial

Uses:

Labeled Uses: Adult patients with acute bacterial skin and skin structure infections caused by susceptible Gram + microorganisms (Staph Aureus, Strep. Pyogenes, Strep agalactiae, Strep dysgalactiae, Strep anginosus, and Vancomycin-susceptible Enterococcus faecalis).

Supplied as a 400mg powder for injection

Mechanism of Action: inhibition of the transglycosylation step of cell wall biosynthesis; inhibition of the transpeptidation step of cell wall biosynthesis; disruption of bacterial membrane integrity

Pharmacokinetics[1,2,3,4,5]:

Absorption:

V_d	87.6L
$t_{½}$ elimination	245 hours
Clearance	0.445L/hour
Protein binding	85%

Distribution: Oritavancin is approximately 85% bound to human plasma proteins. Its distribution into skin blister fluid was approximately 20% of distribution obtained in plasma (AUC 0 to 24 hours) following a single dose of 800 mg administered in healthy subjects. Oritavancin estimated Vd was about 87.6 L, thus indicating extensive tissue distribution.

Distribution half-life: Mean alpha phase t(1/2) was 2.29 hours and the mean beta phase t(1/2) was 13.4 hours

Metabolism: Not metabolized. Oritavancin is a weak inhibitor of 1A2, 2B6, 2D6, 2C9, 2C19, and 3A4, though these effects are thought to be reversible and noncompetitive. It has also been seen to be a nonspecific weak inducer of CYP3A4 and 2D6.

Elimination: Less than 5% is excreted in the urine as unchanged drug. Less than 1% is excreted in the feces as unchanged drug. Total body clearance is 0.445 L/hr, with a mean half-life of approximately 245 hours in patients who receive a single 1200mg dose.

Efficacy:

Dunbar LM, Milata J, McClure T, Wasilewski MM; SIMPLIFI Study Team. (2011). Comparison of the efficacy and safety of oritavancin front-loaded dosing regimens to daily dosing: an analysis of the SIMPLIFI trial. Antimicrob Agents Chemother. 2011 Jul;55(7):3476-84.

Study Design: Multicenter, randomized, double-blind, parallel, active-comparator design study

Description of Study: *Methods*: A total of 302 patients ≥ 18 years of age were randomized into one of three oritavancin treatment groups, receiving either a daily dose (200 mg) administered for 3 to 7 days, a single dose (1,200 mg), or an infrequent dose (800 mg dose, with the option for an additional 400 mg on day 5). *Outcomes:* The primary efficacy outcome was to determine the clinical response rate of each treatment regimen in the clinically evaluable (CE) and intent-to-treat (ITT) population at test of cure (TOC) on days 21 to 29. The secondary outcome of the study was to evaluate the safety of each dosing regimen. All other topical, oral, or systemic antibiotics with activity against gram-positive pathogens were prohibited. A 15% noninferiority margin was considered justified for this phase 2 clinical trial. Cure was defined at each time point as resolution of purulent drainage, pain, edema, fever, erythema, tenderness, and induration. Failure included any of the following: presence of purulent drainage (or aspirate) and/or fever; unanticipated need for abscess drainage, unplanned debridement or increased number of debridements beyond what was initially anticipated at baseline, removal of sutures (for treatment of infection) 48 hours after initiation of study therapy, or treatment with a systemic antibiotic other than study drug having activity against a Gram-positive pathogen for the primary infection site (or use of topical antibiotics at the site of the primary infection at least 24 hours after initiation of study medication therapy). Also, if the patient's infection worsened, then a clinical response of failure was assigned. The primary efficacy analysis was a comparison of the proportion of CE patients in the daily-dose group with a clinical response of cure and the proportions of patients in the 1,200-mg-single-dose group and the infrequent-dose group with a clinical response of cure. *Outcome Results:* In the ITT population, 89.9% [89/100] of patients in the daily-dose group, 88.9% [88/99] of patients in the 1,200 mg single dose group, and 86.4% [89/103] of patients in the infrequent-dose group completed IV therapy. In the ITT population, 31.8% (96/302) of patients had wound infections, 37.7% (114/302) had major abscesses, and 30.5% (92/302) had cellulitis. The clinical cure rates at TOC in the CE population were 72.4% (55/76), 81.5% (66/81), and 77.5% (55/71) in the daily-dose, 1,200 mg single dose, and infrequent dose groups, respectively. The single-dose and infrequent-dose regimens of oritavancin were noninferior to the daily-dose regimen. A statistically higher cure rate (90% CI, 9.2 to 49.1) was seen for patients with cellulitis in the 1,200 mg single dose group (87.5% [21/81]) than for patients with cellulitis in the daily-dose group (58.3% [14/76]). A total of 8.3% (25/302) of patients experienced a serious adverse event. The incidence of serious adverse events was higher in the daily-

dose group (11% [11/100]) than in the 1,200-mg-singledose group (7.1% [7/99]) and the infrequent-dose group (6.8% [7/103]). According to authors, this clinical study demonstrated that oritavancin given as a single dose of 1,200 mg or an infrequent dose of 800 mg with an optional 400 mg dose on day 5 was noninferior to a 200 mg daily dose for 3 to 7 days for the treatment of patients with cSSSI.

