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RESEARCH**

APPLICATION NUMBER:

206334Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ORBACTIV™ safely and effectively. See full prescribing information for ORBACTIV.

ORBACTIV (oritavancin) for injection, for intravenous use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

ORBACTIV is a lipoglycopeptide antibacterial drug indicated for the treatment of adult patients with acute bacterial skin and skin structure infections caused or suspected to be caused by susceptible isolates of designated Gram-positive microorganisms. (1.1)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ORBACTIV and other antibacterial drugs, ORBACTIV should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. (1.2)

DOSAGE AND ADMINISTRATION

A 1200 mg single dose is administered by intravenous infusion over 3 hours. (2.1)

DOSAGE FORMS AND STRENGTHS

For injection: 400 mg of lyophilized powder in a single-use vial for reconstitution. (3)

CONTRAINDICATIONS

- Use of intravenous unfractionated heparin sodium is contraindicated for 48 hours after ORBACTIV administration. (4.1, 5.2)
- Known hypersensitivity to ORBACTIV (4.2, 5.3)

WARNINGS AND PRECAUTIONS

- Concomitant warfarin use: Co-administration of ORBACTIV and warfarin may result in higher exposure of warfarin, which may increase the risk of bleeding. Use ORBACTIV in patients on chronic warfarin therapy only when the benefits can be expected to outweigh the risk of bleeding. (5.1)
- Coagulation test interference: ORBACTIV has been shown to artificially prolong aPTT for up to 48 hours, and may prolong PT and INR for up to 24 hours. (5.2)
- Hypersensitivity reactions have been reported with the use of antibacterial agents including ORBACTIV. Discontinue infusion if signs of acute hypersensitivity occur. Monitor closely patients with known hypersensitivity to glycopeptides. (5.3)
- Infusion-related reactions have been reported. Slow the rate or interrupt infusion if infusion reaction develops. (5.4)
- *Clostridium difficile*-associated colitis: Evaluate patients if diarrhea occurs. (5.5)
- Osteomyelitis: Institute appropriate alternate antibacterial therapy in patients with confirmed or suspected osteomyelitis. (5.6)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 3\%$) in patients treated with ORBACTIV were headache, nausea, vomiting, limb and subcutaneous abscesses, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact The Medicines Company at 1-888-977-6326 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Acute Bacterial Skin and Skin Structure Infections

ORBACTIV™ (Oritavancin) for injection is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive microorganisms:

Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant 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).

1.2 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ORBACTIV and other antibacterial drugs, ORBACTIV should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosing for ORBACTIV is a single 1200 mg dose administered by intravenous infusion over 3 hours in patients 18 years and older.

2.2 Preparation of ORBACTIV for Intravenous Infusion

ORBACTIV is intended for intravenous infusion, only after reconstitution and dilution.

Three ORBACTIV 400 mg vials need to be reconstituted and diluted to prepare a single 1200 mg intravenous dose.

Reconstitution: Aseptic technique should be used to reconstitute three ORBACTIV 400 mg vials.

- Add 40 mL of sterile water for injection (WFI) to reconstitute each vial to provide a 10 mg/mL solution per vial.
- For each vial, gently swirl to avoid foaming and ensure that all ORBACTIV powder is completely reconstituted in solution.
- Each vial should be inspected visually for particulate matter after reconstitution and should appear to be clear, colorless to pale yellow solution.

Dilution: Use ONLY 5% dextrose in sterile water (D5W) for dilution. Do NOT use Normal Saline for dilution as it is incompatible with ORBACTIV and may cause precipitation of the drug. Use aseptic technique to:

- Withdraw and discard 120 mL from a 1000 mL intravenous bag of D5W.
- Withdraw 40 mL from each of the three reconstituted vials and add to D5W intravenous bag to bring the bag volume to 1000 mL. This yields a concentration of 1.2 mg/mL.

Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparing the final intravenous solution.

Diluted intravenous solution in an infusion bag should be used within 6 hours when stored at room temperature, or used within 12 hours when refrigerated at 2 to 8°C (36 to 46°F). 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.

2.3 Incompatibilities

ORBACTIV is administered intravenously. ORBACTIV should only be diluted in D5W. Do NOT use normal saline for dilution as it is incompatible with ORBACTIV and may cause precipitation of the drug. Therefore other intravenous substances, additives or other medications mixed in normal saline should not be added to ORBACTIV single-use vials or infused simultaneously through the same IV line or through a common intravenous port. In addition, drugs formulated at a basic or neutral pH may be incompatible with ORBACTIV. ORBACTIV should not be administered simultaneously with commonly used intravenous drugs through a common intravenous port. If the same intravenous line is used for sequential infusion of additional medications, the line should be flushed before and after infusion of ORBACTIV with D5W.

3 DOSAGE FORMS AND STRENGTHS

ORBACTIV is supplied as sterile, white to off-white lyophilized powder equivalent to 400 mg of oritavancin in a single use 50 mL clear glass vial.

4 CONTRAINDICATIONS

4.1 Intravenous Unfractionated Heparin Sodium

Use of intravenous unfractionated heparin sodium is contraindicated for 48 hours after ORBACTIV administration because the activated partial thromboplastin time (aPTT) test results are expected to remain falsely elevated for approximately 48 hours after ORBACTIV administration [*see Warnings and Precautions (5.2) and Drug Interactions (7.2)*]

4.2 Hypersensitivity

ORBACTIV is contraindicated in patients with known hypersensitivity to ORBACTIV.

