

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use VIBATIV® (telavancin) safely and effectively. See full prescribing information for VIBATIV.

VIBATIV® (telavancin) for injection, for intravenous use  
Initial U.S. Approval: 2009

To reduce the development of drug-resistant bacteria and maintain the effectiveness of VIBATIV and other antibacterial drugs VIBATIV should only be used to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

**WARNINGS**

- Patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) who were treated with VIBATIV for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia had increased mortality observed versus vancomycin. Use of VIBATIV in patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) should be considered only when the anticipated benefit to the patient outweighs the potential risk. (5.1)
- Nephrotoxicity: New onset or worsening renal impairment has occurred. Monitor renal function in all patients. (5.3)
- Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. (5.4, 8.1)
- Avoid use of VIBATIV during pregnancy unless potential benefit to the patient outweighs potential risk to the fetus. (8.1)
- Adverse developmental outcomes observed in 3 animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans. (8.1)

**RECENT MAJOR CHANGES**

Warnings and Precautions (10/2014)

Contraindications (10/2014)

**INDICATIONS AND USAGE**

VIBATIV is a lipoglycopeptide antibacterial drug indicated for the treatment of the following infections in adult patients caused by designated susceptible bacteria:

- Complicated skin and skin structure infections (cSSSI) (1.1)
- Hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Staphylococcus aureus*. VIBATIV should be reserved for use when alternative treatments are not suitable. (1.2)

**DOSAGE AND ADMINISTRATION**

- Complicated skin and skin structure infections (cSSSI):
  - 10 mg/kg by IV infusion over 60 minutes every 24 hours for 7 to 14 days (2.1)
  - Dosage adjustment in patients with renal impairment. (2.3)
- Hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP):
  - 10 mg/kg by IV infusion over 60 minutes every 24 hours for 7 to 21 days (2.2)
  - Dosage adjustment in patients with renal impairment. (2.3)

Creatinine Clearance <sup>a</sup> (CrCl) (mL/min)	VIBATIV Dosage Regimen
>50	10 mg/kg every 24 hours
30-50	7.5 mg/kg every 24 hours
10-<30	10 mg/kg every 48 hours

<sup>a</sup>Calculate using the Cockcroft-Gault formula and ideal body weight (IBW). Use actual body weight if < IBW. (12.3)

Insufficient data are available to make a dosing recommendation for patients with CrCl <10 mL/min, including patients on hemodialysis.

**DOSAGE FORMS AND STRENGTHS**

Single-use vials containing either 250 or 750 mg telavancin. (3)

**CONTRAINDICATIONS**

- Intravenous Unfractionated Heparin Sodium (4.1, 5.5, 7.1)
- Known hypersensitivity to VIBATIV (4.2, 5.6, 6.2)

**WARNINGS AND PRECAUTIONS**

- Decreased efficacy among patients treated for skin and skin structure infections with moderate/severe pre-existing renal impairment: Consider these data when selecting antibacterial therapy for patients with baseline CrCl ≤50 mL/min. (5.2)
- Hypersensitivity reactions: Serious and potentially fatal hypersensitivity reactions, including anaphylactic reactions, may occur after first or subsequent doses. VIBATIV should be used with caution in patients with known hypersensitivity to vancomycin. (5.6, 6.2)
- Infusion-related reactions: Administer VIBATIV over at least 60 minutes to minimize infusion-related reactions. (5.7)
- *Clostridium difficile*-associated disease: May range from mild diarrhea to fatal colitis. Evaluate if diarrhea occurs. (5.8)
- Coagulation test interference: Telavancin interferes with some laboratory coagulation tests, including prothrombin time, international normalized ratio, and activated partial thromboplastin time. (5.5, 7.1)
- QTc prolongation: Avoid use in patients at risk. Use with caution in patients taking drugs known to prolong the QT interval. (5.10)

**ADVERSE REACTIONS**

Most common adverse reaction (≥10% of patients treated with VIBATIV) in the HABP/VABP trials is diarrhea; in the cSSSI trials, the most common adverse reactions (≥10% of patients treated with VIBATIV) include: taste disturbance, nausea, vomiting, and foamy urine. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Theravance Biopharma US, Inc. at 1-855-633-8479 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy registry available. (8.1)
- Pediatric patients: Safety and efficacy not demonstrated. (8.4)

See 17 for PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE

Revised:11/2014

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1 **FULL PRESCRIBING INFORMATION**

2  
3 **WARNINGS**

- 4 ▪ **Patients with pre-existing moderate/severe renal impairment (CrCl ≤ 50 mL/min)**  
5 **who were treated with VIBATIV for hospital-acquired bacterial**  
6 **pneumonia/ventilator-associated bacterial pneumonia had increased mortality**  
7 **observed versus vancomycin. Use of VIBATIV in patients with pre-existing**  
8 **moderate/severe renal impairment (CrCl ≤ 50 mL/min) should be considered only**  
9 **when the anticipated benefit to the patient outweighs the potential risk [see**  
10 ***Warnings and Precautions (5.1)*].**
- 11 ▪ **Nephrotoxicity: New onset or worsening renal impairment has occurred. Monitor**  
12 **renal function in all patients [see *Warnings and Precautions (5.3)*].**
- 13 ▪ **Women of childbearing potential should have a serum pregnancy test prior to**  
14 **administration of VIBATIV [see *Warnings and Precautions (5.4), Use in Specific***  
15 ***Populations (8.1)*].**
- 16 ▪ **Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient**  
17 **outweighs the potential risk to the fetus [see *Warnings and Precautions (5.4), Use***  
18 ***in Specific Populations (8.1)*].**
- 19 ▪ **Adverse developmental outcomes observed in 3 animal species at clinically**  
20 **relevant doses raise concerns about potential adverse developmental outcomes**  
21 **in humans [see *Warnings and Precautions (5.4), Use in Specific Populations (8.1)*]**

22  
23 **1 INDICATIONS AND USAGE**

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

30 Combination therapy may be clinically indicated if the documented or presumed pathogens  
31 include Gram-negative organisms.

32 Appropriate specimens for bacteriological examination should be obtained in order to isolate  
33 and identify the causative pathogens and to determine their susceptibility to telavancin.  
34 VIBATIV may be initiated as empiric therapy before results of these tests are known.

### 35 **1.1 Complicated Skin and Skin Structure Infections**

36 VIBATIV is indicated for the treatment of adult patients with complicated skin and skin  
37 structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive  
38 microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant  
39 isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus*  
40 group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), or *Enterococcus faecalis*  
41 (vancomycin-susceptible isolates only).

### 42 **1.2 HABP/VABP**

43 VIBATIV is indicated for the treatment of adult patients with hospital-acquired and ventilator-  
44 associated bacterial pneumonia (HABP/VABP), caused by susceptible isolates of  
45 *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates). VIBATIV  
46 should be reserved for use when alternative treatments are not suitable.

## 47 **2 DOSAGE AND ADMINISTRATION**

### 48 **2.1 Complicated Skin and Skin Structure Infections**

49 The recommended dosing for VIBATIV is 10 mg/kg administered over a 60-minute period in  
50 patients  $\geq 18$  years of age by intravenous infusion once every 24 hours for 7 to 14 days. The  
51 duration of therapy should be guided by the severity and site of the infection and the  
52 patient's clinical progress.

### 53 **2.2 Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial 54 Pneumonia (HABP/VABP)**

55 The recommended dosing for VIBATIV is 10 mg/kg administered over a 60-minute period in  
56 patients  $\geq 18$  years of age by intravenous infusion once every 24 hours for 7 to 21 days. The  
57 duration of therapy should be guided by the severity of the infection and the patient's clinical  
58 progress.

59 **2.3 Patients with Renal Impairment**

60 Because telavancin is eliminated primarily by the kidney, a dosage adjustment is required  
61 for patients whose creatinine clearance is  $\leq 50$  mL/min, as listed in Table 1 [see *Clinical*  
62 *Pharmacology* (12.3)].

63 Table 1: Dosage Adjustment in Adult Patients with Renal Impairment

<b>Creatinine Clearance<sup>a</sup> (CrCl) (mL/min)</b>	<b>VIBATIV Dosage Regimen</b>
>50	10 mg/kg every 24 hours
30-50	7.5 mg/kg every 24 hours
10-<30	10 mg/kg every 48 hours

<sup>a</sup>Calculate using the Cockcroft-Gault formula and ideal body weight (IBW). Use actual body weight if it is less than IBW. (12.3)

64

65 There is insufficient information to make specific dosage adjustment recommendations for  
66 patients with end-stage renal disease (CrCl <10 mL/min), including patients undergoing  
67 hemodialysis.

68 **2.4 Preparation and Administration**

69 250 mg vial: Reconstitute the contents of a VIBATIV 250 mg vial with **15** mL of 5% Dextrose  
70 Injection, USP; Sterile Water for Injection, USP; or 0.9% Sodium Chloride Injection, USP.  
71 The resultant solution has a concentration of 15 mg/mL (total volume of approximately  
72 17.0 mL).

73 750 mg vial: Reconstitute the contents of a VIBATIV 750 mg vial with **45** mL of 5% Dextrose  
74 Injection, USP; Sterile Water for Injection, USP; or 0.9% Sodium Chloride Injection, USP.  
75 The resultant solution has a concentration of 15 mg/mL (total volume of approximately  
76 50.0 mL).

77 To minimize foaming during product reconstitution, allow the vacuum of the vial to pull the  
78 diluent from the syringe into the vial. Do not forcefully inject the diluent into the vial. Do not  
79 forcefully shake the vial and do not shake final infusion solution.

80 The following formula can be used to calculate the volume of reconstituted VIBATIV solution  
81 required to prepare a dose:

82 **Telavancin dose (mg) = 10 mg/kg or 7.5 mg/kg x patient weight (in kg)** (see Table 1)

83

84 **Volume of reconstituted solution (mL) =  $\frac{\text{Telavancin dose (mg)}}{15 \text{ mg/mL}}$**

85

86

87 For doses of 150 to 800 mg, the appropriate volume of reconstituted solution must be further  
88 diluted in 100 to 250 mL prior to infusion. Doses less than 150 mg or greater than 800 mg  
89 should be further diluted in a volume resulting in a final concentration of 0.6 to 8 mg/mL.  
90 Appropriate infusion solutions include: 5% Dextrose Injection, USP; 0.9% Sodium Chloride  
91 Injection, USP; or Lactated Ringer's Injection, USP. The dosing solution should be  
92 administered by intravenous infusion over a period of 60 minutes.