Limitations: This study was supported by Targanta Therapeutics Corporation, a subsidiary of the Medicines Company, who is the manufacturer of the study drug. Also, three authors were employees of the company, introducing a potential conflict of interest. Small sample size may limit the interpretation of the results. Study endpoints are clinically relevant, but do not completely follow up-to-date FDA guidance.

Conclusion: According to the authors, the study showed that oritavancin given as a 1,200 mg single dose or as an infrequent-dosing (800 mg dose with option for an additional 400 mg on day 5) was clinically safe and effective for the treatment of complicated skin and skin structure infections. The study does show that oritavancin appears to be effective in treating these types of skin infections, including MRSA. The single-dose regimen would be an extreme advantage over current therapy standards, however more studies need to be conducted to assess efficacy and safety compared to therapy standards in place to determine where this specific drug fits into therapeutic regimens.

Corey GR, Kabler H, Mehra P, Gupta S, Overcash JS, Porwal A, Giordano P, Lucasti C, Perez A, Good S, Jiang H, Moeck G, O'Riordan W; SOLO I Investigators. Single-dose oritavancin in the treatment of acute bacterial skin infections. N Engl J Med. 2014 Jun 5;370(23):2180-90.

Study Design: International, double-blind, randomized, parallel group study

Description of Study: *Methods*: 475 patients received a single dose of oritavancin IV followed by IV placebo while 479 patients received an IV dose of vancomycin (1g or 15mg/kg of body weight) every 12 hours for 7 to 10 days. Clinical evaluations were performed at the following time points: 48 to 72 hours after the initiation of the study treatment (early clinical evaluation), day 7 to day 10 (end of therapy) or if discontinued early, the day the patient stopped receiving the study drug or was switched to a non-study drug for primary acute bacterial skin and skin-structure infection; 10 days after the initiation of the study drug; and 7 to 14 days after the end-of-therapy visit (post-therapy evaluation). A follow-up of 60 days was also analyzed for safety evaluations related to effects of oritavancin half-life. *Outcome:* The primary efficacy end point and the end point approved by the FDA was a composite outcome at the time of the early clinical evaluation that comprised the cessation of spreading or a reduction in the size of the baseline lesion, the absence of fever, and the absence of a need for rescue antibiotic medication. Secondary outcomes included clinical cure (determined by a study investigator at post-therapy evaluation) and decrease in lesion area of 20% or more from baseline to the early clinical evaluation. Safety was assessed by evaluating vital signs, lab values, and recording adverse events from the first day of treatment up through the safety follow-up visit on day 60. The authors determined a noninferiority margin of 10%

was acceptable for determining if oritavancin was noninferior to vancomycin with respect to the primary endpoint. *Outcome Results:* The primary end point at the early clinical evaluation (82.3% with oritavancin and 78.9% with vancomycin), the end point of clinical cure at post-therapy evaluation as assessed by a study investigator (79.6% and 80.0%, respectively), and the end point of a reduction in lesion size of 20% or more at early clinical evaluation (86.9% and 82.9%, respectively) remained within the noninferiority margin, since the lower limit of the 95% confidence interval for the between-group difference (oritavancin vs. vancomycin) was above −10%. Similar efficacy was also observed in the MRSA subpopulation (95% CI, 0.8 (-10.1 to 11.7)). Side effect incidence was deemed similar in both groups as well (284 in oritavancin group vs. 307 in vancomycin group).

Limitations: The Medicines Company designed and conducted both the study and statistical plan. An author who is an employee for this sponsor company developed the first draft of the manuscript. The different dosing regimens could also have played a role in potential differences between study groups, as well as the vancomycin dosing being altered/tailored to patient's weight rather than being given at a standard dose for all patients receiving the drug, similar to oritavancin. Also, the authors determined the noniferiority margin for this specific study design, which may or may not truly be an accurate representation of clinical equivalence between oritavancin and vancomycin.

Conclusion: This study utilized both an intent-to-treat population and a modified intent-to-treat population, allowing for results to be concluded for a safety population and a population that actualy received the full-course of study treatment. The results of the study showed that a single dose of oritavancin was noninferior to 7-10 day treatment with vancomycin in adults with acute bacterial infections caused by Gram-positive bacteria, including MRSA. However, based on the potential for bias and differences in dosing schedules, as well as dosing strength equivalence being in question, further studies would need to be completed to determine oritavancin's place in therapy.

