

**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.

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.

**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 (6/2013)

Indications and Usage (1/2013)

Dosage and Administration (1/2013)

Adverse Reactions (6/2013)

Contraindications (6/2013)

-----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)

-----DOSAGE FORMS AND STRENGTHS-----

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

-----CONTRAINDICATIONS-----

Known hypersensitivity to VIBATIV. (4, 5.5, 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. (5.5, 6.2)
- Infusion-related reactions: Administer VIBATIV over at least 60 minutes to minimize infusion-related reactions. (5.6)
- *Clostridium difficile*-associated disease: May range from mild diarrhea to fatal colitis. Evaluate if diarrhea occurs. (5.7)
- QTc prolongation: Avoid use in patients at risk. Use with caution in patients taking drugs known to prolong the QT interval. (5.9)
- Coagulation test interference: Telavancin interferes with some laboratory coagulation tests, including prothrombin time, international normalized ratio, and activated partial thromboplastin time. (5.10, 7.1)

-----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, Inc. at 1-855-MED-THRAX (1-855-633-8479) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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: 02/2014**

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1 **FULL PRESCRIBING INFORMATION**

2  
3 **WARNINGS**

- 4 ▪ **Patients with pre-existing moderate/severe renal impairment (CrCl  $\leq$  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  $\leq$  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

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 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 4 hours when stored at room

100   temperature or within 72 hours under refrigeration at 2 to 8°C (36 to 46°F). The diluted

101   (dosing) solution in the infusion bag should be used within 4 hours when stored at room

102   temperature or used within 72 hours when stored under refrigeration at 2 to 8°C (36 to

103   46°F). However, the total time in the vial plus the time in the infusion bag should not exceed

104   4 hours at room temperature and 72 hours under refrigeration at 2 to 8°C (36 to 46°F).

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

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

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

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

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

110   0.9% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP.

### 111   **3        DOSAGE FORMS AND STRENGTHS**

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

113   sterile, lyophilized powder.

114 **4 CONTRAINDICATIONS**

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

116 **5 WARNINGS AND PRECAUTIONS**

117 **5.1 Increased Mortality in Patients with HABP/VABP and Pre-existing Moderate to**  
118 **Severe Renal Impairment (CrCl ≤50 mL/min)**

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

128 **5.2 Decreased Clinical Response in Patients with cSSSI and Pre-existing**  
129 **Moderate/Severe Renal Impairment (CrCl ≤50 mL/min)**

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

135 Table 2: Clinical Cure by Pre-existing Renal Impairment – Clinically Evaluable  
136 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)

137

138 **5.3 Nephrotoxicity**

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

145 Monitor renal function (i.e., serum creatinine, creatinine clearance) in all patients receiving  
146 VIBATIV. Values should be obtained prior to initiation of treatment, during treatment (at  
147 48- to 72-hour intervals or more frequently, if clinically indicated), and at the end of therapy.  
148 If renal function decreases, the benefit of continuing VIBATIV versus discontinuing and  
149 initiating therapy with an alternative agent should be assessed [see *Dosage and*  
150 *Administration (2)*, *Adverse Reactions (6)*, and *Clinical Pharmacology (12.3)*].

151 In patients with renal dysfunction, accumulation of the solubilizer hydroxypropyl-beta-  
152 cyclodextrin can occur [see *Patients with Renal Impairment (8.6)* and *Clinical Pharmacology*  
153 *(12.3)*].

154 **5.4 Pregnant Women and Women of Childbearing Potential**

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

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

162 **5.5 Hypersensitivity Reactions**

163 Serious and sometimes fatal hypersensitivity reactions, including anaphylactic reactions,  
164 may occur after first or subsequent doses. Discontinue VIBATIV at first sign of skin rash, or  
165 any other sign of hypersensitivity. Telavancin is a semi-synthetic derivative of vancomycin; it  
166 is unknown if patients with hypersensitivity reactions to vancomycin will experience cross-

167 reactivity to telavancin. VIBATIV should be used with caution in patients with known  
168 hypersensitivity to vancomycin [see *Postmarketing Experience* (6.2)].

### 169 **5.6 Infusion-Related Reactions**

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

### 175 **5.7 *Clostridium difficile*-Associated Diarrhea**

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

180 *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hyper-  
181 toxin-producing strains of *C. difficile* cause increased morbidity and mortality, since these  
182 infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must  
183 be considered in all patients who present with diarrhea following antibiotic use. Careful  
184 medical history is necessary because CDAD has been reported to occur more than  
185 2 months after the administration of antibacterial agents.