93 Reconstitution time is generally under 2 minutes, but can sometimes take up to 20 minutes.

94 Mix thoroughly to reconstitute and check to see if the contents have dissolved completely.

95 Parenteral drug products should be inspected visually for particulate matter prior to

96 administration. Discard the vial if the vacuum did not pull the diluent into the vial.

97 Since no preservative or bacteriostatic agent is present in this product, aseptic technique

98 must be used in preparing the final intravenous solution. Studies have shown that the

99 reconstituted solution in the vial should be used within 12 hours when stored at room

100 temperature or within 7 days under refrigeration at 2 to 8°C (36 to 46°F). The diluted

101 (dosing) solution in the infusion bag should be used within 12 hours when stored at room

102 temperature or used within 7 days when stored under refrigeration at 2 to 8°C (36 to 46°F).

103 However, the total time in the vial plus the time in the infusion bag should not exceed

104 12 hours at room temperature and 7 days under refrigeration at 2 to 8°C (36 to 46°F). The

105 diluted (dosing) solution in the infusion bag can also be stored at -30 to -10°C (-22 to 14°F)

106 for up to 32 days.

107 VIBATIV is administered intravenously. Because only limited data are available on the

108 compatibility of VIBATIV with other IV substances, additives or other medications should not

109 be added to VIBATIV single-use vials or infused simultaneously through the same IV line. If

110 the same intravenous line is used for sequential infusion of additional medications, the line

111 should be flushed before and after infusion of VIBATIV with 5% Dextrose Injection, USP;

112 0.9% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP.

### 113 **3 DOSAGE FORMS AND STRENGTHS**

114 VIBATIV is supplied in single-use vials containing either 250 or 750 mg telavancin as a

115 sterile, lyophilized powder.

116 **4 CONTRAINDICATIONS**

117 **4.1 Intravenous Unfractionated Heparin Sodium**

118 Use of intravenous unfractionated heparin sodium is contraindicated with VIBATIV  
119 administration because the activated partial thromboplastin time (aPTT) test results are  
120 expected to be artificially prolonged for 0 to 18 hours after VIBATIV administration [see  
121 *Warnings and Precautions (5.5) and Drug Interactions (7.1)*].

122 **4.2 Known Hypersensitivity to VIBATIV**

123 VIBATIV is contraindicated in patients with known hypersensitivity to telavancin.

124 **5 WARNINGS AND PRECAUTIONS**

125 **5.1 Increased Mortality in Patients with HABP/VABP and Pre-existing Moderate to**  
126 **Severe Renal Impairment (CrCl ≤50 mL/min)**

127 In the analysis of patients (classified by the treatment received) in the two combined  
128 HABP/VABP trials with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min),  
129 all-cause mortality within 28 days of starting treatment was 95/241 (39%) in the VIBATIV  
130 group, compared with 72/243 (30%) in the vancomycin group. All-cause mortality at 28  
131 days in patients without pre-existing moderate/severe renal impairment (CrCl >50 mL/min)  
132 was 86/510 (17%) in the VIBATIV group and 92/510 (18%) in the vancomycin group.  
133 Therefore, VIBATIV use in patients with baseline CrCl ≤50 mL/min should be considered  
134 only when the anticipated benefit to the patient outweighs the potential risk [see *Adverse*  
135 *Reactions, Clinical Trials Experience (6.1) and Clinical Trials, HABP/VABP (14.2)*].

136 **5.2 Decreased Clinical Response in Patients with cSSSI and Pre-existing**  
137 **Moderate/Severe Renal Impairment (CrCl ≤50 mL/min)**

138 In a subgroup analysis of the combined cSSSI trials, clinical cure rates in the VIBATIV-  
139 treated patients were lower in patients with baseline CrCl ≤50 mL/min compared with those  
140 with CrCl >50 mL/min (Table 2). A decrease of this magnitude was not observed in  
141 vancomycin-treated patients. Consider these data when selecting antibacterial therapy for  
142 use in patients with cSSSI and with baseline moderate/severe renal impairment.

143 Table 2: Clinical Cure by Pre-existing Renal Impairment – Clinically Evaluable  
 144 Population

	<b>VIBATIV % (n/N)</b>	<b>Vancomycin % (n/N)</b>
<b>cSSSI Trials</b>		
CrCl >50 mL/min	87.0% (520/598)	85.9% (524/610)
CrCl ≤50 mL/min	67.4% (58/86)	82.7% (67/81)

145

146 **5.3 Nephrotoxicity**

147 In both the HABP/VABP trials and the cSSSI trials, renal adverse events were more likely to  
 148 occur in patients with baseline comorbidities known to predispose patients to kidney  
 149 dysfunction (pre-existing renal disease, diabetes mellitus, congestive heart failure, or  
 150 hypertension). The renal adverse event rates were also higher in patients who received  
 151 concomitant medications known to affect kidney function (e.g., non-steroidal anti-  
 152 inflammatory drugs, ACE inhibitors, and loop diuretics).

153 Monitor renal function (i.e., serum creatinine, creatinine clearance) in all patients receiving  
 154 VIBATIV. Values should be obtained prior to initiation of treatment, during treatment (at  
 155 48- to 72-hour intervals or more frequently, if clinically indicated), and at the end of therapy.  
 156 If renal function decreases, the benefit of continuing VIBATIV versus discontinuing and  
 157 initiating therapy with an alternative agent should be assessed [see *Dosage and*  
 158 *Administration (2), Adverse Reactions (6), and Clinical Pharmacology (12.3)*].

159 In patients with renal dysfunction, accumulation of the solubilizer hydroxypropyl-beta-  
 160 cyclodextrin can occur [see *Patients with Renal Impairment (8.6) and Clinical Pharmacology*  
 161 *(12.3)*].

162 **5.4 Pregnant Women and Women of Childbearing Potential**

163 Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs  
 164 the potential risk to the fetus. VIBATIV caused adverse developmental outcomes in 3 animal  
 165 species at clinically relevant doses. This raises concern about potential adverse  
 166 developmental outcomes in humans.

167 Women of childbearing potential should have a serum pregnancy test prior to administration  
 168 of VIBATIV. If not already pregnant, women of childbearing potential should use effective  
 169 contraception during VIBATIV treatment [see *Use in Specific Populations (8.1)*].

170 **5.5 Coagulation Test Interference**

171 Although telavancin does not interfere with coagulation, it interfered with certain tests used  
 172 to monitor coagulation (Table 3), when conducted using samples drawn 0 to 18 hours after  
 173 VIBATIV administration for patients being treated once every 24 hours. Blood samples for  
 174 these coagulation tests should be collected as close as possible prior to a patient’s next  
 175 dose of VIBATIV. Blood samples for coagulation tests unaffected by VIBATIV may be  
 176 collected at any time [see *Drug Interactions (7.1)*].

177 For patients who require aPTT monitoring while being treated with VIBATIV, a non  
 178 phospholipid dependent coagulation test such as a Factor Xa (chromogenic) assay or an  
 179 alternative anticoagulant not requiring aPTT monitoring may be considered.

180 Table 3: Coagulation Tests Affected and Unaffected by Telavancin

<b>Affected by Telavancin</b>	<b>Unaffected by Telavancin</b>
Prothrombin time/international normalized ratio Activated partial thromboplastin time Activated clotting time Coagulation based factor X activity assay	Thrombin time Whole blood (Lee-White) clotting time Platelet aggregation study Chromogenic anti-factor Xa assay Functional (chromogenic) factor X activity assay Bleeding time D-dimer Fibrin degradation products

181  
 182 No evidence of increased bleeding risk has been observed in clinical trials with VIBATIV.  
 183 Telavancin has no effect on platelet aggregation. Furthermore, no evidence of  
 184 hypercoagulability has been seen, as healthy subjects receiving VIBATIV have normal  
 185 levels of D-dimer and fibrin degradation products.

186 **5.6 Hypersensitivity Reactions**

187 Serious and sometimes fatal hypersensitivity reactions, including anaphylactic reactions,  
 188 may occur after first or subsequent doses. Discontinue VIBATIV at first sign of skin rash, or

189 any other sign of hypersensitivity. Telavancin is a semi-synthetic derivative of vancomycin; it  
190 is unknown if patients with hypersensitivity reactions to vancomycin will experience cross-  
191 reactivity to telavancin. VIBATIV should be used with caution in patients with known  
192 hypersensitivity to vancomycin [see *Postmarketing Experience (6.2)*].

### 193 | **5.7 Infusion-Related Reactions**

194 VIBATIV is a lipoglycopeptide antibacterial agent and should be administered over a period  
195 of 60 minutes to reduce the risk of infusion-related reactions. Rapid intravenous infusions of  
196 the glycopeptide class of antimicrobial agents can cause “Red-man Syndrome”-like  
197 reactions including: flushing of the upper body, urticaria, pruritus, or rash. Stopping or  
198 slowing the infusion may result in cessation of these reactions.

### 199 | **5.8 *Clostridium difficile*-Associated Diarrhea**

200 *Clostridium difficile*-associated diarrhea (CDAD) has been reported with nearly all  
201 antibacterial agents and may range in severity from mild diarrhea to fatal colitis. Treatment  
202 with antibacterial agents alters the flora of the colon and may permit overgrowth of  
203 *C. difficile*.

204 *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hyper-  
205 toxin-producing strains of *C. difficile* cause increased morbidity and mortality, since these  
206 infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must  
207 be considered in all patients who present with diarrhea following antibiotic use. Careful  
208 medical history is necessary because CDAD has been reported to occur more than  
209 2 months after the administration of antibacterial agents.

