

**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

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)
- 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)
- 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)
- 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](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

**WARNING: INCREASED MORTALITY IN HABP/VABP PATIENTS WITH PRE-EXISTING MODERATE OR SEVERE RENAL IMPAIRMENT, NEPHROTOXICITY, POTENTIAL ADVERSE DEVELOPMENTAL OUTCOMES**

See full prescribing information for the complete boxed warning

- 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 (HABP/VABP) 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 three animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans. (8.1)

**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)

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.

**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)

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1 FULL PRESCRIBING INFORMATION

2  
3 **WARNING: INCREASED MORTALITY IN HABP/VABP PATIENTS WITH PRE-EXISTING**  
4 **MODERATE OR SEVERE RENAL IMPAIRMENT, NEPHROTOXICITY, POTENTIAL**  
5 **ADVERSE DEVELOPMENTAL OUTCOMES**

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

24  
25 **1 INDICATIONS AND USAGE**

26 **1.1 Complicated Skin and Skin Structure Infections**

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

33 **1.2 HABP/VABP**

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

38 **1.3 USAGE**

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

41 Appropriate specimens for bacteriological examination should be obtained in order to isolate  
42 and identify the causative pathogens and to determine their susceptibility to telavancin.

43 VIBATIV may be initiated as empiric therapy before results of these tests are known.

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

50 **2 DOSAGE AND ADMINISTRATION**

51 **2.1 Complicated Skin and Skin Structure Infections**

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

56 **2.2 Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial**  
57 **Pneumonia (HABP/VABP)**

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

62 **2.3 Patients with Renal Impairment**

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

66 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)

67

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

71 **2.4 Preparation and Administration**

72 250 mg vial: Reconstitute the contents of a VIBATIV 250 mg vial with **15** mL of 5% Dextrose  
73 Injection, USP; Sterile Water for Injection, USP; or 0.9% Sodium Chloride Injection, USP.

74 The resultant solution has a concentration of 15 mg/mL (total volume of approximately  
75 17.0 mL).

76 750 mg vial: Reconstitute the contents of a VIBATIV 750 mg vial with **45** mL of 5% Dextrose  
77 Injection, USP; Sterile Water for Injection, USP; or 0.9% Sodium Chloride Injection, USP.

78 The resultant solution has a concentration of 15 mg/mL (total volume of approximately  
79 50.0 mL).

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

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

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

86

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

88

89

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

96    Reconstitution time is generally under 2 minutes, but can sometimes take up to 20 minutes.  
97    Mix thoroughly to reconstitute and check to see if the contents have dissolved completely.  
98    Parenteral drug products should be inspected visually for particulate matter prior to  
99    administration. Discard the vial if the vacuum did not pull the diluent into the vial.

100    Since no preservative or bacteriostatic agent is present in this product, aseptic technique  
101    must be used in preparing the final intravenous solution. Studies have shown that the  
102    reconstituted solution in the vial should be used within 12 hours when stored at room  
103    temperature or within 7 days under refrigeration at 2 to 8°C (36 to 46°F). The diluted  
104    (dosing) solution in the infusion bag should be used within 12 hours when stored at room  
105    temperature or used within 7 days when stored under refrigeration at 2 to 8°C (36 to 46°F).  
106    However, the total time in the vial plus the time in the infusion bag should not exceed  
107    12 hours at room temperature and 7 days under refrigeration at 2 to 8°C (36 to 46°F). The  
108    diluted (dosing) solution in the infusion bag can also be stored at -30 to -10°C (-22 to 14°F)  
109    for up to 32 days.

110    VIBATIV is administered intravenously. Because only limited data are available on the  
111    compatibility of VIBATIV with other IV substances, additives or other medications should not  
112    be added to VIBATIV single-use vials or infused simultaneously through the same IV line. If  
113    the same intravenous line is used for sequential infusion of additional medications, the line  
114    should be flushed before and after infusion of VIBATIV with 5% Dextrose Injection, USP;  
115    0.9% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP.

### 116    **3            DOSAGE FORMS AND STRENGTHS**

117    VIBATIV is supplied in single-use vials containing either 250 or 750 mg telavancin as a  
118    sterile, lyophilized powder.