5 WARNINGS AND PRECAUTIONS

5.1 Potential Risk of Bleeding with Concomitant Use of Warfarin

Co-administration of ORBACTIV and warfarin may result in higher exposure of warfarin, which may increase the risk of bleeding. Use ORBACTIV in patients on chronic warfarin therapy only when the benefits can be expected to outweigh the risk of bleeding. Frequently monitor for signs of bleeding. [*see Drug Interactions (7.1), Clinical Pharmacology (12.3)*].

ORBACTIV has been shown to artificially prolong PT and INR for up to 24 hours, making the monitoring of the anticoagulation effect of warfarin unreliable up to 24 hours after an ORBACTIV dose. [*see Warnings and Precautions (5.2)*]

5.2 Coagulation Test Interference

ORBACTIV has been shown to artificially prolong aPTT for 48 hours and the PT and INR for 24 hours by binding to and preventing action of the phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests.

For patients who require aPTT monitoring within 48 hours of ORBACTIV dosing, a non-phospholipid dependent coagulation test such as a Factor Xa (chromogenic) assay or an alternative anticoagulant not requiring aPTT monitoring may be considered.

Effects by ORBACTIV on activated clotting time (ACT) are expected since the phospholipid reagents are also utilized in this coagulation test. ORBACTIV has no effect on the coagulation system. [see *Contraindications (4.1) and Drug Interactions (7.2)*]

5.3 Hypersensitivity

Serious hypersensitivity reactions have been reported with the use of ORBACTIV. If an acute hypersensitivity reaction occurs during ORBACTIV infusion, discontinue ORBACTIV immediately and institute appropriate supportive care. Before using ORBACTIV, inquire carefully about previous hypersensitivity reactions to glycopeptides. Due to the possibility of cross-sensitivity, carefully monitor for signs of hypersensitivity during ORBACTIV infusion in patients with a history of glycopeptide allergy. In the Phase 3 ABSSSI clinical trials, the median onset of hypersensitivity reactions in ORBACTIV-treated patients was 1.2 days and the median duration of these reactions was 2.4 days. [see *Adverse Reactions (6.1)*]

5.4 Infusion Related Reactions

Infusion related reactions have been reported with ORBACTIV including pruritus, urticaria or flushing. If reactions do occur, consider slowing or interrupting ORBACTIV infusion. [see *Adverse Reactions (6.1)*]

5.5 *Clostridium difficile*-associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial drugs, including ORBACTIV, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.6 Osteomyelitis

In Phase 3 ABSSSI clinical trials, more cases of osteomyelitis were reported in the ORBACTIV treated arm than in the vancomycin-treated arm. Monitor patients for signs and symptoms of osteomyelitis. If osteomyelitis is suspected or diagnosed, institute appropriate alternate antibacterial therapy [see *Adverse Reactions (6.1)*].

5.7 Development of Drug Resistant Bacteria

Prescribing ORBACTIV in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria [see *Patient Counseling Information (17)*].

6 ADVERSE REACTIONS

The following adverse reactions are also discussed in the Warnings and Precautions section of the label:

Hypersensitivity Reactions [see *Warnings and Precautions (5.3)*]

Infusion related reactions [see *Warnings and Precautions (5.4)*]

Clostridium difficile-associated diarrhea [see *Warnings and Precautions (5.5)*]

Osteomyelitis [see Warnings and Precautions (5.6)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of ORBACTIV cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ORBACTIV has been evaluated in two, double-blind, controlled ABSSSI clinical trials, which included 976 adult patients treated with a single 1200 mg intravenous dose of ORBACTIV and 983 patients treated with intravenous vancomycin for 7 to 10 days. The median age of patients treated with ORBACTIV was 45.6 years, ranging between 18 and 89 years of age with 8.8% ≥ 65 years of age. Patients treated with ORBACTIV were predominantly male (65.4%), 64.4% were Caucasian, 5.8% were African American, and 28.1% were Asian. Safety was evaluated for up to 60 days after dosing.

In the pooled ABSSSI clinical trials, serious adverse reactions were reported in 57/976 (5.8%) patients treated with ORBACTIV and 58/983 (5.9%) treated with vancomycin. The most commonly reported serious adverse reaction was cellulitis in both treatment groups: 11/976 (1.1%) in ORBACTIV and 12/983 (1.2%) in the vancomycin arms, respectively.

The most commonly reported adverse reactions ($\geq 3\%$) in patients receiving a single 1200 mg dose of ORBACTIV in the pooled ABSSSI clinical trials were: headache, nausea, vomiting, limb and subcutaneous abscesses, and diarrhea.

In the pooled ABSSSI clinical trials, ORBACTIV was discontinued due to adverse reactions in 36/976 (3.7%) of patients; the most common reported reactions leading to discontinuation were cellulitis (4/976, 0.4%) and osteomyelitis (3/976, 0.3%).

Table 1 provides selected adverse reactions occurring in $\geq 1.5\%$ of patients receiving ORBACTIV in the pooled ABSSSI clinical trials. There were 540 (55.3%) patients in the ORBACTIV arm and 559 (56.9%) patients in the vancomycin arm, who reported ≥ 1 adverse reaction.