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

### 214 | **5.9 Development of Drug-Resistant Bacteria**

215 Prescribing VIBATIV in the absence of a proven or strongly suspected bacterial infection is  
216 unlikely to provide benefit to the patient and increases the risk of the development of  
217 drug-resistant bacteria.

218 As with other antibacterial drugs, use of VIBATIV may result in overgrowth of nonsusceptible  
219 organisms, including fungi. Patients should be carefully monitored during therapy. If  
220 superinfection occurs, appropriate measures should be taken.

## 221 **5.10 QTc Prolongation**

222 In a study involving healthy volunteers, doses of 7.5 and 15 mg/kg of VIBATIV prolonged the  
223 QTc interval [see *Clinical Pharmacology (12.2)*]. Caution is warranted when prescribing  
224 VIBATIV to patients taking drugs known to prolong the QT interval. Patients with congenital  
225 long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or  
226 severe left ventricular hypertrophy were not included in clinical trials of VIBATIV. Use of  
227 VIBATIV should be avoided in patients with these conditions.

## 228 **6 ADVERSE REACTIONS**

229 The following serious adverse reactions are also discussed elsewhere in the labeling:

- 230 • Nephrotoxicity [see *Warnings and Precautions (5.3)*]
- 231 • Infusion-related reactions [see *Warnings and Precautions (5.7)*]
- 232 • *Clostridium difficile*-associated diarrhea [see *Warnings and Precautions (5.8)*]

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

### 236 **6.1 Clinical Trials Experience**

#### 237 ***Complicated Skin and Skin Structure Infections***

238 The two Phase 3 cSSSI clinical trials (Trial 1 and Trial 2) for VIBATIV included 929 adult  
239 patients treated with VIBATIV at 10 mg/kg IV once daily. The mean age of patients treated  
240 with VIBATIV was 49 years (range 18-96). There was a slight male predominance (56%) in  
241 patients treated with VIBATIV, and patients were predominantly Caucasian (78%).

242 In the cSSSI clinical trials, <1% (8/929) patients who received VIBATIV died and <1%  
243 (8/938) patients treated with vancomycin died. Serious adverse events were reported in 7%  
244 (69/929) of patients treated with VIBATIV and most commonly included renal, respiratory, or  
245 cardiac events. Serious adverse events were reported in 5% (43/938) of vancomycin-treated  
246 patients, and most commonly included cardiac, respiratory, or infectious events. Treatment

247 discontinuations due to adverse events occurred in 8% (72/929) of patients treated with  
 248 VIBATIV, the most common events being nausea and rash (~1% each). Treatment  
 249 discontinuations due to adverse events occurred in 6% (53/938) of vancomycin-treated  
 250 patients, the most common events being rash and pruritus (~1% each).

251 The most common adverse events occurring in  $\geq 10\%$  of VIBATIV-treated patients observed  
 252 in the VIBATIV Phase 3 cSSSI trials were taste disturbance, nausea, vomiting, and foamy  
 253 urine.

254 Table 4 displays the incidence of treatment-emergent adverse drug reactions reported in  
 255  $\geq 2\%$  of patients treated with VIBATIV possibly related to the drug.

256 Table 4: Incidence of Treatment-Emergent Adverse Drug Reactions Reported in  $\geq 2\%$   
 257 of VIBATIV or Vancomycin Patients Treated in cSSSI Trial 1 and Trial 2

	<b>VIBATIV (N=929)</b>	<b>Vancomycin (N=938)</b>
<b>Body as a Whole</b>		
Rigors	4%	2%
<b>Digestive System</b>		
Nausea	27%	15%
Vomiting	14%	7%
Diarrhea	7%	8%
<b>Metabolic and Nutritional</b>		
Decreased appetite	3%	2%
<b>Nervous System</b>		
Taste disturbance*	33%	7%
<b>Renal System</b>		
Foamy urine	13%	3%

\* Described as a metallic or soapy taste.

258 **HABP/VABP**

259 Two randomized, double-blind Phase 3 trials (Trial 1 and Trial 2) for VIBATIV included 1,503  
 260 adult patients treated with VIBATIV at 10 mg/kg IV once daily or vancomycin at 1 g IV twice  
 261 daily. The mean age of patients treated with VIBATIV was 62 years (range 18-100). In  
 262 patients treated with VIBATIV, 69% of the patients were white and 65% were male. In the  
 263 combined VIBATIV group, 29% were VAP and 71% were HAP patients.

264 Table 5 summarizes deaths using Kaplan-Meier estimates at Day 28 as stratified by  
 265 baseline creatinine clearance categorized into four groups. Patients with pre-existing  
 266 moderate/severe renal impairment (CrCl ≤50 mL/min) who were treated with VIBATIV for  
 267 HABP/VABP had increased mortality observed versus vancomycin in both the trials.

268 Table 5: 28-Day Mortality (Kaplan-Meier Estimates) Stratified by Baseline Creatinine  
 269 Clearance — All-Treated Analysis Population

CrCl (mL/min)	Trial 1			Trial 2		
	VIBATIV N (%)	Vancomycin N (%)	Difference (95% CI)	VIBATIV N (%)	Vancomycin N (%)	Difference (95% CI)
>80	143 (12.2%)	152 (14.1%)	-1.8 (-9.6, 6.0)	181 (10.5%)	181 (18.7%)	-8.2 (-15.5, -0.9)
>50-80	88 (27.4%)	88 (17.7%)	9.7 (-2.7, 22.1)	96 (25.6%)	90 (27.1%)	-1.5 (-14.4, 11.3)
30-50	80 (34.7%)	83 (23.1%)	11.5 (-2.5, 25.5)	62 (27.7%)	68 (23.7%)	4.0 (-11.1, 19.1)
<30	61 (44.3%)	51 (37.3%)	7.0 (-11.2, 25.2)	38 (61.1%)	41(42.1%)	19.0 (-2.9, 40.8)

270

271 Serious adverse events were reported in 31% of patients treated with VIBATIV and 26% of  
 272 patients who received vancomycin. Treatment discontinuations due to adverse events  
 273 occurred in 8% (60/751) of patients who received VIBATIV, the most common events being  
 274 acute renal failure and electrocardiogram QTc interval prolonged (~1% each). Treatment  
 275 discontinuations due to adverse events occurred in 5% (40/752) of vancomycin-patients, the  
 276 most common events being septic shock and multi-organ failure (<1%).

277 Table 6 displays the incidence of treatment-emergent adverse drug reactions reported in  
 278 ≥ 5% of HABP/VABP patients treated with VIBATIV possibly related to the drug.

279 Table 6: Incidence of Treatment-Emergent Adverse Drug Reactions Reported  
 280 in ≥5% of VIBATIV or Vancomycin Patients Treated in HABP/VABP Trial 1  
 281 and Trial 2

	<b>VIBATIV (N=751)</b>	<b>Vancomycin (N=752)</b>
Nausea	5%	4%
Vomiting	5%	4%
Renal Failure Acute	5%	4%

282

283 **Nephrotoxicity**

284 ***Complicated Skin and Skin Structure Infections***

285 In cSSSI trials, the incidence of renal adverse events indicative of renal impairment  
 286 (increased serum creatinine, renal impairment, renal insufficiency, and/or renal failure) was  
 287 30/929 (3%) of VIBATIV-treated patients compared with 10/938 (1%) of vancomycin-treated  
 288 patients. In 17 of the 30 VIBATIV-treated patients, these adverse events had not completely  
 289 resolved by the end of the trials, compared with 6 of the 10 vancomycin-treated patients.

290 Serious adverse events indicative of renal impairment occurred in 11/929 (1%) of VIBATIV-  
 291 treated patients compared with 3/938 (0.3%) of vancomycin-treated patients. Twelve  
 292 patients treated with VIBATIV discontinued treatment due to adverse events indicative of  
 293 renal impairment compared with 2 patients treated with vancomycin.

294 Increases in serum creatinine to 1.5 times baseline occurred more frequently among  
 295 VIBATIV-treated patients with normal baseline serum creatinine (15%) compared with  
 296 vancomycin-treated patients with normal baseline serum creatinine (7%).

297 Fifteen of 174 (9%) VIBATIV-treated patients ≥65 years of age had adverse events  
 298 indicative of renal impairment compared with 16 of 755 patients (2%) <65 years of age [see  
 299 *Use in Specific Populations (8.5)*].

300 ***Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia***

301 In the HABP/VABP trials, the incidence of renal adverse events (increased serum creatinine,  
 302 renal impairment, renal insufficiency, and/or renal failure) was 10% for VIBATIV vs. 8% for  
 303 vancomycin. Of the patients who had at least one renal adverse event, 54% in each  
 304 treatment group recovered completely, recovered with sequelae, or were improving from the  
 305 renal AE at the last visit. Three percent of VIBATIV-treated patients and 2% of vancomycin-

306 treated patients experienced at least one serious renal adverse event. Renal adverse events  
307 resulted in discontinuation of study medication in 14 VIBATIV-treated patients (2%) and 7  
308 vancomycin-treated patients (1%).

309 Increases in serum creatinine to 1.5 times baseline occurred more frequently among  
310 VIBATIV-treated patients (16%) compared with vancomycin-treated patients (10%).

311 Forty-four of 399 (11.0%) VIBATIV-treated patients  $\geq 65$  years of age had adverse events  
312 indicative of renal impairment compared with 30 of 352 patients (8%)  $< 65$  years of age [see  
313 *Use in Specific Populations (8.5)*].

## 314 **6.2 Postmarketing Experience**

315 The following adverse reactions have been identified during post-approval use of VIBATIV.  
316 Because these events are reported voluntarily from a population of uncertain size, it is not  
317 always possible to reliably estimate their frequency or establish a causal relationship to drug  
318 exposure.