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

### 190 **5.8 Development of Drug-Resistant Bacteria**

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

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

197 **5.9 QTc Prolongation**

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

204 **5.10 Coagulation Test Interference**

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

211 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

212

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

217 **6 ADVERSE REACTIONS**

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

- 219 • Nephrotoxicity [see *Warnings and Precautions* (5.3)]
  - 220 • Infusion-related reactions [see *Warnings and Precautions* (5.6)]
  - 221 • *Clostridium difficile*-associated diarrhea [see *Warnings and Precautions* (5.7)]
- 222 Because clinical trials are conducted under widely varying conditions, adverse reaction rates  
223 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical  
224 trials of another drug and may not reflect the rates observed in practice.

## 225 **6.1 Clinical Trials Experience**

### 226 ***Complicated Skin and Skin Structure Infections***

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

231 In the cSSSI clinical trials, <1% (8/929) patients who received VIBATIV died and <1%  
232 (8/938) patients treated with vancomycin died. Serious adverse events were reported in 7%  
233 (69/929) of patients treated with VIBATIV and most commonly included renal, respiratory, or  
234 cardiac events. Serious adverse events were reported in 5% (43/938) of vancomycin-treated  
235 patients, and most commonly included cardiac, respiratory, or infectious events. Treatment  
236 discontinuations due to adverse events occurred in 8% (72/929) of patients treated with  
237 VIBATIV, the most common events being nausea and rash (~1% each). Treatment  
238 discontinuations due to adverse events occurred in 6% (53/938) of vancomycin-treated  
239 patients, the most common events being rash and pruritus (~1% each).

240 The most common adverse events occurring in ≥10% of VIBATIV-treated patients observed  
241 in the VIBATIV Phase 3 cSSSI trials were taste disturbance, nausea, vomiting, and foamy  
242 urine.

243 Table 4 displays the incidence of treatment-emergent adverse drug reactions reported in  
244 ≥2% of patients treated with VIBATIV possibly related to the drug.

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

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

\* Described as a metallic or soapy taste.

247

248 **HABP/VABP**

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

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

258 Table 5: 28-Day Mortality (Kaplan-Meier Estimates) Stratified by Baseline Creatinine  
259 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)

260

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

267 Table 6 displays the incidence of treatment-emergent adverse drug reactions reported in  
268  $\geq$  5% of HABP/VABP patients treated with VIBATIV possibly related to the drug.

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

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

272

### 273 **Nephrotoxicity**

#### 274 ***Complicated Skin and Skin Structure Infections***

275 In cSSSI trials, the incidence of renal adverse events indicative of renal impairment  
276 (increased serum creatinine, renal impairment, renal insufficiency, and/or renal failure) was  
277 30/929 (3%) of VIBATIV-treated patients compared with 10/938 (1%) of vancomycin-treated  
278 patients. In 17 of the 30 VIBATIV-treated patients, these adverse events had not completely  
279 resolved by the end of the trials, compared with 6 of the 10 vancomycin-treated patients.  
280 Serious adverse events indicative of renal impairment occurred in 11/929 (1%) of VIBATIV-  
281 treated patients compared with 3/938 (0.3%) of vancomycin-treated patients. Twelve  
282 patients treated with VIBATIV discontinued treatment due to adverse events indicative of  
283 renal impairment compared with 2 patients treated with vancomycin.

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

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

#### 290 ***Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia***

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

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

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

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

## 304 **6.2 Postmarketing Experience**

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

309 Serious hypersensitivity reactions have been reported after first or subsequent doses of  
310 VIBATIV, including anaphylactic reactions. It is unknown if patients with hypersensitivity  
311 reactions to vancomycin will experience cross-reactivity to telavancin. [see *Hypersensitivity*  
312 *Reactions (5.5)*].

## 313 **7 DRUG INTERACTIONS**

### 314 **7.1 Drug-Laboratory Test Interactions**

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

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

323

324 Urine Protein Tests

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

328 **8 USE IN SPECIFIC POPULATIONS**

329 **8.1 Pregnancy**

330 Teratogenic Effects: Pregnancy Category C

331 *Pregnancy Exposure Registry*

332 There is a pregnancy registry that monitors pregnancy outcomes in women exposed to  
333 VIBATIV during pregnancy. Physicians are encouraged to register pregnant patients, or  
334 pregnant women may enroll themselves in the VIBATIV pregnancy registry by calling 1-855-  
335 MED-THRX (1-855-633-8479).

336 *Fetal Risk Summary*

337 All pregnancies have a background risk of birth defects (about 3%), pregnancy loss (about  
338 15%), or other adverse outcomes regardless of drug exposure.