Table 1: Incidence of Selected Adverse Reactions Occurring in $\geq 1.5\%$ of Patients Receiving ORBACTIV in the Pooled ABSSSI Clinical Trials

Adverse Reactions	ORBACTIV N=976 (%)	Vancomycin N=983 (%)
Gastrointestinal disorders		
Diarrhea	36 (3.7)	32 (3.4)
Nausea	97 (9.9)	103 (10.5)
Vomiting	45 (4.6)	46 (4.7)
Nervous system disorders		
Dizziness	26 (2.7)	26 (2.6)
Headache	69 (7.1)	66 (6.7)
General disorders and administration		
Infusion site phlebitis	24 (2.5)	15 (1.5)
Infusion site reaction	19 (1.9)	34 (3.5)
Infections and infestations		
Abscess (limb and subcutaneous)	37 (3.8)	23 (2.3)
Investigations		
Alanine aminotransferase increased	27 (2.8)	15 (1.5)
Aspartate aminotransferase increased	18 (1.8)	15 (1.5)
Cardiac disorders		
Tachycardia	24 (2.5)	11 (1.1)

The following selected adverse reactions were reported in ORBACTIV-treated patients at a rate of less than 1.5%:

Blood and lymphatic system disorders: anemia, eosinophilia

General Disorders and administration site conditions: infusion site erythema, extravasation, induration, pruritis, rash, edema peripheral

Immune system disorders: hypersensitivity

Infections and infestations: osteomyelitis

Investigations: total bilirubin increased, hyperuricemia

Metabolism and nutrition disorders: hypoglycemia

Musculoskeletal and connective tissue disorders: tenosynovitis, myalgia

Respiratory, thoracic and mediastinal disorders: bronchospasm, wheezing

Skin and Subcutaneous Tissue Disorders: urticaria, angioedema, erythema multiforme, pruritis, leucocytoclastic vasculitis, rash.

7 DRUG INTERACTIONS

7.1 Effect of ORBACTIV on CYP Substrates

A cocktail drug-drug interaction study was conducted in healthy volunteers (n=16) evaluating the concomitant administration of a single 1200 mg dose of ORBACTIV with probe substrates for several CYP450 enzymes. ORBACTIV was found to be a nonspecific, weak inhibitor (CYP2C9 and CYP2C19) or inducer (CYP3A4 and CYP2D6) of several CYP isoforms [see *Clinical Pharmacology* ([12.3](#))].

Caution should be used when administering ORBACTIV concomitantly with drugs with a narrow therapeutic window that are predominantly metabolized by one of the affected CYP450 enzymes (e.g., warfarin), as co-administration may increase (e.g. for CYP2C9 substrates) or decrease (e.g. for CYP2D6 substrates) concentrations of the narrow therapeutic range drug. Patients should be closely monitored for signs of toxicity or lack of efficacy if they have been given ORBACTIV while on a potentially affected compound (e.g. patients should be monitored for bleeding if concomitantly receiving ORBACTIV and warfarin) [see *Warnings and Precautions* ([5.1](#))].

7.2 Drug-Laboratory Test Interactions

ORBACTIV has been shown to artificially prolong aPTT for 48 hours and PT and INR for up to 24 hours by binding to and preventing action of the phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests. Effects by ORBACTIV on ACT are expected since the phospholipid reagents are also utilized in this coagulation test. ORBACTIV has no effect on the coagulation system. [see *Warnings and Precautions* ([5.2](#))].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to oritavancin at the highest concentrations administered, 30 mg/kg/day and 15 mg/kg/day, respectively. Those daily doses would be equivalent to a human dose of 300 mg, or 25% of the single clinical dose of 1200 mg. Higher doses were not evaluated in nonclinical developmental and reproductive toxicology studies.

There are no adequate and well-controlled trials in pregnant women. ORBACTIV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is unknown whether oritavancin is excreted in human milk. Following a single intravenous infusion in lactating rats, radio-labeled [^{14}C]-oritavancin was excreted in milk and absorbed by nursing pups. Caution should be exercised when ORBACTIV is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of ORBACTIV in pediatric patients (younger than 18 years of age) has not been studied.

8.5 Geriatric Use

The pooled Phase 3 ABSSSI clinical trials of ORBACTIV did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dosage adjustment of ORBACTIV is needed in patients with mild or moderate renal impairment [see *Dosage and Administration* (2.1), *Clinical Pharmacology* (12.3)]. The pharmacokinetics of ORBACTIV in severe renal impairment have not been evaluated. ORBACTIV is not removed from blood by hemodialysis.

8.7 Hepatic Impairment

No dosage adjustment of ORBACTIV is needed in patients with mild or moderate hepatic impairment. The pharmacokinetics of ORBACTIV in patients with severe hepatic insufficiency has not been studied [see *Dosage and Administration* (2.1), *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

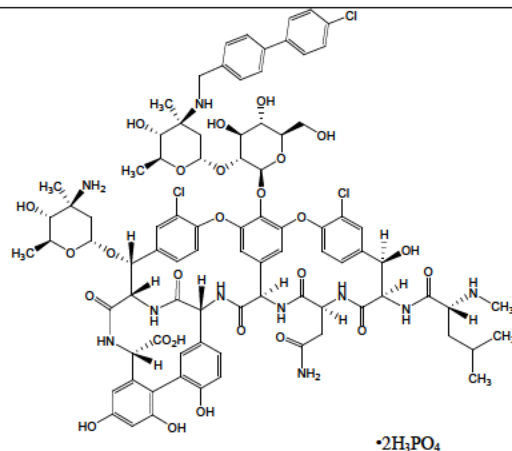
In the ORBACTIV clinical program there was no incidence of accidental overdose of ORBACTIV.

Based on an in vitro hemodialysis study, ORBACTIV is unlikely to be removed from blood by hemodialysis. In the event of overdose, supportive measures should be taken.