319 Serious hypersensitivity reactions have been reported after first or subsequent doses of  
320 VIBATIV, including anaphylactic reactions. It is unknown if patients with hypersensitivity  
321 reactions to vancomycin will experience cross-reactivity to telavancin. [see *Hypersensitivity*  
322 *Reactions (5.6)*]

## 323 **7 DRUG INTERACTIONS**

### 324 **7.1 Drug-Laboratory Test Interactions**

#### 325 Effects of Telavancin on Coagulation Test Parameters

326 Telavancin binds to the artificial phospholipid surfaces added to common anticoagulation  
327 tests, thereby interfering with the ability of the coagulation complexes to assemble on the  
328 surface of the phospholipids and promote clotting *in vitro*. These effects appear to depend  
329 on the type of reagents used in commercially available assays. Thus, when measured  
330 shortly after completion of an infusion of VIBATIV, increases in the PT, INR, aPTT, and ACT  
331 have been observed. These effects dissipate over time, as plasma concentrations of  
332 telavancin decrease.

#### 333 Urine Protein Tests

334 Telavancin interferes with urine qualitative dipstick protein assays, as well as quantitative  
335 dye methods (e.g., pyrogallol red-molybdate). However, microalbumin assays are not  
336 affected and can be used to monitor urinary protein excretion during VIBATIV treatment.

## 337 **8 USE IN SPECIFIC POPULATIONS**

### 338 **8.1 Pregnancy**

#### 339 Teratogenic Effects: Pregnancy Category C

##### 340 *Pregnancy Exposure Registry*

341 There is a pregnancy registry that monitors pregnancy outcomes in women exposed to  
342 VIBATIV during pregnancy. Physicians are encouraged to register pregnant patients, or  
343 pregnant women may enroll themselves in the VIBATIV pregnancy registry by calling 1-855-  
344 633-8479.

##### 345 *Fetal Risk Summary*

346 All pregnancies have a background risk of birth defects (about 3%), pregnancy loss (about  
347 15%), or other adverse outcomes regardless of drug exposure.

348 There are no data on VIBATIV use in pregnant women. In 3 animal species, VIBATIV  
349 exposure during pregnancy at clinically relevant doses caused reduced fetal weights and  
350 increased rates of digit and limb malformations in offspring. These data raise concern about  
351 potential adverse developmental outcomes in humans (see *Data*).

##### 352 *Clinical Considerations*

353 Given the lack of human data and the risks suggested by animal data, avoid using VIBATIV  
354 in pregnant women unless the benefits to the patient outweigh the potential risks to the  
355 fetus.

##### 356 *Data*

###### 357 Human Data

358 There are no data on human pregnancies exposed to VIBATIV.

###### 359 Animal Data

360 In embryo-fetal development studies in rats, rabbits, and minipigs, telavancin demonstrated  
361 the potential to cause limb and skeletal malformations when given intravenously during the  
362 period of organogenesis at doses up to 150, 45, or 75 mg/kg/day, respectively. These doses

363 resulted in exposure levels approximately 1- to 2-fold the human exposure (AUC) at the  
364 maximum clinical recommended dose. Malformations observed at <1% (but absent or at  
365 lower rates in historical or concurrent controls), included brachymelia (rats and rabbits),  
366 syndactyly (rats, minipigs), adactyly (rabbits), and polydactyly (minipigs). Additional findings  
367 in rabbits included flexed front paw and absent ulna, and in the minipigs included misshapen  
368 digits and deformed front leg. Fetal body weights were decreased in rats.

369 In a prenatal/perinatal development study, pregnant rats received intravenous telavancin at  
370 up to 150 mg/kg/day (approximately the same AUC as observed at the maximum clinical  
371 dose) from the start of organogenesis through lactation. Offspring showed decreases in fetal  
372 body weight and an increase in the number of stillborn pups. Brachymelia was also  
373 observed. Developmental milestones and fertility of the pups were unaffected.

### 374 **8.3 Nursing Mothers**

375 It is not known whether telavancin is excreted in human milk. Because many drugs are  
376 excreted in human milk, caution should be exercised when VIBATIV is administered to a  
377 nursing woman.

### 378 **8.4 Pediatric Use**

379 The safety and effectiveness of VIBATIV in pediatric patients has not been studied.

### 380 **8.5 Geriatric Use**

381 Of the 929 patients treated with VIBATIV at a dose of 10 mg/kg once daily in clinical trials of  
382 cSSSI, 174 (19%) were  $\geq 65$  years of age and 87 (9%) were  $\geq 75$  years of age. In the cSSSI  
383 trials, lower clinical cure rates were observed in patients  $\geq 65$  years of age compared with  
384 those  $< 65$  years of age. Overall, treatment-emergent adverse events occurred with similar  
385 frequencies in patients  $\geq 65$  (75% of patients) and  $< 65$  years of age (83% of patients).  
386 Fifteen of 174 (9%) patients  $\geq 65$  years of age treated with VIBATIV had adverse events  
387 indicative of renal impairment compared with 16 of 755 (2%) patients  $< 65$  years of age [see  
388 *Warnings and Precautions (5.3), Clinical Trials (14.1)*].

389 Of the 749 HAP/VABP patients treated with VIBATIV at a dose of 10 mg/kg once daily in  
390 clinical trials of HAP/VABP, 397 (53%) were  $\geq 65$  years of age and 230 (31%) were  
391  $\geq 75$  years of age. Treatment-emergent adverse events as well as deaths and other serious

392 adverse events occurred more often in patients  $\geq 65$  years of age than in those  $< 65$  years of  
393 age in both treatment groups.

394 Telavancin is substantially excreted by the kidney, and the risk of adverse reactions may be  
395 greater in patients with impaired renal function. Because elderly patients are more likely to  
396 have decreased renal function, care should be taken in dose selection in this age group.

397 The mean plasma AUC values of telavancin were similar in healthy young and elderly  
398 subjects. Dosage adjustment for elderly patients should be based on renal function [see  
399 *Dosage and Administration (2), Clinical Pharmacology (12.3)*].

## 400 **8.6 Patients with Renal Impairment**

401 The HABP/VABP and cSSSI trials included patients with normal renal function and patients  
402 with varying degrees of renal impairment. Patients with underlying renal dysfunction or risk  
403 factors for renal dysfunction had a higher incidence of renal adverse events [see *Warnings*  
404 *and Precautions (5.3)*].

405 In the HABP/VABP studies higher mortality rates were observed in the VIBATIV-treated  
406 patients with baseline CrCl  $\leq 50$  mL/min. Use of VIBATIV in patients with pre-existing  
407 moderate/severe renal impairment should be considered only when the anticipated benefit  
408 to the patient outweighs the potential risk [see *Warnings and Precautions (5.1)*].

409 VIBATIV-treated patients in the cSSSI studies with baseline creatinine clearance  
410  $\leq 50$  mL/min had lower clinical cure rates. Consider these data when selecting antibacterial  
411 therapy in patients with baseline moderate/severe renal impairment (CrCl  $\leq 50$  mL/min) [see  
412 *Warnings and Precautions (5.2)*].

413 Dosage adjustment is required in patients with  $\leq 50$  mL/min renal impairment [see *Dosage*  
414 *and Administration (2)*]. There is insufficient information to make specific dosage adjustment  
415 recommendations for patients with end-stage renal disease (CrCl  $< 10$  mL/min), including  
416 patients receiving hemodialysis [see *Overdosage (10), Clinical Pharmacology (12.3)*].

417 Hydroxypropyl-beta-cyclodextrin is excreted in urine and may accumulate in patients with  
418 renal impairment. Serum creatinine should be closely monitored and, if renal toxicity is  
419 suspected, an alternative agent should be considered [see *Warnings and Precautions (5.3),*  
420 *Clinical Pharmacology (12.3)*].

421 **8.7 Patients with Hepatic Impairment**

422 The HABP/VABP and cSSSI trials included patients with normal hepatic function and with  
423 hepatic impairment. No dosage adjustment is recommended in patients with mild or  
424 moderate hepatic impairment [see *Clinical Pharmacology (12.3)*].

425 **10 OVERDOSAGE**

426 In the event of overdose, VIBATIV should be discontinued and supportive care is advised  
427 with maintenance of glomerular filtration and careful monitoring of renal function. Following  
428 administration of a single dose of VIBATIV 7.5 mg/kg to subjects with end-stage renal  
429 disease, approximately 5.9% of the administered dose of telavancin was recovered in the  
430 dialysate following 4 hours of hemodialysis. However, no information is available on the use  
431 of hemodialysis to treat an overdose [see *Clinical Pharmacology (12.3)*].

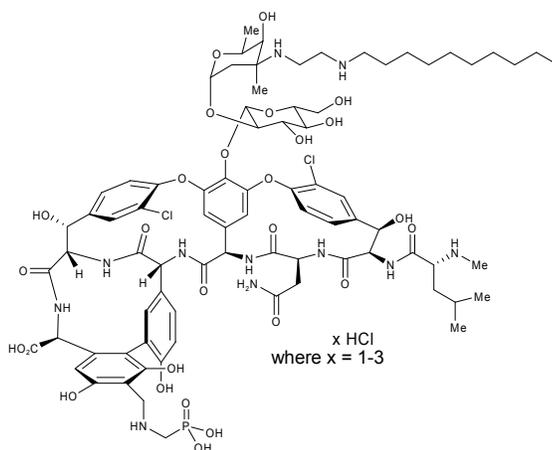
432 The clearance of telavancin by continuous venovenous hemofiltration (CVVH) was  
433 evaluated in an *in vitro* study [see *Nonclinical Toxicology (13.2)*]. Telavancin was cleared by  
434 CVVH and the clearance of telavancin increased with increasing ultrafiltration rate.  
435 However, the clearance of telavancin by CVVH has not been evaluated in a clinical study;  
436 thus, the clinical significance of this finding and use of CVVH to treat an overdose is  
437 unknown.

438 **11 DESCRIPTION**

439 VIBATIV contains telavancin hydrochloride (Figure 1), a lipoglycopeptide antibacterial that is  
440 a synthetic derivative of vancomycin.