119 **4 CONTRAINDICATIONS**

120 **4.1 Intravenous Unfractionated Heparin Sodium**

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

125 **4.2 Known Hypersensitivity to VIBATIV**

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

127 **5 WARNINGS AND PRECAUTIONS**

128 **5.1 Increased Mortality in Patients with HABP/VABP and Pre-existing Moderate to**  
129 **Severe Renal Impairment (CrCl  $\leq$ 50 mL/min)**

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

139 **5.2 Decreased Clinical Response in Patients with cSSSI and Pre-existing**  
140 **Moderate/Severe Renal Impairment (CrCl  $\leq$ 50 mL/min)**

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

146 Table 2: Clinical Cure by Pre-existing Renal Impairment – Clinically Evaluable  
147 Population

	VIBATIV % (n/N)	Vancomycin % (n/N)
<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)

148

### 149 **5.3 Nephrotoxicity**

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

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

162 In patients with renal dysfunction, accumulation of the solubilizer hydroxypropyl-beta-  
163 cyclodextrin can occur [see *Patients with Renal Impairment (8.6) and Clinical Pharmacology*  
164 *(12.3)*].

### 165 **5.4 Pregnant Women and Women of Childbearing Potential**

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

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

### 173 **5.5 Coagulation Test Interference**

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

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

183 Table 3: Coagulation Tests Affected and Unaffected by Telavancin

Affected by Telavancin	Unaffected by Telavancin
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

184

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

### 189 **5.6 Hypersensitivity Reactions**

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

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

### 196 **5.7 Infusion-related Reactions**

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

### 202 **5.8 Clostridium difficile-Associated Diarrhea**

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

207 *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hyper-  
208 toxin-producing strains of *C. difficile* cause increased morbidity and mortality, since these  
209 infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must  
210 be considered in all patients who present with diarrhea following antibiotic use. Careful  
211 medical history is necessary because CDAD has been reported to occur more than  
212 2 months after the administration of antibacterial agents.

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

### 217 **5.9 Development of Drug-Resistant Bacteria**

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

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

#### 224 **5.10 QTc Prolongation**

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

### 231 **6 ADVERSE REACTIONS**

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

- 233 • Nephrotoxicity [see *Warnings and Precautions* (5.3)]
- 234 • Infusion-related reactions [see *Warnings and Precautions* (5.7)]
- 235 • *Clostridium difficile*-associated diarrhea [see *Warnings and Precautions* (5.8)]

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

#### 239 **6.1 Clinical Trials Experience**

##### 240 ***Complicated Skin and Skin Structure Infections***

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

245 In the cSSSI clinical trials, <1% (8/929) patients who received VIBATIV died and <1%  
246 (8/938) patients treated with vancomycin died. Serious adverse events were reported in 7%  
247 (69/929) of patients treated with VIBATIV and most commonly included renal, respiratory, or  
248 cardiac events. Serious adverse events were reported in 5% (43/938) of vancomycin-treated  
249 patients, and most commonly included cardiac, respiratory, or infectious events. Treatment

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

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

257 Table 4 displays the incidence of treatment-emergent adverse drug reactions reported in  
258 ≥2% of patients treated with VIBATIV possibly related to the drug.

259 Table 4: Incidence of Treatment-Emergent Adverse Drug Reactions Reported in ≥2%  
260 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.

261 **HABP/VABP**

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

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

271 Table 5: 28-Day Mortality (Kaplan-Meier Estimates) Stratified by Baseline Creatinine  
272 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)

273

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

280 Table 6 displays the incidence of treatment-emergent adverse drug reactions reported in  
281 ≥ 5% of HABP/VABP patients treated with VIBATIV possibly related to the drug.

282 Table 6: Incidence of Treatment-Emergent Adverse Drug Reactions Reported in  $\geq 5\%$   
283 of VIBATIV or Vancomycin Patients Treated in HAPB/VABP Trial 1 and  
284 Trial 2

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

285

## 286 **Nephrotoxicity**

### 287 ***Complicated Skin and Skin Structure Infections***

288 In cSSSI trials, the incidence of renal adverse events indicative of renal impairment  
289 (increased serum creatinine, renal impairment, renal insufficiency, and/or renal failure) was  
290 30/929 (3%) of VIBATIV-treated patients compared with 10/938 (1%) of vancomycin-treated  
291 patients. In 17 of the 30 VIBATIV-treated patients, these adverse events had not completely  
292 resolved by the end of the trials, compared with 6 of the 10 vancomycin-treated patients.  
293 Serious adverse events indicative of renal impairment occurred in 11/929 (1%) of VIBATIV-  
294 treated patients compared with 3/938 (0.3%) of vancomycin-treated patients. Twelve  
295 patients treated with VIBATIV discontinued treatment due to adverse events indicative of  
296 renal impairment compared with 2 patients treated with vancomycin.