11 DESCRIPTION

ORBACTIV (oritavancin) for injection contains oritavancin diphosphate, a semisynthetic lipoglycopeptide antibacterial drug.

The chemical name for oritavancin is [4''R]-22-O-(3-amino-2,3,6-trideoxy-3-C-methyl- α -L-arabino-hexopyranosyl)-N3''-[(4'-chloro[1,1'-biphenyl]-4-yl)methyl] vancomycin phosphate [1:2] [salt]. The empirical formula of oritavancin diphosphate is $\text{C}_{86}\text{H}_{97}\text{N}_{10}\text{O}_{26}\text{Cl}_3 \cdot 2\text{H}_3\text{PO}_4$ and the molecular weight is 1989.09. The chemical structure is represented below:



ORBACTIV is supplied as a sterile white to off-white lyophilized powder for intravenous infusion that contains oritavancin diphosphate, mannitol (an inactive ingredient) and phosphoric acid (to adjust pH 3.1 to 4.3). Each 50 ml capacity glass vial contains 449 mg oritavancin diphosphate (equivalent to 405 mg of oritavancin, 5 mg excess is to ensure withdrawal of 400 mg oritavancin), 400 mg oritavancin (free base equivalent).

Each vial is reconstituted with sterile water for injection and further diluted with 5% Dextrose in sterile Water for intravenous infusion. Both the reconstituted solution and the diluted solution for infusion should be clear, colorless to pale yellow solution [see *Dosage and Administration* (2.2)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oritavancin is an antibacterial drug [see *Clinical Pharmacology* (12.4)].

12.2 Pharmacodynamics

The antimicrobial activity of oritavancin appears to correlate with the ratio of area under the concentration-time curve to minimal inhibitory concentration (AUC/MIC) based on animal models of infection.

Exposure-response analyses from both preclinical and clinical studies support the treatment of clinically relevant Gram-positive microorganisms (e.g. *S. aureus* and *S. pyogenes*) causative of ABSSSI with a single 1200 mg dose of ORBACTIV.

Cardiac Electrophysiology

In a thorough QTc study of 135 healthy subjects at a dose 1.3 times the 1200 mg recommended dose, ORBACTIV did not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

The population PK analysis was derived using data from the two Phase 3 ABSSSI clinical trials in 297 patients. The mean pharmacokinetic parameters of oritavancin in patients following a single 1200 mg dose are presented in Table 2.

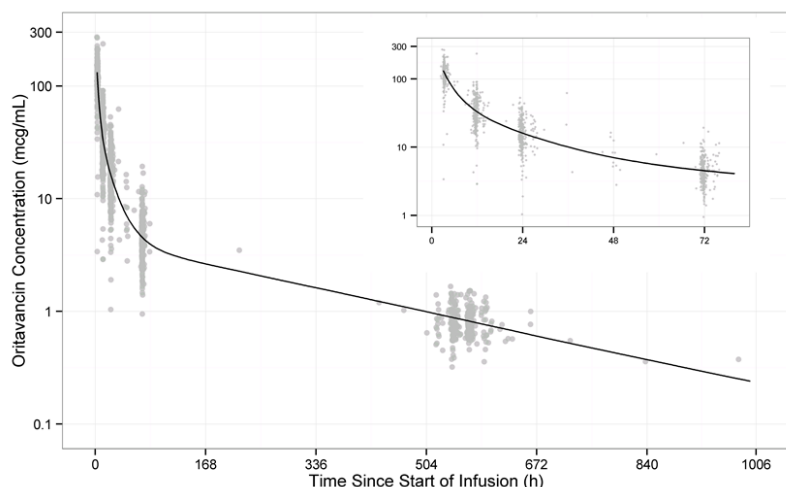
Table 2: Mean PK parameters for patients receiving a single 1200 mg dose for ABSSSI (n=297)

Parameter	Mean (CV%)
$C_{\max}$ (µg/mL)	138 (23.0%)
AUC_{0-24} (µg•h/mL)	1110 (33.9%)
$AUC_{0-\infty}$ (µg•h/mL)	2800 (28.6%)
$T_{1/2,\alpha}$ (h)	2.29 (49.8%)
$T_{1/2,\beta}$ (h)	13.4 (10.5%)
$T_{1/2,\gamma}$ (h)	245 (14.9%)

C_{max} , Maximum plasma concentration; AUC_{0-24} , Area under the plasma concentration-time curve from time zero to 24 hours, $AUC_{0-\infty}$ = Area under the plasma concentration time curve from time zero to infinity; $T_{1/2,\alpha}$, Half-life for the alpha phase, $T_{1/2,\beta}$, Half-life for the beta phase; $T_{1/2,\gamma}$, Half-life for the gamma phase; CV% = Percent Coefficient of variation.

Oritavancin exhibits linear pharmacokinetics at a dose up to 1200 mg. The mean, population-predicted oritavancin concentration-time profile displays a multi-exponential decline with a long terminal plasma half-life as shown in Figure 1.

Figure 1: Population Mean Plasma Concentration-Time Profile after a Single 1200 mg dose of Oritavancin Administered Intravenously Over 3 Hours – Semi-Log Scale



Distribution

Oritavancin is approximately 85% bound to human plasma proteins.

Based on population PK analysis, the population mean total volume of distribution is estimated to be approximately 87.6 L, indicating oritavancin is extensively distributed into the tissues.

Exposures of oritavancin in skin blister fluid were approximately 20% of those in plasma (AUC_{0-24}) after single 800 mg dose in healthy subjects.