441 The chemical name of telavancin hydrochloride is  
442 vancomycin, N3"-[2-(decylamino)ethyl]-29-[[[(phosphono-methyl)-amino]-methyl]-  
443 hydrochloride. Telavancin hydrochloride has the following chemical structure:

444 Figure 1: Telavancin Hydrochloride



445 Telavancin hydrochloride

446 Telavancin hydrochloride is an off-white to slightly colored amorphous powder with the  
447 empirical formula  $C_{80}H_{106}Cl_2N_{11}O_{27}P \cdot xHCl$  (where  $x = 1$  to  $3$ ) and a free-base molecular  
448 weight of 1755.6. It is highly lipophilic and slightly soluble in water.

449 VIBATIV is a sterile, preservative-free, white to slightly colored lyophilized powder containing  
450 telavancin hydrochloride (equivalent to either 250 mg or 750 mg of telavancin as the free  
451 base) for intravenous use. The inactive ingredients are Hydroxypropylbetadex, Ph. Eur  
452 (hydroxypropyl-beta-cyclodextrin) (2500 mg per 250 mg telavancin, 7500 mg per 750 mg  
453 telavancin), mannitol (312.5 mg per 250 mg telavancin, 937.5 mg per 750 mg telavancin),  
454 and sodium hydroxide and hydrochloric acid used in minimal quantities for pH adjustment.  
455 When reconstituted, it forms a clear to slightly colored solution with a pH of 4.5 (4.0 to 5.0).

## 456 12 CLINICAL PHARMACOLOGY

### 457 12.1 Mechanism of Action

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

### 459 12.2 Pharmacodynamics

460 The antimicrobial activity of telavancin appears to best correlate with the ratio of area under  
461 the concentration-time curve to minimum inhibitory concentration (AUC/MIC) for  
462 *Staphylococcus aureus* based on animal models of infection. Exposure-response analyses  
463 of the clinical trials support the dose of 10 mg/kg every 24 hours.

464 Cardiac Electrophysiology

465 The effect of telavancin on cardiac repolarization was assessed in a randomized,  
 466 double-blind, multiple-dose, positive-controlled, and placebo-controlled, parallel study  
 467 (n=160). Healthy subjects received VIBATIV 7.5 mg/kg, VIBATIV 15 mg/kg, positive control,  
 468 or placebo infused over 60 minutes once daily for 3 days. Based on interpolation of the data  
 469 from VIBATIV 7.5 mg/kg and 15 mg/kg, the mean maximum baseline-corrected, placebo-  
 470 corrected QTc prolongation at the end of infusion was estimated to be 12-15 msec for  
 471 VIBATIV 10 mg/kg and 22 msec for the positive control (Table 7). By 1 hour after infusion  
 472 the maximum QTc prolongation was 6-9 msec for VIBATIV and 15 msec for the positive  
 473 control.

474 Table 7: Mean and Maximum QTcF Changes from Baseline Relative to Placebo

	QTcF <sup>1</sup> Change from Baseline	
	Mean (Upper 90% Confidence Limit <sup>2</sup> ) msec	Maximum (Upper 90% Confidence Limit) msec
VIBATIV 7.5 mg/kg	4.1 (7)	11.6 (16)
VIBATIV 15 mg/kg	4.6 (8)	15.1 (20)
Positive Control	9.5 (13)	21.6 (26)

475 <sup>1</sup> Fridericia corrected

476 <sup>2</sup> Upper CL from a 2-sided 90% CI on difference from placebo (msec)  
 477

478 ECGs were performed prior to and during the treatment period in patients receiving VIBATIV  
 479 10 mg/kg in 3 cSSSI studies to monitor QTc intervals. In these trials, 214 of 1029 (21%)  
 480 patients allocated to treatment with VIBATIV and 164 of 1033 (16%) allocated to  
 481 vancomycin received concomitant medications known to prolong the QTc interval and  
 482 known to be associated with definite or possible risk of torsades de pointes. The incidence  
 483 of QTc prolongation >60 msec was 1.5% (15 patients) in the VIBATIV group and 0.6%  
 484 (6 patients) in the vancomycin group. Nine of the 15 VIBATIV patients received concomitant  
 485 medications known to prolong the QTc interval and definitely or possibly associated with a  
 486 risk of torsades de pointes, compared with 1 of the 6 patients who received vancomycin. A  
 487 similar number of patients in each treatment group (<1%) who did not receive a concomitant  
 488 medication known to prolong the QTc interval experienced a prolongation >60 msec from  
 489 baseline. In a separate analysis, 1 patient in the VIBATIV group and 2 patients in the  
 490 vancomycin group experienced QTc >500 msec. No cardiac adverse events were ascribed

491 to prolongation of the QTc interval. In the Phase 3 HABP/VABP studies, the incidence of  
 492 QTc prolongation >60 msec or mean value >500 msec was 8% (52 patients) in the  
 493 telavancin group and 7% (48 patients) in the vancomycin group.

### 494 12.3 Pharmacokinetics

495 The mean pharmacokinetic parameters of telavancin (10 mg/kg) after a single and multiple  
 496 60-minute intravenous infusions (10 mg/kg every 24 hours) are summarized in Table 8.

497 Table 8: Pharmacokinetic Parameters of Telavancin in Healthy Adults, 10 mg/kg

	Single Dose (n=42)	Multiple Dose (n=36)
C <sub>max</sub> (mcg/mL)	93.6 ± 14.2	108 ± 26
AUC <sub>0-∞</sub> (mcg·hr/mL)	747 ± 129	-- <sup>1</sup>
AUC <sub>0-24h</sub> (mcg·hr/mL)	666 ± 107	780 ± 125
t <sub>1/2</sub> (hr)	8.0 ± 1.5	8.1 ± 1.5
Cl (mL/hr/kg)	13.9 ± 2.9	13.1 ± 2.0
V <sub>ss</sub> (mL/kg)	145 ± 23	133 ± 24

C<sub>max</sub> maximum plasma concentration

AUC area under concentration-time course

t<sub>1/2</sub> terminal elimination half-life

Cl clearance

V<sub>ss</sub> apparent volume of distribution at steady state

<sup>1</sup> Data not available

498 In healthy young adults, the pharmacokinetics of telavancin administered intravenously were  
 499 linear following single doses from 5 to 12.5 mg/kg and multiple doses from 7.5 to 15 mg/kg  
 500 administered once daily for up to 7 days. Steady-state concentrations were achieved by the  
 501 third daily dose.

### 502 Distribution

503 Telavancin binds to human plasma proteins, primarily to serum albumin, in a  
 504 concentration-independent manner. The mean binding is approximately 90% and is not  
 505 affected by renal or hepatic impairment.

506 Concentrations of telavancin in pulmonary epithelial lining fluid (ELF) and alveolar  
 507 macrophages (AM) were measured through collection of bronchoalveolar lavage fluid at  
 508 various times following administration of VIBATIV 10 mg/kg once daily for 3 days to healthy

509 adults. Telavancin concentrations in ELF and AM exceeded the MIC<sub>90</sub> for *S. aureus*  
510 (0.5 mcg/mL) for at least 24 hours following dosing.

511 Concentrations of telavancin in skin blister fluid were 40% of those in plasma  
512 (AUC<sub>0-24hr</sub> ratio) after 3 daily doses of 7.5 mg/kg VIBATIV in healthy young adults.

### 513 Metabolism

514 No metabolites of telavancin were detected in *in vitro* studies using human liver microsomes,  
515 liver slices, hepatocytes, and kidney S9 fraction. None of the following recombinant CYP  
516 450 isoforms were shown to metabolize telavancin in human liver microsomes: CYP 1A2,  
517 2C9, 2C19, 2D6, 3A4, 3A5, 4A11. The clearance of telavancin is not expected to be altered  
518 by inhibitors of any of these enzymes.

519 In a mass balance study in male subjects using radiolabeled telavancin, 3 hydroxylated  
520 metabolites were identified with the predominant metabolite (THRX-651540) accounting for  
521 <10% of the radioactivity in urine and <2% of the radioactivity in plasma. The metabolic  
522 pathway for telavancin has not been identified.

### 523 Excretion

524 Telavancin is primarily eliminated by the kidney. In a mass balance study, approximately  
525 76% of the administered dose was recovered from urine and <1% of the dose was  
526 recovered from feces (collected up to 216 hours) based on total radioactivity.

### 527 Specific Populations

#### 528 *Geriatric Patients*

529 The impact of age on the pharmacokinetics of telavancin was evaluated in healthy young  
530 (range 21-42 years) and elderly (range 65-83 years) subjects. The mean CrCl of elderly  
531 subjects was 66 mL/min. Age alone did not have a clinically meaningful impact on the  
532 pharmacokinetics of telavancin [see *Use in Specific Populations (8.5)*].

#### 533 *Pediatric Patients*

534 The pharmacokinetics of telavancin in patients less than 18 years of age have not been  
535 studied.

536 *Gender*

537 The impact of gender on the pharmacokinetics of telavancin was evaluated in healthy male  
538 (n=8) and female (n=8) subjects. The pharmacokinetics of telavancin were similar in males  
539 and females. No dosage adjustment is recommended based on gender.

540 *Renal Impairment*

541 The pharmacokinetics of telavancin were evaluated in subjects with normal renal function  
542 and subjects with varying degrees of renal impairment following administration of a single  
543 dose of telavancin 7.5 mg/kg (n=28). The mean AUC<sub>0-∞</sub> values were approximately 13%,  
544 29%, and 118% higher for subjects with CrCl >50 to 80 mL/min, CrCl 30 to 50 mL/min, and  
545 CrCl <30 mL/min, respectively, compared with subjects with normal renal function. Dosage  
546 adjustment is required in patients with CrCl ≤50 mL/min [see *Dosage and Administration*  
547 (2)].

548 Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault  
549 formula:

550

$$551 \quad \text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{ideal body weight (kg)}^* \{ \times 0.85 \text{ for female patients} \}}{72 \times \text{serum creatinine (mg/dL)}} \\ 552$$

553 \*Use actual body weight if < ideal body weight (IBW)

554 IBW (male) = 50 kg + 0.9 kg/cm over 152 cm height

555 IBW (female) = 45.5 kg + 0.9 kg/cm over 152 cm height

556 Following administration of a single dose of VIBATIV 7.5 mg/kg to subjects with end-stage  
557 renal disease, approximately 5.9% of the administered dose of telavancin was recovered in  
558 the dialysate following 4 hours of hemodialysis. The effects of peritoneal dialysis have not  
559 been studied.