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

343 *Clinical Considerations*

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

347 *Data*

348 Human Data

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

350

351

352 Animal Data

353 In embryo-fetal development studies in rats, rabbits, and minipigs, telavancin demonstrated  
354 the potential to cause limb and skeletal malformations when given intravenously during the  
355 period of organogenesis at doses up to 150, 45, or 75 mg/kg/day, respectively. These doses  
356 resulted in exposure levels approximately 1- to 2-fold the human exposure (AUC) at the  
357 maximum clinical recommended dose. Malformations observed at <1% (but absent or at  
358 lower rates in historical or concurrent controls), included brachymelia (rats and rabbits),  
359 syndactyly (rats, minipigs), adactyly (rabbits), and polydactyly (minipigs). Additional findings  
360 in rabbits included flexed front paw and absent ulna, and in the minipigs included misshapen  
361 digits and deformed front leg. Fetal body weights were decreased in rats.

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

367 **8.3 Nursing Mothers**

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

371 **8.4 Pediatric Use**

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

373 **8.5 Geriatric Use**

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

382 Of the 749 HABP/VABP patients treated with VIBATIV at a dose of 10 mg/kg once daily in  
383 clinical trials of HABP/VABP, 397 (53%) were  $\geq 65$  years of age and 230 (31%) were  
384  $\geq 75$  years of age. Treatment-emergent adverse events as well as deaths and other serious  
385 adverse events occurred more often in patients  $\geq 65$  years of age than in those  $< 65$  years of  
386 age in both treatment groups.

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

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

### 393 **8.6 Patients with Renal Impairment**

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

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

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

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

410 Hydroxypropyl-beta-cyclodextrin is excreted in urine and may accumulate in patients with  
411 renal impairment. Serum creatinine should be closely monitored and, if renal toxicity is

412 suspected, an alternative agent should be considered [see *Warnings and Precautions (5.3)*,  
413 *Clinical Pharmacology (12.3)*].

#### 414 **8.7 Patients with Hepatic Impairment**

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

### 418 **10 OVERDOSAGE**

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

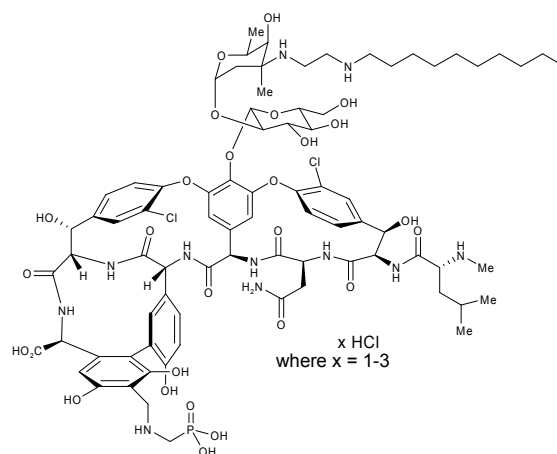
425 The clearance of telavancin by continuous venovenous hemofiltration (CVVH) was  
426 evaluated in an *in vitro* study [see *Nonclinical Toxicology (13.2)*]. Telavancin was cleared by  
427 CVVH and the clearance of telavancin increased with increasing ultrafiltration rate.  
428 However, the clearance of telavancin by CVVH has not been evaluated in a clinical study;  
429 thus, the clinical significance of this finding and use of CVVH to treat an overdosage is  
430 unknown.

### 431 **11 DESCRIPTION**

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

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

437 Figure 1: Telavancin Hydrochloride



438

Telavancin hydrochloride

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

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

## 449 12 CLINICAL PHARMACOLOGY

### 450 12.1 Mechanism of Action

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

### 452 12.2 Pharmacodynamics

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

457 Cardiac Electrophysiology

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

467 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)

468 <sup>1</sup> Fridericia corrected

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

470

471 ECGs were performed prior to and during the treatment period in patients receiving VIBATIV  
472 10 mg/kg in 3 cSSSI studies to monitor QTc intervals. In these trials, 214 of 1029 (21%)  
473 patients allocated to treatment with VIBATIV and 164 of 1033 (16%) allocated to  
474 vancomycin received concomitant medications known to prolong the QTc interval and  
475 known to be associated with definite or possible risk of torsades de pointes. The incidence  
476 of QTc prolongation >60 msec was 1.5% (15 patients) in the VIBATIV group and 0.6%  
477 (6 patients) in the vancomycin group. Nine of the 15 VIBATIV patients received concomitant  
478 medications known to prolong the QTc interval and definitely or possibly associated with a  
479 risk of torsades de pointes, compared with 1 of the 6 patients who received vancomycin. A  
480 similar number of patients in each treatment group (<1%) who did not receive a concomitant  
481 medication known to prolong the QTc interval experienced a prolongation >60 msec from  
482 baseline. In a separate analysis, 1 patient in the VIBATIV group and 2 patients in the  
483 vancomycin group experienced QTc >500 msec. No cardiac adverse events were ascribed

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

487 **12.3 Pharmacokinetics**

488 The mean pharmacokinetic parameters of telavancin (10 mg/kg) after a single and multiple  
489 60-minute intravenous infusions (10 mg/kg every 24 hours) are summarized in Table 8.