Metabolism/Excretion

Non-clinical studies including in vitro human liver microsome studies indicated that oritavancin is not metabolized. No mass balance study has been conducted in humans. In humans, 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.

Oritavancin has a terminal half-life of approximately 245 hours and a clearance of 0.445 L/h based on population pharmacokinetic analyses.

Specific Populations

No dosage adjustments of ORBACTIV are required for patients with mild to severe renal or mild to moderate hepatic impairment or other subpopulations including age, gender, race and weight.

Renal Impairment

The pharmacokinetics of oritavancin was examined in the Phase 3 ABSSSI trials in patients with normal renal function, $CrCL \geq 80$ mL/min ($n=238$), mild renal impairment, $CrCL 50-79$ mL/min ($n=48$), and moderate renal impairment, $CrCL 30-49$ mL/min ($n=11$). Population pharmacokinetic analysis indicated that mild to moderate

renal impairment had no clinically relevant effect on the exposure of oritavancin. No dedicated studies in dialysis patients have been conducted.

Dosage adjustment of ORBACTIV is not needed in patients with mild or moderate renal impairment. The pharmacokinetics of oritavancin in patients with severe renal impairment have not been evaluated.

Hepatic Impairment

The pharmacokinetics of oritavancin were evaluated in study of subjects with moderate hepatic impairment (Child-Pugh Class B) (n=20) and compared with healthy subjects (n=20) matched for gender, age and weight. There were no relevant changes in pharmacokinetics of oritavancin in subjects with moderate hepatic impairment.

Dosage adjustment of ORBACTIV is not needed in patients with mild or moderate hepatic impairment. The pharmacokinetics of oritavancin in patients with severe hepatic insufficiency has not been studied.

Pediatric

The pharmacokinetics of ORBACTIV in pediatric populations (<18 years of age) has not been studied [*see Use in Specific Populations (8.4)*].

Age, Gender, Weight and Race

Population pharmacokinetic analysis from the Phase 3 ABSSSI trials in patients indicated that gender, age, weight or race had no clinically relevant effect on the exposure of ORBACTIV. No dosage adjustment is warranted in these subpopulations.

Drug Interactions

In vitro studies with human liver microsomes showed that oritavancin inhibited the activities of cytochrome P450 (CYP) enzymes 1A2, 2B6, 2D6, 2C9, 2C19, and 3A4. The observed inhibition of multiple CYP isoforms by oritavancin in vitro is likely to be reversible and the mechanism of inhibition, noncompetitive. In vitro studies indicate that oritavancin is neither a substrate nor an inhibitor of the efflux transporter P-glycoprotein (P-gp).

Drugs that Inhibit or Induce CYP450 Enzymes

Results from a drug-drug interaction study in healthy volunteers (n=16) evaluating a single 1200 mg dose of ORBACTIV showed that ORBACTIV is a weak inducer of CYP3A4 (a decrease of 18% in the mean AUC of midazolam) and CYP2D6 (decrease of 31% in the ratio of dextromethorphan to dextrorphan concentrations in the urine after administration of dextromethorphan). ORBACTIV was also a weak inhibitor of CYP2C19 (increase of 15% in the ratio of omeprazole to 5-OH-omeprazole concentrations in the plasma after administration of omeprazole) and also showed to be a weak inhibitor of CYP2C9 (with an increase of 31% in the mean AUC of warfarin) [*see Warnings and Precautions (5.1)*, and *Drug Interactions (7.1)*].

Co-administration of ORBACTIV resulted in an increase of 18% in the ratio of 1-methylxanthine + 1 methylurate + 5-acetylamino-6-formylamino-3-methyluracil (1X + 1U + AFMU) to 1,7-dimethylurate (17U) concentrations in the urine after administration of caffeine (CYP1A2 probe substrate), and an increase of 16% in the ratio of AFMU to (1X +1U) concentrations in the urine after administration of caffeine (N-Acetyltransferase- 2 probe substrate). Co-administration of ORBACTIV did not change the mean systemic exposure of caffeine metabolite (Xanthine oxidase probe substrate).

12.4 Microbiology

ORBACTIV is a semi-synthetic, lipoglycopeptide antibacterial drug. ORBACTIV exerts a concentration-dependent bactericidal activity in vitro against *S. aureus*, *S. pyogenes*, and *E. faecalis*.

Mechanism of Action

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; and (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.

Mechanism of Resistance

In serial passage studies, resistance to oritavancin was observed in isolates of *S. aureus* and *E. faecalis*. Resistance to oritavancin was not observed in clinical studies.

Interaction with Other Antimicrobial Agents

In in vitro studies, oritavancin exhibits synergistic bactericidal activity in combination with gentamicin, moxifloxacin or rifampicin against isolates of methicillin-susceptible *S. aureus* (MSSA), with gentamicin or linezolid against isolates of heterogeneous vancomycin-intermediate *S. aureus* (hVISA), VISA, and vancomycin-resistant *S. aureus* (VRSA), and with rifampin against isolates of VRSA. In vitro studies demonstrated no antagonism between oritavancin and gentamicin, moxifloxacin, linezolid or rifampin.

Antibacterial Activity

Oritavancin has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections as described in the Indications and Usage section [see *Indications and Usage* ([1.1](#))].

Staphylococcus aureus (including methicillin-resistant isolates)

Streptococcus agalactiae

Streptococcus anginosus group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*)

Streptococcus dysgalactiae

Streptococcus pyogenes

Enterococcus faecalis (vancomycin-susceptible isolates only)

The following in vitro data are available but their clinical significance has not been established. At least 90% of isolates of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to 0.12 mcg/mL for oritavancin. However, the safety and effectiveness of oritavancin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Enterococcus faecium (vancomycin-susceptible isolates only)

Susceptibility Testing Methods

When available, the clinical microbiology laboratory should provide cumulative results of in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial drug for treatment.