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

300 Fifteen of 174 (9%) VIBATIV-treated patients  $\geq 65$  years of age had adverse events  
301 indicative of renal impairment compared with 16 of 755 patients (2%)  $< 65$  years of age [see  
302 *Use in Specific Populations (8.5)*].

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

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

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

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

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

## 317 **6.2 Postmarketing Experience**

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

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

## 326 **7 DRUG INTERACTIONS**

### 327 **7.1 Drug-Laboratory Test Interactions**

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

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

#### 336 Urine Protein Tests

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

## 340 **8 USE IN SPECIFIC POPULATIONS**

### 341 **8.1 Pregnancy**

#### 342 Teratogenic Effects: Pregnancy Category C

##### 343 *Pregnancy Exposure Registry*

344 There is a pregnancy registry that monitors pregnancy outcomes in women exposed to  
345 VIBATIV during pregnancy. Physicians are encouraged to register pregnant patients, or  
346 pregnant women may enroll themselves in the VIBATIV pregnancy registry by calling 1-855-  
347 633-8479.

##### 348 *Fetal Risk Summary*

349 All pregnancies have a background risk of birth defects (about 3%), pregnancy loss (about  
350 15%), or other adverse outcomes regardless of drug exposure.

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

##### 355 *Clinical Considerations*

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

##### 359 *Data*

###### 360 Human Data

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

###### 362 Animal Data

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

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

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

### 377 **8.3 Nursing Mothers**

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

### 381 **8.4 Pediatric Use**

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

### 383 **8.5 Geriatric Use**

384 Of the 929 patients treated with VIBATIV at a dose of 10 mg/kg once daily in clinical trials of  
385 cSSSI, 174 (19%) were ≥65 years of age and 87 (9%) were ≥75 years of age. In the cSSSI  
386 trials, lower clinical cure rates were observed in patients ≥65 years of age compared with  
387 those <65 years of age. Overall, treatment-emergent adverse events occurred with similar  
388 frequencies in patients ≥65 (75% of patients) and <65 years of age (83% of patients).

389 Fifteen of 174 (9%) patients ≥65 years of age treated with VIBATIV had adverse events  
390 indicative of renal impairment compared with 16 of 755 (2%) patients <65 years of age [see  
391 *Warnings and Precautions (5.3), Clinical Trials (14.1)*].

392 Of the 749 HABP/VABP patients treated with VIBATIV at a dose of 10 mg/kg once daily in  
393 clinical trials of HABP/VABP, 397 (53%) were ≥65 years of age and 230 (31%) were  
394 ≥75 years of age. Treatment-emergent adverse events as well as deaths and other serious

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

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

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

#### 403 **8.6 Patients with Renal Impairment**

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

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

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

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

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

424 **8.7 Patients with Hepatic Impairment**

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

428 **10 OVERDOSAGE**

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

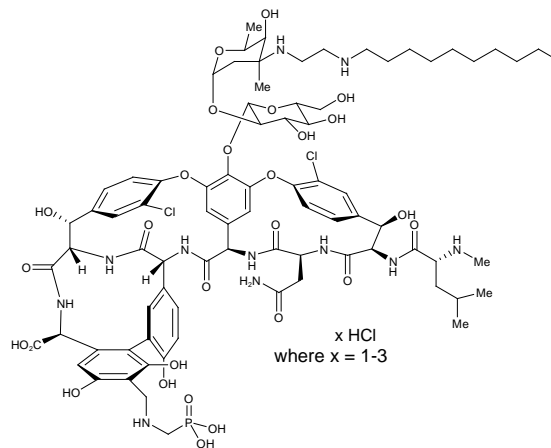
435 The clearance of telavancin by continuous venovenous hemofiltration (CVVH) was  
436 evaluated in an *in vitro* study [see *Nonclinical Toxicology* (13.2)]. Telavancin was cleared by  
437 CVVH and the clearance of telavancin increased with increasing ultrafiltration rate.  
438 However, the clearance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

441 **11 DESCRIPTION**

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

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

447 Figure 1: Telavancin Hydrochloride



448

Telavancin hydrochloride

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

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

## 459 12 CLINICAL PHARMACOLOGY

### 460 12.1 Mechanism of Action

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

### 462 12.2 Pharmacodynamics

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

467 Cardiac Electrophysiology

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

477 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)

478 <sup>1</sup> Fridericia corrected

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

480

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

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

497 **12.3 Pharmacokinetics**

498 The mean pharmacokinetic parameters of telavancin (10 mg/kg) after a single and multiple  
499 60-minute intravenous infusions (10 mg/kg every 24 hours) are summarized in Table 8.

