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NCCN Guidelines Panel: Prevention and Treatment of Cancer-Related Infections

On behalf of The Medicines Company, I respectfully request the *NCCN Prevention and Treatment of Cancer-Related Infections* Panel to review the enclosed data supporting the inclusion of ORBACTIV® (oritavancin) for Injection in both the treatment pathway and table for cellulitis/skin and soft tissue infections.

Specific Changes Requested: Inclusion of ORBACTIV as a therapeutic option for the treatment of cellulitis/skin and soft tissue infections by: (1) adding ORBACTIV to the FEV-9 *Cellulitis/Skin and Soft Tissue Infections, Vascular Access Devices, Vesicular Lesions, Disseminated Papules or Other Lesions, and Central Nervous System Symptoms* pathway for the treatment of cellulitis/skin and soft tissue infections; and (2) adding ORBACTIV to the FEV-A *Antibacterial Agents: Gram-positive Activity* table.

FDA Indication and Usage (approved Aug 6, 2014): ORBACTIV is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused or suspected to be 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). ORBACTIV is administered as a 1200 mg single dose by intravenous infusion over 3 hours.¹

Rationale: As stated in the US FDA approved product labeling, a single 1200 mg dose of ORBACTIV demonstrated non-inferiority in achievement of clinical response at early clinical evaluation or ECE (48 to 72 hours following treatment initiation) defined as a composite of: (1) cessation of spreading or reduction in size of baseline lesion, (2) absence of fever, and (3) no rescue antibiotic medication compared to vancomycin 1 g or 15 mg/kg every 12 hours for 7 to 10 days in adults with cellulitis/erysipelas, wound infection, or major cutaneous abscesses in two double-blind, active-controlled, multicenter, randomized trials of 1959 patients (modified intent-to-treat population, 405 patients with confirmed MRSA).¹

Two randomized, identically designed Phase 3 clinical trials demonstrated that a single dose of ORBACTIV has a comparable efficacy and safety profile and is non-inferior to a multi-dose (every 12 hours for 7 to 10 days) regimen of vancomycin.^{2,3} In the pooled Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections (SOLO I and SOLO II) clinical trials, 40.2% of enrolled patients received ORBACTIV in an outpatient setting (i.e., ED or infusion center) only.⁴ ORBACTIV dosage adjustment is not required for mild-to-moderate renal or hepatic insufficiency, age (≥ 18 years), weight, gender, or race.¹

A summary of key ORBACTIV data derived from the Phase III SOLO Trial Results (n = 1959; Trial 1 = Corey 2014^{2,5} and Trial 2 = Corey 2015)^{3,6} includes:

- Early clinical response at 48 to 72 hours (cessation of spread or reduction in size of baseline lesion, absence of fever, and no rescue antibacterial drug after initiation of therapy) with ORBACTIV was non-inferior to vancomycin (Trial 1: 82.3% vs. 78.9%; Trial 2: 80.1% vs. 82.9%).
- Lesion size reduction $\geq 20\%$, at 48 to 72 hours, with ORBACTIV was non-inferior to vancomycin (Trial 1: 86.9% vs. 82.9%; Trial 2: 85.9% vs. 85.3%).
- Investigator-assessed clinical cure at 14 to 24 days following initiation of treatment demonstrated that ORBACTIV was non-inferior to vancomycin (Trial 1: 79.6% vs. 80.0%; Trial 2: 82.7% vs. 80.5%).
- The combined SOLO trials provide the largest database on MRSA outcomes in ABSSSI (n=405 mMITT) whereby early clinical response (ORBACTIV 81.4%; vancomycin 80.6%), lesion size reduction $\geq 20\%$ (ORBACTIV 93.1%; vancomycin 87.1%) and clinical success (ORBACTIV 83.3%; vancomycin 84.1%) were similar.