Dilution technique

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds.¹ Oritavancin MICs should be determined using a standardized procedure which are based on a broth microdilution method or equivalent with standardized inoculum concentrations and standardized concentrations of oritavancin. Oritavancin powder is dissolved and diluted in the presence of 0.002% polysorbate 80 and broth test medium is supplemented with polysorbate 80 to a final concentration of 0.002%. The MIC values should be interpreted according to the criteria provided in the Table 3.

Table 3: Susceptibility Interpretive Criteria for ORBACTIV^a

Microorganism	Minimum Inhibitory Concentration (MIC, mcg/mL)		
	S	I ^b	R ^b
<i>Staphylococcus aureus</i> (including methicillin-resistant isolates)	≤0.12	-	-
<i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , <i>Streptococcus dysgalactiae</i> , <i>Streptococcus anginosus</i> , <i>Streptococcus constellatus</i> , and <i>Streptococcus intermedius</i> .	≤0.25	-	-
<i>Enterococcus faecalis</i> (vancomycin-susceptible isolates only)	≤0.12	-	-

Abbreviations: MIC, minimum inhibitory concentration; S, Susceptible; I, intermediate; R, Resistant

^a As determined by broth microdilution with 0.002% polysorbate-80 during oritavancin dissolution and dilution and in the final assay.

^b The current absence of resistant isolates precludes defining any results other than “Susceptible”. Isolates yielding test results other than “Susceptible” should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

A report of “Susceptible” indicates that the antimicrobial drug is likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentration usually achievable at the site of infection.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor and ensure the accuracy and precision of supplies and reagents used in the assay and the techniques of the individuals performing the test. Acceptable oritavancin MIC ranges for the quality control strains are shown in Table 4.

Quality control microorganisms are specific strains of organisms with intrinsic biological properties, and are very stable strains that will give a standard and reproducible susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant.

Table 4: Acceptable Quality Control Ranges for Oritavancin Susceptibility Testing^a

Quality Control Organism	Minimum Inhibitory Concentration Range (MIC in mcg/mL)
<i>Staphylococcus aureus</i> ATCC 29213	0.015 – 0.12
<i>Streptococcus pneumoniae</i> ATCC 49619	0.001 – 0.004
<i>Enterococcus faecalis</i> ATCC 29212	0.008 – 0.03

ATCC = American Type Culture Collection.

^a As determined by broth microdilution with 0.002% polysorbate-80 during oritavancin dissolution and dilution and in the final assay.^{1,2}

Diffusion technique

The use of the disk diffusion method is not recommended since quality control ranges have not been defined for oritavancin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been conducted to determine the carcinogenic potential of oritavancin.

No mutagenic or clastogenic potential of oritavancin was found in a battery of tests, including an Ames assay, *in vitro* chromosome aberration assay in Chinese hamster ovary cells, *in vitro* forward mutation assay in mouse lymphoma cells and an *in vivo* mouse micronucleus assay.

Oritavancin did not affect the fertility or reproductive performance of male rats (exposed to daily doses up to 30 mg/kg for at least 4 weeks) and female rats (exposed to daily doses up to 30 mg/kg for at least 2 weeks prior to mating). Those daily doses would be equivalent to a human dose of 300 mg, or 25% of clinical dose. Higher doses were not evaluated in nonclinical fertility studies.

14 CLINICAL STUDIES

14.1 Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

A total of 1987 adults with clinically documented ABSSSI suspected or proven to be due to Gram-positive pathogens were randomized into two identically designed, randomized, double-blind, multi-center, multinational, non-inferiority trials (Trial 1 and Trial 2) comparing a single 1200 mg intravenous dose of ORBACTIV to intravenous vancomycin (1 g or 15 mg/kg every 12 hours) for 7 to 10 days. The primary analysis population (modified intent to treat, mITT) included all randomized patients who received any study drug. Patients could receive concomitant aztreonam or metronidazole for suspected Gram-negative and anaerobic infection, respectively. Patient demographic and baseline characteristics were balanced between treatment groups. Approximately 64% of patients were Caucasian and 65% were males. The mean age was 45 years and the mean body mass index was 27 kg/m². Across both trials, approximately 60% of patients were enrolled from the United States and 27% of patients from Asia. A history of diabetes was present in 14% of patients. The types of ABSSSI across both trials included cellulitis/erysipelas (40%), wound infection (29%), and major cutaneous abscesses (31%). Median infection area at baseline across both trials was 266.6 cm².

The primary endpoint in both trials was early clinical response (responder), defined as cessation of spread or reduction in size of baseline lesion, absence of fever, and no rescue antibacterial drug at 48 to 72 hours after initiation of therapy.

Table 5 provides the efficacy results for the primary endpoint in Trial 1 and Trial 2 in the primary analysis population.

Table 5: Clinical Response Rates in ABSSSI Trials using Responders^{1, 2} at 48-72 Hours after Initiation of Therapy

	ORBACTIV n /N (%)	Vancomycin n /N (%)	Difference (95% CI) ³
Trial 1	391/475(82.3)	378/479(78.9)	3.4 (-1.6, 8.4)
Trial 2	403/503 (80.1)	416/502(82.9)	-2.7(-7.5, 2.0)

¹Cessation of spread or reduction in size of baseline lesion, absence of fever (<37.7°C) and no rescue antibacterial drug at 48 to 72 hours.