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

	<b>Single Dose (n=42)</b>	<b>Multiple Dose (n=36)</b>
$C_{max}$ (mcg/mL)	93.6 ± 14.2	108 ± 26
$AUC_{0-\infty}$ (mcg·hr/mL)	747 ± 129	-- <sup>1</sup>
$AUC_{0-24h}$ (mcg·hr/mL)	666 ± 107	780 ± 125
$t_{1/2}$ (hr)	8.0 ± 1.5	8.1 ± 1.5
Cl (mL/hr/kg)	13.9 ± 2.9	13.1 ± 2.0
$V_{ss}$ (mL/kg)	145 ± 23	133 ± 24

$C_{max}$  maximum plasma concentration

AUC area under concentration-time course

$t_{1/2}$  terminal elimination half-life

Cl clearance

$V_{ss}$  apparent volume of distribution at steady state

<sup>1</sup> Data not available

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

505 Distribution

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

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

512 adults. Telavancin concentrations in ELF and AM exceeded the MIC<sub>90</sub> for *S. aureus*  
513 (0.5 mcg/mL) for at least 24 hours following dosing.

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

#### 516 Metabolism

517 No metabolites of telavancin were detected in *in vitro* studies using human liver microsomes,  
518 liver slices, hepatocytes, and kidney S9 fraction. None of the following recombinant CYP  
519 450 isoforms were shown to metabolize telavancin in human liver microsomes: CYP 1A2,  
520 2C9, 2C19, 2D6, 3A4, 3A5, 4A11. The clearance of telavancin is not expected to be altered  
521 by inhibitors of any of these enzymes.

522 In a mass balance study in male subjects using radiolabeled telavancin, 3 hydroxylated  
523 metabolites were identified with the predominant metabolite (THR-651540) accounting for  
524 <10% of the radioactivity in urine and <2% of the radioactivity in plasma. The metabolic  
525 pathway for telavancin has not been identified.

#### 526 Excretion

527 Telavancin is primarily eliminated by the kidney. In a mass balance study, approximately  
528 76% of the administered dose was recovered from urine and <1% of the dose was  
529 recovered from feces (collected up to 216 hours) based on total radioactivity.

#### 530 Specific Populations

##### 531 *Geriatric Patients*

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

##### 536 *Pediatric Patients*

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

539 *Gender*

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

543 *Renal Impairment*

544 The pharmacokinetics of telavancin were evaluated in subjects with normal renal function  
545 and subjects with varying degrees of renal impairment following administration of a single  
546 dose of telavancin 7.5 mg/kg (n=28). The mean AUC<sub>0-∞</sub> values were approximately 13%,  
547 29%, and 118% higher for subjects with CrCl >50 to 80 mL/min, CrCl 30 to 50 mL/min, and  
548 CrCl <30 mL/min, respectively, compared with subjects with normal renal function. Dosage  
549 adjustment is required in patients with CrCl ≤50 mL/min [see *Dosage and Administration*  
550 (2)].

551 Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault  
552 formula:

553 
$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{ideal body weight (kg)}^* \{ \times 0.85 \text{ for female patients} \}}{[72 \times \text{serum creatinine (mg/dL)}]}$$
  
554

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

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

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

568 *Hepatic Impairment*

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

573 Drug Interactions

574 *In Vitro*

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

580 *Midazolam*

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

586 *Aztreonam*

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

592 *Piperacillin-tazobactam*

593 The impact of telavancin on the pharmacokinetics of piperacillin-tazobactam was evaluated  
594 in 12 healthy adult subjects following administration of a single dose of VIBATIV 10 mg/kg,  
595 piperacillin-tazobactam 4.5 g, and both. Telavancin had no impact on the pharmacokinetics

596 of piperacillin-tazobactam and piperacillin-tazobactam had no effect on the  
597 pharmacokinetics of telavancin. No dosage adjustment of telavancin or piperacillin-  
598 tazobactam is recommended when both drugs are coadministered.