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

	<b>Single Dose (n=42)</b>	<b>Multiple Dose (n=36)</b>
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

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

495

496 Distribution

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

500 Concentrations of telavancin in pulmonary epithelial lining fluid (ELF) and alveolar  
501 macrophages (AM) were measured through collection of bronchoalveolar lavage fluid at

502 various times following administration of VIBATIV 10 mg/kg once daily for 3 days to healthy  
503 adults. Telavancin concentrations in ELF and AM exceeded the MIC<sub>90</sub> for *S. aureus*  
504 (0.5 mcg/mL) for at least 24 hours following dosing.

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

#### 507 Metabolism

508 No metabolites of telavancin were detected in *in vitro* studies using human liver microsomes,  
509 liver slices, hepatocytes, and kidney S9 fraction. None of the following recombinant CYP  
510 450 isoforms were shown to metabolize telavancin in human liver microsomes: CYP 1A2,  
511 2C9, 2C19, 2D6, 3A4, 3A5, 4A11. The clearance of telavancin is not expected to be altered  
512 by inhibitors of any of these enzymes.

513 In a mass balance study in male subjects using radiolabeled telavancin, 3 hydroxylated  
514 metabolites were identified with the predominant metabolite (THRX-651540) accounting for  
515 <10% of the radioactivity in urine and <2% of the radioactivity in plasma. The metabolic  
516 pathway for telavancin has not been identified.

#### 517 Excretion

518 Telavancin is primarily eliminated by the kidney. In a mass balance study, approximately  
519 76% of the administered dose was recovered from urine and <1% of the dose was  
520 recovered from feces (collected up to 216 hours) based on total radioactivity.

#### 521 Specific Populations

##### 522 *Geriatric Patients*

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

527

528

529 *Pediatric Patients*

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

532 *Gender*

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

536 *Renal Impairment*

537 The pharmacokinetics of telavancin were evaluated in subjects with normal renal function  
538 and subjects with varying degrees of renal impairment following administration of a single  
539 dose of telavancin 7.5 mg/kg (n=28). The mean  $AUC_{0-\infty}$  values were approximately 13%,  
540 29%, and 118% higher for subjects with CrCl >50 to 80 mL/min, CrCl 30 to 50 mL/min, and  
541 CrCl <30 mL/min, respectively, compared with subjects with normal renal function. Dosage  
542 adjustment is required in patients with CrCl ≤50 mL/min [see *Dosage and Administration*  
543 (2)].

544 Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault  
545 formula:

546

$$547 \quad CrCl = \frac{[140 - \text{age (years)}] \times \text{ideal body weight (kg)}^* \{ \times 0.85 \text{ for female patients} \}}{548 \quad [72 \times \text{serum creatinine (mg/dL)}]}$$

549 \*Use actual body weight if < ideal body weight (IBW)  
550 IBW (male) = 50 kg + 0.9 kg/cm over 152 cm height  
551 IBW (female) = 45.5 kg + 0.9 kg/cm over 152 cm height

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

556 Following a single intravenous dose of VIBATIV 7.5 mg/kg, the clearance of hydroxypropyl-  
557 beta-cyclodextrin was reduced in subjects with renal impairment, resulting in a higher  
558 exposure to hydroxypropyl-beta-cyclodextrin. In subjects with mild, moderate, and severe  
559 renal impairment, the mean clearance values were 38%, 59%, and 82% lower, respectively,  
560 compared with subjects with normal renal function. Multiple infusions of VIBATIV may result  
561 in accumulation of hydroxypropyl-beta-cyclodextrin.

#### 562 *Hepatic Impairment*

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

#### 567 Drug Interactions

##### 568 *In Vitro*

569 The inhibitory activity of telavancin against the following CYP 450 enzymes was evaluated in  
570 human liver microsomes: CYP 1A2, 2C9, 2C19, 2D6, and 3A4/5. Telavancin inhibited CYP  
571 3A4/5 at potentially clinically relevant concentrations. Upon further evaluation in a Phase 1  
572 clinical trial, telavancin was found not to inhibit the metabolism of midazolam, a sensitive  
573 CYP3A substrate (see below).