560 Following a single intravenous dose of VIBATIV 7.5 mg/kg, the clearance of hydroxypropyl-  
561 beta-cyclodextrin was reduced in subjects with renal impairment, resulting in a higher  
562 exposure to hydroxypropyl-beta-cyclodextrin. In subjects with mild, moderate, and severe  
563 renal impairment, the mean clearance values were 38%, 59%, and 82% lower, respectively,

564 compared with subjects with normal renal function. Multiple infusions of VIBATIV may result  
565 in accumulation of hydroxypropyl-beta-cyclodextrin.

#### 566 *Hepatic Impairment*

567 The pharmacokinetics of telavancin were not altered in subjects with moderate hepatic  
568 impairment (n= 8, Child-Pugh B) compared with healthy subjects with normal hepatic  
569 function matched for gender, age, and weight. The pharmacokinetics of telavancin have not  
570 been evaluated in patients with severe hepatic impairment (Child-Pugh C).

#### 571 Drug Interactions

##### 572 *In Vitro*

573 The inhibitory activity of telavancin against the following CYP 450 enzymes was evaluated in  
574 human liver microsomes: CYP 1A2, 2C9, 2C19, 2D6, and 3A4/5. Telavancin inhibited CYP  
575 3A4/5 at potentially clinically relevant concentrations. Upon further evaluation in a Phase 1  
576 clinical trial, telavancin was found not to inhibit the metabolism of midazolam, a sensitive  
577 CYP3A substrate (see below).

##### 578 *Midazolam*

579 The impact of telavancin on the pharmacokinetics of midazolam (CYP 3A4/5 substrate) was  
580 evaluated in 16 healthy adult subjects following administration of a single dose of VIBATIV  
581 10 mg/kg, intravenous midazolam 1 mg, and both. The results showed that telavancin had  
582 no impact on the pharmacokinetics of midazolam and midazolam had no effect on the  
583 pharmacokinetics of telavancin.

##### 584 *Aztreonam*

585 The impact of telavancin on the pharmacokinetics of aztreonam was evaluated in 11 healthy  
586 adult subjects following administration of a single dose of VIBATIV 10 mg/kg, aztreonam  
587 2 g, and both. Telavancin had no impact on the pharmacokinetics of aztreonam and  
588 aztreonam had no effect on the pharmacokinetics of telavancin. No dosage adjustment of  
589 telavancin or aztreonam is recommended when both drugs are coadministered.

##### 590 *Piperacillin-tazobactam*

591 The impact of telavancin on the pharmacokinetics of piperacillin-tazobactam was evaluated  
592 in 12 healthy adult subjects following administration of a single dose of VIBATIV 10 mg/kg,  
593 piperacillin-tazobactam 4.5 g, and both. Telavancin had no impact on the pharmacokinetics  
594 of piperacillin-tazobactam and piperacillin-tazobactam had no effect on the  
595 pharmacokinetics of telavancin. No dosage adjustment of telavancin or piperacillin-  
596 tazobactam is recommended when both drugs are coadministered.

## 597 **12.4 Microbiology**

598 Telavancin is a semisynthetic, lipoglycopeptide antibiotic. Telavancin exerts  
599 concentration-dependent, bactericidal activity against Gram-positive organisms *in vitro*, as  
600 demonstrated by time-kill assays and MBC/MIC (minimum bactericidal  
601 concentration/minimum inhibitory concentration) ratios using broth dilution methodology. *In*  
602 *vitro* studies demonstrated a telavancin post-antibiotic effect ranging from 1 to 6 hours  
603 against *S. aureus* and other Gram-positive pathogens.

### 604 Mechanism of Action

605 Telavancin inhibits cell wall biosynthesis by binding to late-stage peptidoglycan precursors,  
606 including lipid II. Telavancin also binds to the bacterial membrane and disrupts membrane  
607 barrier function.

### 608 Interactions with Other Antibacterial Drugs

609 *In vitro* investigations demonstrated no antagonism between telavancin and amikacin,  
610 aztreonam, cefepime, ceftriaxone, ciprofloxacin, gentamicin, imipenem, meropenem,  
611 oxacillin, piperacillin/tazobactam, rifampin, and trimethoprim/sulfamethoxazole when tested  
612 in various combinations against telavancin-susceptible staphylococci, streptococci, and  
613 enterococci. This information is not available for other bacteria.

### 614 Cross-Resistance

615 Some vancomycin-resistant enterococci have a reduced susceptibility to telavancin. There is  
616 no known cross-resistance between telavancin and other classes of antibacterial drugs.

### 617 Antibacterial Activity

618 Telavancin has been shown to be active against most isolates of the following  
619 microorganisms both *in vitro* and in clinical infections as described in the Indications and  
620 Usage section [see *Indications and Usage (1)*]:

621 Facultative Gram-Positive Microorganisms

622 *Staphylococcus aureus* (including methicillin-resistant isolates)  
623 *Enterococcus faecalis* (vancomycin-susceptible isolates only)  
624 *Streptococcus agalactiae*  
625 *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and  
626 *S. constellatus*)  
627 *Streptococcus pyogenes*  
628

629 Greater than 90% of the following microorganisms exhibit an *in vitro* MIC less than or equal  
630 to the telavancin-susceptible breakpoint for organisms of similar genus shown in Table 9.  
631 The safety and effectiveness of telavancin in treating clinical infections due to these  
632 microorganisms have not been established in adequate and well-controlled clinical trials.

633 Facultative Gram-Positive Microorganisms

634 *Enterococcus faecium* (vancomycin-susceptible isolates only)  
635 *Staphylococcus haemolyticus*  
636 *Streptococcus dysgalactiae* subsp. *equisimilis*  
637 *Staphylococcus epidermidis*  
638

639 Susceptibility Test Methods

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

645 *Dilution technique*

646 Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations  
647 (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial  
648 compounds. The MICs should be determined using a standardized procedure [see  
649 *References (15)*]. Standardized procedures are based on a broth dilution method or

650 equivalent with standardized inoculum concentrations and standardized concentrations of  
 651 telavancin powder. The test method treats telavancin as a water-insoluble agent. Dimethyl  
 652 sulfoxide is used as solvent and diluent, and the cation-adjusted Mueller Hinton Broth test  
 653 medium is supplemented with polysorbate 80 to a final concentration of 0.002%. Telavancin  
 654 should not be tested by the agar dilution method. The MIC values should be interpreted  
 655 according to the criteria provided in Table 9.

656 *Diffusion technique*

657 Quantitative methods that require measurement of zone diameters also provide reproducible  
 658 estimates of the susceptibility of bacteria to antimicrobial compounds. One such  
 659 standardized procedure requires the use of standardized inoculum concentrations [see  
 660 *References (15)*]. This procedure uses paper disks impregnated with 30 mcg of telavancin  
 661 to test the susceptibility of microorganisms to telavancin. The disk diffusion interpretive  
 662 criteria are provided in Table 9.

663 Table 9: Susceptibility Interpretive Criteria for Telavancin

	Susceptibility Interpretive Criteria <sup>1</sup>					
	Minimum Inhibitory Concentration (mcg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (including methicillin-resistant isolates)	≤ 0.12	--	--	≥ 15	--	--
<i>Streptococcus pyogenes</i> <i>Streptococcus agalactiae</i>	≤ 0.12	--	--	≥ 15	--	--
<i>Streptococcus anginosus</i> group	≤ 0.06			≥ 15		
<i>Enterococcus faecalis</i> (vancomycin-susceptible isolates only)	≤ 0.25	--	--	≥ 15	--	--

<sup>1</sup> The current absence of resistant isolates precludes defining any results other than “susceptible.” Isolates yielding results other than susceptible should be subjected to additional testing.

664

665 A report of “susceptible” indicates that the antimicrobial is likely to inhibit growth of the  
 666 pathogen if the antimicrobial compound in the blood reaches the concentrations usually  
 667 achievable.

668 *Quality Control*

669 Standardized susceptibility test procedures require the use of laboratory control  
 670 microorganisms to monitor the performance of the supplies and reagents used in the assay,  
 671 and the techniques of the individuals performing the test [see *References (15)*]. Standard  
 672 telavancin powder should provide the range of values noted in Table 10.

673 Quality control microorganisms are specific strains of organisms with intrinsic biological  
 674 properties relating to resistance mechanisms and their genetic expression within bacteria;  
 675 the specific strains used for microbiological quality control are not clinically significant.

676 Table 10: Acceptable Quality Control Ranges for Telavancin to be used in Validation of  
 677 Susceptibility Test Results

	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration (mcg/mL)	Disk Diffusion Zone Diameter (mm)
<i>Enterococcus faecalis</i> ATCC 29212	0.03 – 0.12	Not applicable
<i>Staphylococcus aureus</i> ATCC 29213	0.03 - 0.12	Not applicable
<i>Staphylococcus aureus</i> ATCC 25923	Not applicable	16-20
<i>Streptococcus pneumoniae</i> ATCC 49619 <sup>1</sup>	0.004 – 0.015	17-24

<sup>1</sup> This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*

678

## 679 13 NONCLINICAL TOXICOLOGY

### 680 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

681 Long-term studies in animals to determine the carcinogenic potential of telavancin have not  
 682 been performed.

683 Neither mutagenic nor clastogenic potential of telavancin was found in a battery of tests  
 684 including: assays for mutagenicity (Ames bacterial reversion), an *in vitro* chromosome  
 685 aberration assay in human lymphocytes, and an *in vivo* mouse micronucleus assay.

686 Telavancin did not affect the fertility or reproductive performance of adult male rats (exposed  
 687 to telavancin for at least 4 weeks prior to mating) or female rats (exposed to telavancin for at  
 688 least 2 weeks prior to mating).

689 Male rats given telavancin for 6 weeks, at exposures similar to those measured in clinical  
690 studies, displayed altered sperm parameters that were reversible following an 8-week  
691 recovery period.