Corey GR, Good S, Jiang H, Moeck G, Wikler M, Green S, Manos P, Keech R, Singh R, Heller B, Bubnova N, O'Riordan W; SOLO II Investigators. Single-dose oritavancin versus 7-10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study. Clin Infect Dis. 2015 Jan 15;60(2):254-62.

Study Design: Randomized, multinational, double-blind study

Description of Study: *Methods*: This study was very similar to the SOLO I clinical trial mentioned above. In this study, 503 patients received oritavancin while 502 patients received vancomycin. This study utilized a modified-intent-to-treat analysis. The dosing regimens and outcomes for SOLO I were again utilized in this clinical trial to again determine noninferiority of oritavancin compared to vancomycin for the treatment of acute bacterial skin infections, including MRSA. *Outcomes:* The primary efficacy endpoint was a composite outcome at early clinical evaluation (ECE) that comprised of: cessation of spreading or reduction in the size of the

baseline lesion, absence of fever, and no rescue antibiotic medication, as defined by the FDA. The key secondary endpoint was investigator-assessed clinical cure at post therapy evaluation (PTE). An additional secondary efficacy outcome was lesion area decrease ≥20% from baseline at ECE, as suggested by the Foundation for the National Institutes of Health. Treatment emergent adverse events (TEAE) were also analyzed from the first dose up through the safety follow-up visit at day 60. *Outcome Results*: Efficacy and safety conclusions from this trial were consistent with those in the Solo I study. Oritavancin was considered non-inferior to vancomycin for the primary endpoint at ECE (80.1% oritavancin vs 82.9% vancomycin), the investigator assessed clinical cure endpoint at post therapy evaluation (PTE) (82.7% vs 80.5%, respectively) and the >20% reduction in lesion size endpoint at ECE (85.9% vs 85.3%, respectively) since the lower limit of the 95% confidence interval for each endpoint was above -10%. Similar efficacy was seen across the two treatment groups in the MRSA and MSSA subpopulations for the primary and secondary endpoints. Frequency of treatment emergent adverse events was also similar between study groups.

Limitations: There were differences in response rates between treatment groups in the diabetes subgroup, but these analyses were based off a small number of patients and are not consistent with results seen in the SOLO I study which had a greater number of patients with diabetes and showed similar response rates between treatments. As with the SOLO I study, this study had similar limitations, including sponsorship by The Medicines Company and incompatible dosing schedules. They also determined the noninferiority margin for this study, which may not be an accurate representation of true potential equivalence between therapies.

Conclusion: The results from this study back-up the results from the SOLO I study. According to the authors it is important to note that the extended 60 day follow-up of the oritavancin population failed to identify prolonged or delayed adverse events. Even though these results are similar to those from a previous trial and the use of a single-dose therapy for acute bacterial skin infections appears promising, it is still a very costly drug and would need further testing to determine if it should technically be used in place of current therapies. Its place in therapy is still yet to be determined, and has only been studied in adult subjects. However, it does appear to be a potential alternative to current therapies for the treatment acute bacterial skin and skin structures infections, especially if resistance becomes an issue.

Contraindications[1,2,3,4,5]:

- Use of intravenous unfractionated heparin sodium is contraindicated within 48 hours after Orbactiv administration.
- Known hypersensitivity to Orbactiv.

Precautions[1,2,3,4,5]:

- **Concomitant warfarin use:** Co-administration may result in increased exposure of warfarin, increasing the risk of bleeding. Orbactiv should only be used in patients on chronic warfarin therapy when benefits outweigh the risk of bleeding.
- **Coagulation test interference:** Orbactiv has been shown to prolong aPTT for up to 48 hours, and can potentially prolong PT and INR for up to 24 hours.
- **Hypersensitivity Reactions:** Serious hypersensitivity reactions have been reported; discontinue immediately if an allergic reaction occurs. Also, previous hypersensitivity reaction to glycopeptides may cause cross-sensitivity; monitoring recommended.
- **Other precautions:**
    - Clostridium difficile-associated diarrhea, which has occurred more than 2 months after administration; if suspected or confirmed, utilize appropriate medical management.
    - Infusion-related reactions, including pruritus, urticaria or flushing; if reaction occurs, slowing or stopping infusion may be necessary.
    - Osteomyelitis has been reported; if suspected or confirmed, utilize appropriate medical management

Adverse Effects[1,2,3,4,5]:

Occurring in >2% of patients:

- **Gastrointestinal:** Nausea (9.9%), Vomiting (4.6%), Diarrhea (3.7%)
- **Neurologic:** Headache (7.1%), Dizziness (2.7%)

Occuring in <2% of patients:

- **Gastrointestinal:** Clostridium difficile diarrhea (less than 1%)
- **Hematologic:** Activated partial thromboplastin time abnormal, Bleeding, INR raised, Prothrombin time increased, Anemia (less than 1.5%), Eosinophilia (less than 1.5%)
- **Hepatic:** Increased Serum ALT (0.03%), Increased Serum AST (0.02%), Increased Serum Bilirubin (less than 2%)
- **Immunologic:** Hypersensitivity reaction (less than 1.5%)
- **Musculoskeletal:** Osteomyelitis (less than 1.5%), Myalgia (less than 1.5%)
- **Respiratory:** Bronchospasm (less than 2%), Wheezing (less than 2%)
- **Other:** Complication of infusion (1.9%), Cellulitis (less than 1.5%), Hyperuricemia (less than 1.5%), Hypoglycemia (less than 1.5%)

Drug Interactions[1,2,3,4,5]:

Contraindicated:

- Concurrent use of heparin and oritavancin may result in falsely elevated aPTT test results.

Major Interactions:

- Concurrent use of carbamazepine and oritavancin may result in decreased carbamazepine exposure.

- Concurrent use of oritavancin and warfarin may result in increased warfarin exposure.

- Concurrent use of oritavancin and phenytoin may result in increased phenytoin exposure.

Other Interactions:

- Midazolam: Concomitant use of oritavancin (single 1200mg dose) and midazolam results in an 18% decrease in the mean area under the plasma concentration-time curve (AUC) of midazolam.

- Omeprazole: Concomitant use of oritavancin (single 1200mg dose) and omeprazole results in a 15% increase in the ratio of omeprazole to 5-hydroxyomeprazole concentrations in plasma.

- Dextromethorphan: Concomitant use of oritavancin (single 1200mg dose) and dextromethorphan results in a 31% decrease in the ratio of dextromethorphan to dextrorphan concentrations in urine.

Dosing/Administration[1,2,3,4,5]:

Adult Dosing

The recommended dosage of oritavancin for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults is a single 1200mg dose given via IV infusion over 3 hours.

Pediatrics

Safety and efficacy have not been established in pediatric patients.

Elderly

Dose adjustments are not necessary in geriatric patients.

Renal impairment

Dosage adjustments are not needed in patients with mild or moderate renal impairment. Severe renal impairment has not been studied

Hepatic impairment

Dosage adjustments are not needed in patients with mild or moderate hepatic impairment. Severe hepatic impairment has not been studied

*Slow or interrupt infusion if an infusion reaction occurs

Use in special circumstances[1,2,3,4,5]:

- **Pregnancy Category: Category C (All Trimesters):** Either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
- **Breastfeeding/Lactation:** Risk cannot be ruled out. Inform clinician before breastfeeding.

Conclusion:

Oritavancin does appear to be an effective therapy for patients with acute bacterial skin and skin structure infections. Studies have determined oritavancin's place in the treatment of acute bacterial infections, however more studies must be completed to determine if the drug is superior to current standard therapies for these infections. The side effects and adverse events of the drug appear to be minimal. However, it is difficult to see the advancement of this drug in place of already established therapies due in part to its high cost. With its tolerability, minimal drug interactions, effectiveness in acute bacterial skin infections and potential use in other Gram-positive infections, oritavancin appears to be another clinically useful antibacterial agent that could be used in place of common standard therapies in the near future.

Recommended References:

1. Oritavancin. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2015. Available at: http://www.clinicalpharmacology.com Accessed: September 25, 2015.
2. Oritavancin. Lexi-Drugs [database online]. Lexi-Comp, Inc; September 25, 2015.
3. Orbactiv [package insert].Parsippany, NJ: The Medicines Company.: 2008.
4. Oritavancin. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Truven Health Analytics Micromedex Solutions. Updated periodically. Accessed September 25, 2015.
5. Oritavancin Injection. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed: September 25, 2015.
6. Dunbar LM, Milata J, McClure T, Wasilewski MM; SIMPLIFI Study Team. Comparison of the efficacy and safety of oritavancin front-loaded dosing regimens to daily dosing: an analysis of the SIMPLIFI trial. Antimicrob Agents Chemother. 2011 Jul; 55(7):3476-84.
7. Corey GR, Kabler H, Mehra P, Gupta S, Overcash JS, Porwal A, Giordano P, Lucasti C, Perez A, Good S, Jiang H, Moeck G, O'Riordan W; SOLO I Investigators. Single-dose oritavancin in the treatment of acute bacterial skin infections. N Engl J Med. 2014 Jun 5; 370(23):2180-90.
8. Corey GR, Good S, Jiang H, Moeck G, Wikler M, Green S, Manos P, Keech R, Singh R, Heller B, Bubnova N, O'Riordan W; SOLO II Investigators. Single-dose oritavancin versus 7-10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study. Clin Infect Dis. 2015 Jan 15; 60(2):254-62.

Prepared by: Evan Cavallo, Doctor of Pharmacy Candidate