##### 574 *Midazolam*

575 The impact of telavancin on the pharmacokinetics of midazolam (CYP 3A4/5 substrate) was  
576 evaluated in 16 healthy adult subjects following administration of a single dose of VIBATIV  
577 10 mg/kg, intravenous midazolam 1 mg, and both. The results showed that telavancin had  
578 no impact on the pharmacokinetics of midazolam and midazolam had no effect on the  
579 pharmacokinetics of telavancin.

##### 580 *Aztreonam*

581 The impact of telavancin on the pharmacokinetics of aztreonam was evaluated in 11 healthy  
582 adult subjects following administration of a single dose of VIBATIV 10 mg/kg, aztreonam  
583 2 g, and both. Telavancin had no impact on the pharmacokinetics of aztreonam and

584 aztreonam had no effect on the pharmacokinetics of telavancin. No dosage adjustment of  
585 telavancin or aztreonam is recommended when both drugs are coadministered.

#### 586 *Piperacillin-tazobactam*

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

### 593 **12.4 Microbiology**

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

#### 600 Mechanism of Action

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

#### 604 Interactions with Other Antibacterial Drugs

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

610

611

612 Cross-Resistance

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

615 Antibacterial Activity

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

619 Facultative Gram-Positive Microorganisms

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

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

631 Facultative Gram-Positive Microorganisms

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

637 Susceptibility Test Methods

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

643 *Dilution technique*

644 Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations  
645 (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial  
646 compounds. The MICs should be determined using a standardized procedure [see  
647 *References (15)*]. Standardized procedures are based on a broth dilution method or  
648 equivalent with standardized inoculum concentrations and standardized concentrations of  
649 telavancin powder. The test method treats telavancin as a water-insoluble agent. Dimethyl  
650 sulfoxide is used as solvent and diluent, and the cation-adjusted Mueller Hinton Broth test  
651 medium is supplemented with polysorbate 80 to a final concentration of 0.002%. Telavancin  
652 should not be tested by the agar dilution method. The MIC values should be interpreted  
653 according to the criteria provided in Table 9.

654 *Diffusion technique*

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

661 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 group</i>	≤ 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.

662

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

666 *Quality Control*

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

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

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

	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration (mcg/mL)	Disk Diffusion Zone Diameter (mm)
<i>Enterococcus faecalis</i> ATCC 29212	-0. 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*

676

677 **13 NONCLINICAL TOXICOLOGY**

678 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

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

690 **13.2 Animal Toxicology and/or Pharmacology**

691 Two-week administration of telavancin in rats produced minimal renal tubular vacuolization  
692 with no changes in BUN or creatinine. These effects were not seen in studies conducted in

693 dogs for similar duration. Four weeks of treatment resulted in reversible elevations in BUN  
694 and/or creatinine in association with renal tubular degeneration that further progressed  
695 following 13 weeks of treatment.

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

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

## 702 **14 CLINICAL TRIALS**

### 703 **14.1 Complicated Skin and Skin Structure Infections**

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

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

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

719 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

720

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

724 Table 12: Clinical Cure at Test-of-Cure in cSSSI Trials 1 and 2 – ATe and CE  
725 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%	71.6%	0.9 (-5.3, 7.2)	74.7%	74.0%	0.7 (-5.1, 6.5)
	(309/426)	(307/429)		(342/458)	(356/481)	
<b>CE</b>	84.3%	82.8%	1.5 (-4.3, 7.3)	83.9%	87.7%	-3.8 (-9.2, 1.5)
	(289/343)	(288/348)		(302/360)	(315/359)	

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

727

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

730 Table 13: Clinical Cure Rates at the Test-of-Cure for the Most Common Pathogens in  
731 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).

732

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

743 **14.2 HABP/VABP**

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

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

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

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

768 Table 14: All-Cause Mortality at Day 28 in Patients with at least One Baseline Gram-  
769 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)	

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

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

781 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%)	

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

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

784

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798  
799 **16 HOW SUPPLIED/STORAGE AND HANDLING**

- 800 • Cartons of 10 individually packaged 250 mg single-dose vials (NDC 52118-002-01)
- 801 • Cartons of 10 individually packaged 750 mg single-dose vials (NDC 52118-001-01)
- 802 Store original packages at refrigerated temperatures of 2 to 8°C (35 to 46 °F). Excursions to  
803 ambient temperatures (up to 25 °C (77 °F)) are acceptable. Avoid excessive heat.

804 **17 PATIENT COUNSELING INFORMATION**

805 *See Medication Guide.*

806 Use During Pregnancy and By Women of Childbearing Potential

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

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