## 692 **13.2 Animal Toxicology and/or Pharmacology**

693 Two-week administration of telavancin in rats produced minimal renal tubular vacuolization  
694 with no changes in BUN or creatinine. These effects were not seen in studies conducted in  
695 dogs for similar duration. Four weeks of treatment resulted in reversible elevations in BUN  
696 and/or creatinine in association with renal tubular degeneration that further progressed  
697 following 13 weeks of treatment.

698 These effects occurred at exposures (based on AUCs) that were similar to those measured  
699 in clinical trials.

700 The potential effects of continuous venovenous hemofiltration (CVVH) on the clearance of  
701 telavancin were examined in an *in vitro* model using bovine blood. Telavancin was cleared  
702 by CVVH and the clearance of telavancin increased with increasing ultrafiltration rate [see  
703 *Overdosage (10)*].

## 704 **14 CLINICAL TRIALS**

### 705 **14.1 Complicated Skin and Skin Structure Infections**

706 Adult patients with clinically documented complicated skin and skin structure infections  
707 (cSSSI) were enrolled in two randomized, multinational, multicenter, double-blinded trials  
708 (Trial 1 and Trial 2) comparing VIBATIV (10 mg/kg IV every 24 hours) with vancomycin (1 g  
709 IV every 12 hours) for 7 to 14 days. Vancomycin dosages could be adjusted per site-specific  
710 practice. Patients could receive concomitant aztreonam or metronidazole for suspected  
711 Gram-negative and anaerobic infection, respectively. These trials were identical in design,  
712 enrolling approximately 69% of their patients from the United States.

713 The trials enrolled adult patients with cSSSI with suspected or confirmed MRSA as the  
714 primary cause of infection. The all-treated efficacy (ATe) population included all patients  
715 who received any amount of study medication according to their randomized treatment  
716 group and were evaluated for efficacy. The clinically evaluable population (CE) included  
717 patients in the ATe population with sufficient adherence to the protocol.

718 The ATe population consisted of 1,794 patients. Of these, 1,410 (79%) patients were  
 719 clinically evaluable (CE). Patient baseline infection types were well-balanced between  
 720 treatment groups and are presented in Table 11.

721 Table 11: Baseline Infection Types in Patients in cSSSI Trials 1 and 2 – ATe Population

	<b>VIBATIV (N=884)<sup>1</sup></b>	<b>Vancomycin (N=910)<sup>1</sup></b>
Type of infection		
Major Abscess	375 (42.4%)	397 (43.6%)
Deep/Extensive Cellulitis	309 (35.0%)	337 (37.0%)
Wound Infection	139 (15.7%)	121 (13.3%)
Infected Ulcer	45 (5.1%)	46 (5.1%)
Infected Burn	16 (1.8%)	9 (1.0%)

<sup>1</sup> Includes all patients randomized, treated, and evaluated for efficacy

722

723 The primary efficacy endpoints in both trials were the clinical cure rates at a follow-up  
 724 (Test of Cure) visit in the ATe and CE populations. Clinical cure rates in Trials 1 and 2 are  
 725 displayed for the ATe and CE population in Table 12.

726 Table 12: Clinical Cure at Test-of-Cure in cSSSI Trials 1 and 2 – ATe and CE  
 727 Populations

	<b>Trial 1</b>			<b>Trial 2</b>		
	<b>VIBATIV</b>	<b>Vancomycin</b>	<b>Difference</b>	<b>VIBATIV</b>	<b>Vancomycin</b>	<b>Difference</b>
	<b>% (n/N)</b>	<b>% (n/N)</b>	<b>(95% CI)<sup>1</sup></b>	<b>% (n/N)</b>	<b>% (n/N)</b>	<b>(95% CI)<sup>1</sup></b>
<b>ATe</b>	72.5% (309/426)	71.6% (307/429)	0.9 ( -5.3, 7.2)	74.7% (342/458)	74.0% (356/481 )	0.7 ( -5.1, 6.5)
<b>CE</b>	84.3% (289/343)	82.8% (288/348)	1.5 ( -4.3, 7.3)	83.9% (302/360)	87.7% (315/359 )	-3.8 ( -9.2, 1.5)

728 <sup>1</sup>95% CI computed using a continuity correction

729

730 The cure rates by pathogen for the microbiologically evaluable (ME) population are  
 731 presented in Table 13.

732 Table 13: Clinical Cure Rates at the Test-of-Cure for the Most Common Pathogens in  
 733 cSSSI Trials 1 and 2 – ME Population<sup>1</sup>

	<b>VIBATIV % (n/N)</b>	<b>Vancomycin % (n/N)</b>
<i>Staphylococcus aureus</i> (MRSA)	87.0% (208/239)	85.9% (225/262)
<i>Staphylococcus aureus</i> (MSSA)	82.0% (132/161)	85.1% (131/154)
<i>Enterococcus faecalis</i>	95.6% (22/23)	80.0% (28/35)
<i>Streptococcus pyogenes</i>	84.2% (16/19)	90.5% (19/21)
<i>Streptococcus agalactiae</i>	73.7% (14/19)	86.7% (13/15)
<i>Streptococcus anginosus</i> group	76.5% (13/17)	100.0% (9/9)

<sup>1</sup> The ME population included patients in the CE population who had Gram-positive pathogens isolated at baseline and had central identification and susceptibility of the microbiological isolate(s).

734

735 In the two cSSSI trials, clinical cure rates were similar across gender and race. Clinical cure  
 736 rates in the VIBATIV clinically evaluable (CE) population were lower in patients ≥65 years of  
 737 age compared with those <65 years of age. A decrease of this magnitude was not observed  
 738 in the vancomycin CE population. Clinical cure rates in the VIBATIV CE population  
 739 <65 years of age were 503/581 (87%) and in those ≥65 years were 88/122 (72%). In the  
 740 vancomycin CE population clinical cure rates in patients <65 years of age were 492/570  
 741 (86%) and in those ≥65 years was 111/137 (82%). Clinical cure rates in the VIBATIV-treated  
 742 patients were lower in patients with baseline CrCl ≤50 mL/min compared with those with  
 743 CrCl >50 mL/min. A decrease of this magnitude was not observed in the vancomycin-treated  
 744 patients [see *Warnings and Precautions (5.2)*].

745 **14.2 HABP/VABP**

746 Adult patients with hospital-acquired and ventilator-associated pneumonia were enrolled in  
 747 two randomized, parallel-group, multinational, multicenter, double-blinded trials of identical  
 748 design comparing VIBATIV (10 mg/kg IV every 24 hours) with vancomycin (1 g IV every  
 749 12 hours) for 7 to 21 days. Vancomycin dosages could be adjusted for body weight and/or  
 750 renal function per local guidelines. Patients could receive concomitant aztreonam or

751 metronidazole for suspected Gram-negative and anaerobic infection, respectively. The  
752 addition of piperacillin/tazobactam was also permitted for coverage of Gram-negative  
753 organisms if resistance to aztreonam was known or suspected. Patients with known or  
754 suspected infections due to methicillin-resistant *Staphylococcus aureus* were enrolled in the  
755 studies.

756 Of the patients enrolled across both trials, 64% were male and 70% were white. The mean  
757 age was 63 years. At baseline, more than 50% were admitted to an intensive care unit,  
758 about 23% had chronic obstructive pulmonary disease, about 29% had ventilator-associated  
759 pneumonia and about 6% had bacteremia. Demographic and baseline characteristics were  
760 generally well-balanced between treatment groups; however, there were differences  
761 between HABP/VABP Trial 1 and HABP/VABP Trial 2 with respect to a baseline history of  
762 diabetes mellitus (31% in Trial 1, 21% in Trial 2) and baseline renal insufficiency  
763 (CrCl  $\leq$  50 mL/min) (36% in Trial 1, 27% in Trial 2).

764 All-cause mortality was evaluated because there is historical evidence of treatment effect for  
765 this endpoint. This was a protocol pre-specified secondary endpoint. The 28-day all-cause  
766 mortality outcomes (overall and by baseline creatinine clearance categorization) in the group  
767 of patients who had at least one baseline Gram-positive respiratory pathogen are shown in  
768 Table 14. This group of patients included those who had mixed Gram-positive/Gram-  
769 negative infections.

770 Table 14: All-Cause Mortality at Day 28 in Patients with at least One Baseline Gram-  
771 Positive Pathogen

		Trial 1		Trial 2	
		VIBATIV	Vancomycin	VIBATIV	Vancomycin
All Patients	Mortality <sup>a</sup>	28.7% N=187	24.3% N=180	24.3% N=224	22.3% N=206
	Difference (95% CI)	4.4% (-4.7%, 13.5%)		2.0% (-6.1%, 10%)	
CrCl ≤ 50 mL/min	Mortality <sup>a</sup>	41.8% N=63	35.4% N=68	43.9% N=53	29.6% N=58
	Difference (95% CI)	6.4% (-10.4, 23.2)		14.3% (-3.6, 32.2)	
CrCl > 50 mL/min	Mortality <sup>a</sup>	22.0% N=124	17.6% N=112	18.2% N=171	19.3% N=148
	Difference (95% CI)	4.4% (-5.9, 14.7)		-1.1% (-9.8, 7.6)	

772 <sup>a</sup>Mortality rates are based on Kaplan-Meier estimates at Study Day 28. There were 84 patients (5.6%)  
773 whose survival statuses were not known up to 28 days after initiation of study drug and were  
774 considered censored at the last day known to be alive. Thirty-five of these patients were treated with  
775 VIBATIV and 45 were treated with vancomycin.  
776

777 The protocol-specified analysis included clinical cure rates at the TOC (7 to 14 days after  
778 the last dose of study drug) in the co-primary All-Treated (AT) and Clinically Evaluable (CE)  
779 populations (Table 15). Clinical cure was determined by resolution of signs and symptoms,  
780 no further antibacterial therapy for HABP/VABP after end-of-treatment, and improvement or  
781 no progression of baseline radiographic findings. However, the quantitative estimate of  
782 treatment effect for this endpoint has not been established.