- Patients enrolled into SOLO with systemic inflammatory response syndrome (SIRS) at baseline (n=342, 17.5%) demonstrated similar clinical efficacy at the primary early clinical response time point (ORBACTIV 68.6%; vancomycin 73.4%; 95% CI, -14.9, 4.1).^{5,6} [SIRS criteria was defined as two of the following: temperature > 38°C, pulse > 90 beats per minute, respiratory rate > 20 breaths per minute, white blood cell count > 12,000 cells/μL or white blood cell count < 4,000 cells/μL, or > 10% bandemia]
- Demographics and baseline characteristics of those patients treated in the outpatient setting (n=787) were similar between two treatment groups. The primary composite endpoint rates at ECE were 80.6% and 78.3% for ORBACTIV and vancomycin treated patients respectively (95% CI: -3.4%, 7.9%). The rates of patients who achieved lesion size reduction ≥20% at ECE were 87.0% in the ORBACTIV group vs. 84.3% in the vancomycin group (95% CI: -2.3%, 7.5%). The investigator-assessed clinical cure at PTE was 83.9% in the ORBACTIV group compared to 81.8% in the vancomycin group (95% CI: -3.2%, 7.3%).⁷
- The Eron classification was developed by an expert panel of clinicians and researchers to categorize severity to guide initial site of care decisions for patients with skin and soft tissue infections. In the Eron classification, patients are grouped into four categories of ascending severity according to signs and symptoms of infection and comorbidities. During the development of criteria for assignment of SOLO patients into an Eron category, cancer patients were included in class III.⁴ While there were few patients enrolled in the SOLO trials with active oncologic processes, it would be appropriate to include such patients in class III as these patients may appear toxic, or they may appear nontoxic but have unstable comorbidities. There were 600 patients in Class III, 189 (31.5%) of whom were treated completely as outpatients; 89 patients received ORBACTIV and 100 received vancomycin. Primary and secondary endpoints for clinical cure of outpatient-treated class III patients were as follows: primary composite endpoint at ECE, ORBACTIV 70.8% and vancomycin 75.0%; lesion size reduction >20% at ECE, ORBACTIV 80.9% and vancomycin 80.0%; and, investigator-defined clinical cure at PTE, ORBACTIV 79.8% and vancomycin 82.0%. The 95% CI was non-inferior for ORBACTIV in all subgroups above.

In vitro studies indicate that ORBACTIV exhibits concentration-dependent bactericidal activity.¹ This is attributed to ORBACTIV's three mechanisms of action. In vitro activity does not necessarily correlate to clinical efficacy. Also, ORBACTIV plasma pharmacokinetics may be described by a three-compartment model. Following initial distribution and elimination phases, oritavancin plasma concentrations have a long terminal elimination phase with a half-life of 245 hours. This unique pharmacokinetic profile allows for microbiological activity to be present for several days following a single dose. ORBACTIV rapidly distributes to extravascular tissue sites. The terminal serum half-life of 245 hours, penetration of extravascular tissue sites, and multiple mechanisms of action are primary characteristics which combine to allow ORBACTIV to be administered as a single dose for the treatment of ABSSSI.

Common adverse drug reactions observed in at least 3% of patients treated with ORBACTIV included: nausea (9.9%), headache (7.1%), vomiting (4.6%), limb and subcutaneous abscesses (3.8%), diarrhea (3.7%).¹ Further, in the pooled SOLO I and SOLO II clinical trials, serious adverse events were reported for 5.8% of patients who received ORBACTIV and 5.9% for those who received vancomycin. The most commonly reported serious adverse event was cellulitis, 1.1% for ORBACTIV and 1.2% for those who received vancomycin.

I respectfully request your consideration for inclusion of ORBACTIV within the *NCCN Prevention and Treatment of Cancer-Related Infections* guidelines due to the demonstrated efficacy of ORBACTIV for ABSSSI gram-positive infections while providing an alternative to the multi-day, multi-dose regimens of many current IV ABSSSI antibacterial drugs.

Sincerely,

Mark Redell, Pharm.D.

References used as support in this letter:

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4. Deck DH, Jordan JM, Holland TL, et al. Single-dose oritavancin treatment of acute bacterial skin and skin structure infections: SOLO trial efficacy by Eron severity and management setting. *Infect Dis Ther.* 2016; [epub ahead of print].
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7. LaPensee K, Fan W, Lodise T, et al. Efficacy and safety of single dose oritavancin compared to 7-10 days of vancomycin in patients with acute bacterial skin and skin structure infections treated in the outpatient setting. ICAAC 2014; Washington DC: Poster L-1729.

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4. Holland T, Wikler M, Moeck G, et al. A single dose of oritavancin compared to 7-10 days of vancomycin in the treatment of acute bacterial skin and skin structure infection (ABSSSI): An analysis of the MRSA subpopulation in the SOLO non-inferiority studies. The Society of Hospital Medicine 2014;Las Vegas, NV; Poster 170.
5. Corey GR, Good S, Jiang H, et al. Concordance between early (48-72 hours) and late (7-14 days post therapy) clinical response: An analysis from the SOLO non-inferiority clinical studies. 24th European Congress of the Clinical Microbiology and Infectious Diseases (ECCMID) 2014:Poster eP418.
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8. Corey GR, O'Riordan W, Huang N-Y, et al. Time to onset and duration of adverse events in patients with acute bacterial skin and skin structure infections treated with oritavancin – the SOLO studies. ID Week 2014 2014;October 8-12, 2014:Philadelphia, PA.