²Patients who died at 48 to 72 hours, after initiation of therapy or who had increase in lesion size at 48 to 72 hours, after initiation of therapy or who used non-study antibacterial therapy during first 72 hours or who had an additional, unplanned, surgical procedure or who had missing measurements during the first 72 hours from initiation of study drug were classified as non-responders.

³95% CI based on the Normal approximation to Binomial distribution.

A key secondary endpoint in these two ABSSSI trials evaluated the percentage of patients achieving a 20% or greater reduction in lesion area from baseline at 48-72 hours after initiation of therapy. Table 6 summarizes the findings for this endpoint in the two ABSSSI trials.

Table 6: Clinical Response Rates¹ in ABSSSI Trials using Reduction in Lesion Area of 20% or Greater at 48-72 Hours after Initiation of Therapy

	ORBACTIV n /N(%)	Vancomycin n /N(%)	Difference (95% CI) ²
Trial 1	413/475(86.9)	397/479(82.9)	4.1(-0.5, 8.6)
Trial 2	432/503(85.9)	428/502(85.3)	0.6(-3.7, 5.0)

¹Patients who died at 48 to 72 hours, after initiation of therapy or who had increase in lesion size at 48 to 72 hours, after initiation of therapy or who used non-study antibacterial therapy during first 72 hours or who had an additional, unplanned, surgical procedure or who had missing measurements during the first 72 hours from initiation of study drug were classified as non-responders.

²95% CI based on the Normal approximation to Binomial distribution.

Another secondary efficacy endpoint in the two trials was investigator-assessed clinical success at post therapy evaluation at day 14 to 24 (7 to 14 days from end of blinded therapy). A patient was categorized as a clinical success if the patient experienced a complete or nearly complete resolution of baseline signs and symptoms related to primary ABSSSI site (erythema, induration/edema, purulent drainage, fluctuance, pain, tenderness, local increase in heat/warmth) such that no further treatment with antibacterial drugs was needed.

Table 7 summarizes the findings for this endpoint in the mITT and clinically evaluable population in these two ABSSSI trials. Note that there are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at the post therapy visits. Therefore, comparisons of ORBACTIV to vancomycin based on clinical success rates at these visits cannot be utilized to establish non-inferiority conclusions.

Table 7: Clinical Success Rates¹ in ABSSSI Trials at the Follow-Up Visit (7-14 days after end of therapy)

	ORBACTIV n /N(%)	Vancomycin n /N(%)	Difference (95% CI) ²
Trial 1			
mITT	378/475(79.6)	383/479(80.0)	-0.4 (-5.5, 4.7)
CE	362/394(91.9)	370/397(93.2)	-1.3 (-5.0,2.3)
Trial 2			
mITT	416/503(82.7)	404/502(80.5)	2.2 (-2.6, 7.0)
CE	398/427(93.2)	387/408(94.9)	-1.6 (-4.9,1.6)

¹Clinical success was defined if the patient experienced a complete or nearly complete resolution of baseline signs and symptoms as described above.

²95% CI based on the Normal approximation to Binomial distribution

³ mITT population consisted of all randomized patients who received study drug; CE population consisted of all mITT patients who did not have violations of inclusion and exclusion criteria, completed treatment and had investigator assessment at the Follow-Up Visit.

Outcomes by Baseline Pathogen: Table 8 shows outcomes in patients with an identified baseline pathogen in the microbiological Intent-to-Treat (microITT) population in a pooled analysis of Trial 1 and Trial 2. The outcomes shown in the table are clinical response rates at 48 to 72 hours and clinical success rates at follow-up study day 14 to 24.

Table 8: Outcomes by Baseline Pathogen (microITT)

	At 48-72 hours				Study day14 to 24	
	Early Clinical Responder ¹		≥ 20% reduction in lesion size ²		Clinical Success ³	
Pathogen ⁴	ORBACTIV n/N (%)	Vancomycin n/N (%)	ORBACTIV n/N (%)	Vancomycin n/N (%)	ORBACTIV n/N (%)	Vancomycin n/N (%)
<i>Staphylococcus aureus</i>	388/472(82.2)	395/473(83.5)	421/472(89.2)	407/473(86.0)	390/472(82.6)	398/473 (84.1)
Methicillin-susceptible	222/268(82.8)	233/272(85.7)	231/268(86.2)	232/272(85.3)	220/268(82.1)	229/272(84.2)
Methicillin-resistant	166/204(81.4)	162/201(80.6)	190/204(93.1)	175/201(87.1)	170/204(83.3)	169/201(84.1)
<i>Streptococcus pyogenes</i>	21/31(67.7)	23/32(71.9)	24/31(77.4)	24/32(75.0)	25/31(80.6)	23/32(71.9)
<i>Streptococcus agalactiae</i>	7/8(87.5)	12/12(100.0)	8/8(100.0)	12/12(100.0)	7/8(87.5)	11/12(91.7)
<i>Streptococcus dysgalactiae</i>	7/9(77.8)	6/6(100.0)	6/9(66.7)	5/6(83.3)	7/9(77.8)	3/6(50.0)
<i>Streptococcus anginosus group</i>	28/33(84.8)	40/45(88.9)	29/33(87.9)	42/45(93.3)	25/33(75.8)	38/45(84.4)
<i>Enterococcus faecalis</i>	11/13(84.6)	10/12(83.3)	10/13(76.9)	8/12(66.7)	8/13(61.5)	9/12(75.0)

¹ Early clinical response defined as a composite of the cessation of spread or reduction in size of baseline lesion, absence of fever and no rescue antibacterial drug at 48-72 hours

² Patients achieving a 20% or greater reduction in lesion area from baseline at 48-72 hours after initiation of therapy

³ Clinical success was defined if the patient experienced a complete or nearly complete resolution of baseline signs and symptoms as described above.