783 Table 15: Clinical Response Rates in Trials 1 and 2 – AT and CE Populations

	Trial 1		Trial 2	
	VIBATIV	Vancomycin	VIBATIV	Vancomycin
AT <sup>a</sup>	57.5% (214/372)	59.1% (221/374)	60.2% (227/377)	60.0% (228/380)
Difference (95% CI)	-1.6% (-8.6%, 5.5%)		0.2% (-6.8%, 7.2%)	
CE <sup>b</sup>	83.7% (118/141)	80.2% (138/172)	81.3% (139/171)	81.2% (138/170)
Difference (95% CI)	3.5% (-5.1%, 12.0%)		0.1% (-8.2%, 8.4%)	

784 <sup>a</sup>All-Treated (AT) Population: Patients who received at least one dose of study medication

785 <sup>b</sup>Clinically Evaluable (CE) Population: Patients who were clinically evaluable  
786

787 **15 REFERENCES**

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798 document M100-S24, Clinical and Laboratory Standards Institute, 950 West Valley  
799 Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2014.

800  
801 **16 HOW SUPPLIED/STORAGE AND HANDLING**

- 802 • Cartons of 10 individually packaged 250 mg single-dose vials (NDC 62847-002-01)
- 803 • Cartons of 10 individually packaged 750 mg single-dose vials (NDC 62847-001-01)

804 Store original packages at refrigerated temperatures of 2 to 8°C (35 to 46 °F). Excursions to  
805 ambient temperatures (up to 25 °C (77 °F)) are acceptable. Avoid excessive heat.

806 **17 PATIENT COUNSELING INFORMATION**

807 *See Medication Guide.*

808 Use During Pregnancy and By Women of Childbearing Potential

809 Women of childbearing potential (those who have **not** had: complete absence of menses for  
810 at least 24 months or medically confirmed menopause, medically confirmed primary ovarian  
811 failure, a history of hysterectomy, bilateral oophorectomy, or tubal ligation) should:

- 812 • Be informed about the potential risk of fetal harm if VIBATIV is used during  
813 pregnancy
- 814 • Have a pregnancy test prior to administration of VIBATIV
- 815 • If not pregnant, use effective contraceptive methods to prevent pregnancy during  
816 VIBATIV treatment
- 817 • Notify their prescribing physician/ healthcare provider if they become pregnant during  
818 VIBATIV treatment

819

820 Pregnancy Registry

821 There is a pregnancy registry that monitors pregnancy outcomes in women exposed to  
822 VIBATIV during pregnancy. Physicians are encouraged to register pregnant patients, or  
823 pregnant women may enroll themselves in the pregnancy registry by calling 1-855-633-  
824 8479.

825 Diarrhea

826 Diarrhea is a common problem caused by antibiotics that usually ends when the antibiotic is  
827 discontinued. Sometimes after starting treatment with antibiotics, patients can develop  
828 watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or  
829 more months after having received the last dose of the antibiotic. If this occurs, patients  
830 should contact their physician as soon as possible.

831 Correct Use of Antibacterial Drugs

832 Patients should be counseled that antibacterial drugs including VIBATIV should only be  
833 used to treat bacterial infections. They do not treat viral infections (e.g., the common cold).  
834 When VIBATIV is prescribed to treat a bacterial infection, patients should be told that  
835 although it is common to feel better early in the course of therapy, the medication should be  
836 taken exactly as directed. Skipping doses or not completing the full course of therapy may:  
837 (1) decrease the effectiveness of immediate treatment, and (2) increase the likelihood that  
838 the bacteria will develop resistance and will not be treatable by VIBATIV or other  
839 antibacterial drugs in the future.

840 Common Adverse Effects

841 Patients should be informed about the common adverse effects of VIBATIV including  
842 diarrhea, taste disturbance, nausea, vomiting, headache, and foamy urine. Patients should  
843 be instructed to inform their healthcare provider if they develop any unusual symptom, or if  
844 any known symptom persists or worsens. Patients should be instructed to inform their  
845 healthcare provider of any other medications they are currently taking with VIBATIV,  
846 including over-the-counter medications.

847 **Manufactured by:**

848 Theravance Biopharma Antibiotics, Inc.

849 **Marketed by:**

850 Theravance Biopharma US, Inc.

851 South San Francisco, CA 94080

852 US Patent Nos. 6,635,618 B2; 6,858,584 B2; 6,872,701 B2; 7,008,923 B2; 7,208,471 B2;  
853 7,351,691 B2; 7,531,623 B2; 7,544,364 B2; 7,700,550 B2; 8,101,575 B2; 8,158,580 B2.  
854 | THERAVANCE<sup>®</sup>, the Cross/Star logo, VIBATIV<sup>®</sup> and the VIBATIV<sup>®</sup> logo are registered  
855 | trademarks of the Theravance Biopharma group of companies.

**MEDICATION GUIDE**  
**VIBATIV® (vy-'ba-tiv)**  
**(telavancin)**  
**for injection**

Read this Medication Guide before you receive VIBATIV. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

**What is the most important information I should know about VIBATIV?**

**VIBATIV can cause serious side effects, including:**

- **Increased risk of death.** VIBATIV was associated with an increased risk of death compared to vancomycin in people who already had kidney problems and were treated for bacterial pneumonia that you can get when you are in the hospital.
- **New or worsening kidney problems.** Your healthcare provider should do a blood test to check your kidneys before you start, while you receive, and after you stop receiving VIBATIV.
- **VIBATIV may harm your unborn baby. Women who can become pregnant should have a blood pregnancy test before receiving VIBATIV.**
  - Talk to your healthcare provider if you are pregnant or plan to become pregnant. Your healthcare provider will decide if VIBATIV is the right medicine for you.
  - Women who can become pregnant should use effective birth control (contraception) while receiving VIBATIV.
  - If you become pregnant while receiving VIBATIV, tell your healthcare provider right away. Talk to your healthcare provider about taking part in the VIBATIV Pregnancy Registry. This is a study to learn how VIBATIV affects pregnancy and babies. You can enroll in this registry by calling 1-855-633-8479.

**What is VIBATIV?**

VIBATIV is a prescription antibacterial medicine used alone, or with other medicines, to treat adults with certain types of germs (bacteria) that cause:

- Serious skin infections
- Hospital-Acquired Bacterial Pneumonia (HABP)
- Ventilator-Associated Bacterial Pneumonia (VABP)

It is not known if VIBATIV is safe or effective in children under 18 years of age.

## Who should not take VIBATIV?

### Do not take VIBATIV if you:

- are allergic to telavancin or any of the ingredients in VIBATIV. See the end of this Medication Guide for a complete list of ingredients in VIBATIV.

## What should I tell my healthcare provider before receiving VIBATIV?

Before you receive VIBATIV, tell your healthcare provider if you:

- have had a serious allergic reaction to VIBATIV or vancomycin
- have kidney problems
- have diabetes
- have or have had heart problems, including QTc prolongation or a family history of it
- have high blood pressure
- have any other medical conditions
- are breastfeeding or plan to breastfeed. It is not known if VIBATIV passes into breast milk. You and your healthcare provider should decide if you will breastfeed while receiving VIBATIV.

**Tell your healthcare provider about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. VIBATIV and other medicines can affect each other causing side effects.

Especially tell your healthcare provider if you take:

- a Non-Steroidal Anti-Inflammatory Drug (NSAID)
- certain blood pressure medicines called ACE Inhibitors or ARBs
- water pills (diuretics)
- a blood thinner
- medicine to control your heart rate or rhythm (antiarrhythmics)

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

## How will I receive VIBATIV?

- VIBATIV is given by your healthcare provider through a needle placed into your vein (IV infusion) slowly over 1 hour, 1 time each day, for 7 to 21 days.
- **Do not** stop receiving VIBATIV unless your healthcare provider tells you to, even if you feel better.
- Your healthcare provider will do blood tests before you start and while you receive VIBATIV.

## What are the possible side effects of VIBATIV?

### VIBATIV may cause serious side effects, including:

See “What is the most important information I should know about VIBATIV?”

- **Serious allergic reactions.** Allergic reactions can happen in people who take VIBATIV, even after only one dose. Stop taking VIBATIV and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:
  - hives
  - trouble breathing or swallowing
  - swelling of the lips, tongue, face
  - throat tightness, hoarseness
  - rapid heartbeat
  - faint
- **Infusion-related reactions.** People who receive VIBATIV too quickly can have a certain type of skin reaction called “Red-man Syndrome”. Signs and symptoms of Red-man Syndrome can include:
  - red color (flushing)
  - rash
  - itching
- **Problems with the electrical system of your heart (QTc prolongation).** Tell your healthcare provider right away if you have a change in your heartbeat such as a fast or irregular heartbeat or if you had a fainting episode.

Call your healthcare provider right away if you have any of the serious side effects listed above.

### The most common side effects of VIBATIV include:

- change in your sense of taste
- nausea
- vomiting
- foamy urine
- diarrhea

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all the possible side effects of VIBATIV. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### **How should I store VIBATIV?**

- Store VIBATIV in the original package
- Keep VIBATIV refrigerated between 35°F to 46°F (2°C to 8°C)
- Keep out of heat

Keep VIBATIV and all medicines out of the reach of children.

### **General Information about the safe and effective use of VIBATIV.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VIBATIV for a condition for which it is not prescribed.

This Medication Guide summarizes the most important information about VIBATIV. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about VIBATIV that is written for health professionals.

For more information, go to [www.vibativ.com](http://www.vibativ.com) or call 1-855-633-8479.

### **What are the ingredients in VIBATIV?**

**Active ingredient:** telavancin hydrochloride

**Inactive ingredients:** hydroxypropylbetadex, Ph. Eur (hydroxypropyl-beta-cyclodextrin), mannitol, sodium hydroxide and hydrochloric acid

This Medication Guide has been approved by the U.S. Food and Drug Administration

#### **Manufactured by:**

Theravance Biopharma Antibiotics, Inc.

#### **Marketed by:**

Theravance Biopharma US, Inc.

South San Francisco, CA 94080

VIBATIV® is a registered trademark of the Theravance Biopharma group of companies.

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