## 599 **12.4 Microbiology**

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

### 606 Mechanism of Action

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

### 610 Interactions with Other Antibacterial Drugs

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

### 616 Cross-Resistance

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

### 619 Antibacterial Activity

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

#### 623 Gram-Positive Bacteria

624 *Staphylococcus aureus* (including methicillin-resistant isolates)  
625 *Enterococcus faecalis* (vancomycin-susceptible isolates only)  
626 *Streptococcus agalactiae*  
627 *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and  
628 *S. constellatus*)  
629 *Streptococcus pyogenes*  
630

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

635 Gram-Positive Bacteria

636 *Enterococcus faecium* (vancomycin-susceptible isolates only)  
637 *Staphylococcus haemolyticus*  
638 *Streptococcus dysgalactiae* subsp. *equisimilis*  
639 *Staphylococcus epidermidis*  
640

641 Susceptibility Test Methods

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

647 *Dilution technique*

648 Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations  
649 (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial  
650 compounds. The MICs should be determined using a standardized test method<sup>1, 2</sup>. The test  
651 method treats telavancin as a water-insoluble agent. Dimethyl sulfoxide is used as solvent  
652 and diluent, and the cation-adjusted Mueller Hinton Broth test medium is supplemented with  
653 polysorbate 80 to a final concentration of 0.002%. Telavancin should not be tested by the  
654 agar dilution method. The MIC values should be interpreted according to the criteria  
655 provided in Table 9.

656 Table 9: Susceptibility Test Interpretive Criteria for Telavancin

Pathogen	Minimum Inhibitory Concentration (mcg/mL)		
	S	I	R
<i>Staphylococcus aureus</i> (including methicillin-resistant isolates)	≤ 0.12	--	--
<i>Streptococcus pyogenes</i> <i>Streptococcus agalactiae</i>	≤ 0.12	--	--
<i>Streptococcus anginosus</i> group	≤ 0.06		
<i>Enterococcus faecalis</i> (vancomycin-susceptible isolates only)	≤ 0.25	--	--

657 A report of *Susceptible* (S) indicates that the antimicrobial is likely to inhibit growth of the  
 658 pathogen if the antimicrobial compound reaches the concentrations usually achievable at  
 659 the site of infection.

660 *Quality Control*

661 Standardized susceptibility test procedures require the use of laboratory control  
 662 microorganisms to monitor the accuracy and precision of supplies and reagents used in the  
 663 assay, and the techniques of the individuals performing the test <sup>1,2</sup>. Standard telavancin  
 664 powder should provide the range of MIC values noted in Table 10.

665 Table 10: Acceptable Quality Control Ranges for Telavancin

QC Strain	Minimum Inhibitory Concentration (mcg/mL)
<i>Enterococcus faecalis</i> ATCC 29212	0.03 – 0.12
<i>Staphylococcus aureus</i> ATCC 29213	0.03 - 0.12
<i>Streptococcus pneumoniae</i> ATCC 49619	0.004 – 0.015

666

667 **13 NONCLINICAL TOXICOLOGY**

668 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

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

## 680 **13.2 Animal Toxicology and/or Pharmacology**

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

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

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

## 692 **14 CLINICAL TRIALS**

### 693 **14.1 Complicated Skin and Skin Structure Infections**

694 Adult patients with clinically documented complicated skin and skin structure infections  
695 (cSSSI) were enrolled in two randomized, multinational, multicenter, double-blinded trials  
696 (Trial 1 and Trial 2) comparing VIBATIV (10 mg/kg IV every 24 hours) with vancomycin (1 g  
697 IV every 12 hours) for 7 to 14 days. Vancomycin dosages could be adjusted per site-specific  
698 practice. Patients could receive concomitant aztreonam or metronidazole for suspected

699 Gram-negative and anaerobic infection, respectively. These trials were identical in design,  
700 enrolling approximately 69% of their patients from the United States.

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

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

709 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

710

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

714 Table 12: Clinical Cure at Test-of-Cure in cSSSI Trials 1 and 2 – ATe and CE  
715 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)

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

717

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

720 Table 13: Clinical Cure Rates at the Test-of-Cure for the Most Common Pathogens in  
721 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).