⁴ Baseline bacteremia in the oritavancin arm with relevant microorganisms causing ABSSSI included four subjects with MSSA and seven subjects with MRSA. Eight of these eleven subjects were responders at 48 to 72 hours after initiation of therapy.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Ninth Edition*. CLSI document M7-A09, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087, 2012.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fourth Informational Supplement*, CLSI document M100-S24, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2014.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied/Storage

ORBACTIV is supplied as single use 50 mL capacity glass vials containing sterile lyophilized powder equivalent to 400 mg of oritavancin (NDC 65293-004-01). Three vials are packaged in a carton to supply for a single 1200 mg dose treatment (NDC 65293-004-03).

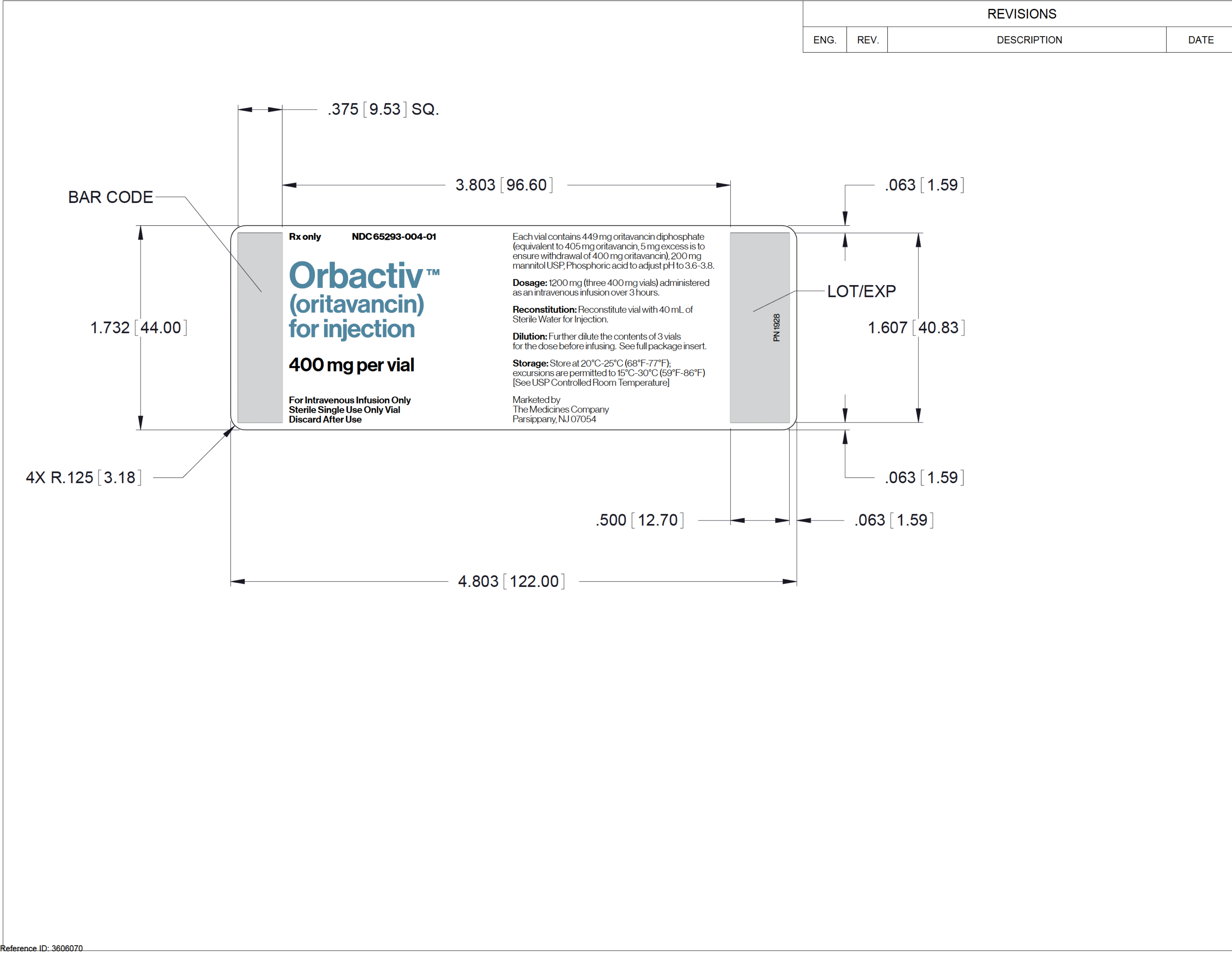
ORBACTIV vials should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP, Controlled Room Temperature (CRT)].

17 PATIENT COUNSELING INFORMATION

Patients should be advised that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. They should inform their healthcare provider about any previous hypersensitivity reactions to ORBACTIV, other glycopeptides (vancomycin, telavancin, or dalbavancin) or other allergens.

Patients should be advised that diarrhea is a common problem caused by antibacterial drugs including ORBACTIV, which usually resolves when the drug is discontinued. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, patients should contact their healthcare provider.

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/s/

JOHN J FARLEY
08/06/2014