722

723 Of the 1784 patients in the ATe population in the two cSSSI trials, 32 patients had baseline  
724 *S. aureus* bacteremia: 21 patients (2.4%, including 13 with MRSA) were treated with  
725 VIBATIV and 11 patients (1.2%, including 4 with MRSA) were treated with vancomycin. In  
726 these bacteremic patients, the clinical cure rate at Test-of-Cure was 57.1% (12/21) for the  
727 VIBATIV-treated patients and 54.6% (6/11) for the vancomycin-treated patients. Given the  
728 limited sample size in this subgroup, the interpretation of these results is limited.

729 In the two cSSSI trials, clinical cure rates were similar across gender and race. Clinical cure  
730 rates in the VIBATIV clinically evaluable (CE) population were lower in patients ≥65 years of  
731 age compared with those <65 years of age. A decrease of this magnitude was not observed  
732 in the vancomycin CE population. Clinical cure rates in the VIBATIV CE population  
733 <65 years of age were 503/581 (87%) and in those ≥65 years were 88/122 (72%). In the  
734 vancomycin CE population clinical cure rates in patients <65 years of age were 492/570  
735 (86%) and in those ≥65 years was 111/137 (82%). Clinical cure rates in the VIBATIV-treated

736 patients were lower in patients with baseline CrCl  $\leq$ 50 mL/min compared with those with  
737 CrCl >50 mL/min. A decrease of this magnitude was not observed in the vancomycin-treated  
738 patients [see *Warnings and Precautions* (5.2)].

#### 739 **14.2 HABP/VABP**

740 Adult patients with hospital-acquired and ventilator-associated pneumonia were enrolled in  
741 two randomized, parallel-group, multinational, multicenter, double-blinded trials of identical  
742 design comparing VIBATIV (10 mg/kg IV every 24 hours) with vancomycin (1 g IV every  
743 12 hours) for 7 to 21 days. Vancomycin dosages could be adjusted for body weight and/or  
744 renal function per local guidelines. Patients could receive concomitant aztreonam or  
745 metronidazole for suspected Gram-negative and anaerobic infection, respectively. The  
746 addition of piperacillin/tazobactam was also permitted for coverage of Gram-negative  
747 organisms if resistance to aztreonam was known or suspected. Patients with known or  
748 suspected infections due to methicillin-resistant *Staphylococcus aureus* were enrolled in the  
749 studies.

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

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

764 Table 14: All-Cause Mortality at Day 28 in Patients with at least One Baseline Gram-  
 765 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)	

766 <sup>a</sup> Mortality rates are based on Kaplan-Meier estimates at Study Day 28. There were 84 patients  
 767 (5.6%) whose survival statuses were not known up to 28 days after initiation of study drug and were  
 768 considered censored at the last day known to be alive. Thirty-five of these patients were treated with  
 769 VIBATIV and 45 were treated with vancomycin.  
 770

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

777 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%)	

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

779 <sup>b</sup>Clinically Evaluable (CE) Population: Patients who were clinically evaluable  
 780

781 Among the 797 patients with at least one Gram-positive respiratory pathogen at baseline,  
782 73 patients had concurrent *S. aureus* bacteremia: 35 patients (8.5%, including 21 with  
783 MRSA) were treated with VIBATIV and 38 patients (9.8%, including 24 with MRSA) were  
784 treated with vancomycin. In these bacteremic patients, the 28-day all-cause mortality rate  
785 was 40.0% (14/35) for VIBATIV-treated patients and 39.5% (15/38) for vancomycin-treated  
786 patients. Given the limited sample size in this subgroup, the interpretation of these results is  
787 limited.

788

## 789 **15 REFERENCES**

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797 Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA.

798

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

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

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 Advise the patient to read the FDA-approved patient labeling (*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

817

818 Pregnancy Registry

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

823 Diarrhea

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

829 Correct Use of Antibacterial Drugs

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

838 Common Adverse Effects

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

845 **Manufactured by:**

846 Theravance Biopharma Antibiotics, Inc.

847 **Marketed by:**

848 Theravance Biopharma US, Inc.

849 South San Francisco, CA 94080

850 US Patent Nos. 6,635,618 B2; 6,858,584 B2; 6,872,701 B2; 7,008,923 B2; 7,208,471 B2;  
851 7,351,691 B2; 7,531,623 B2; 7,544,364 B2; 7,700,550 B2; 8,101,575 B2; 8,158,580 B2.

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854