

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 ^a (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

^aCalculate 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-THR (1-855-633-8479) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE

Revised: xx/2013

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1 **FULL PRESCRIBING INFORMATION**

2
3 **WARNINGS**

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

22
23 **1 INDICATIONS AND USAGE**

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

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

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

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

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

42 **1.2 HABP/VABP**

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

47 **2 DOSAGE AND ADMINISTRATION**

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

49 The recommended dosing for VIBATIV is 10 mg/kg administered over a 60-minute period in
50 patients ≥ 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 ≥ 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 ≤ 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^a (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

^aCalculate using the Cockcroft-Gault formula and ideal body weight (IBW). Use actual body weight if it is less than IBW. (12.3)

64

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

68 **2.4 Preparation and Administration**

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

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

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

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

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

83

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

85

86

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

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

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

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

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

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

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

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

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

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

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

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

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

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

106 for up to 32 days.

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

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

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

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

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

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

113 **3 DOSAGE FORMS AND STRENGTHS**

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

115 sterile, lyophilized powder.

116 **4 CONTRAINDICATIONS**

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

118 **5 WARNINGS AND PRECAUTIONS**

119 **5.1 Increased Mortality in Patients with HABP/VABP and Pre-existing Moderate to**
120 **Severe Renal Impairment (CrCl ≤50 mL/min)**

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

130 **5.2 Decreased Clinical Response in Patients with cSSSI and Pre-existing**
131 **Moderate/Severe Renal Impairment (CrCl ≤50 mL/min)**

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

137 Table 2: Clinical Cure by Pre-existing Renal Impairment – Clinically Evaluable
138 Population

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

139

140 **5.3 Nephrotoxicity**

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

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

153 In patients with renal dysfunction, accumulation of the solubilizer hydroxypropyl-beta-
154 cyclodextrin can occur [see *Patients with Renal Impairment (8.6) and Clinical Pharmacology*
155 *(12.3)*].

156 **5.4 Pregnant Women and Women of Childbearing Potential**

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

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

164 **5.5 Hypersensitivity Reactions**

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

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

171 **5.6 Infusion-Related Reactions**

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

177 **5.7 *Clostridium difficile*-Associated Diarrhea**

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

182 *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hyper-
183 toxin-producing strains of *C. difficile* cause increased morbidity and mortality, since these
184 infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must
185 be considered in all patients who present with diarrhea following antibiotic use. Careful
186 medical history is necessary because CDAD has been reported to occur more than
187 2 months after the administration of antibacterial agents.

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

192 **5.8 Development of Drug-Resistant Bacteria**

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

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

199 **5.9 QTc Prolongation**

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

206 **5.10 Coagulation Test Interference**

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

213 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

214

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

219 **6 ADVERSE REACTIONS**

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

- 221 • Nephrotoxicity [see *Warnings and Precautions* (5.3)]
- 222 • Infusion-related reactions [see *Warnings and Precautions* (5.6)]
- 223 • *Clostridium difficile*-associated diarrhea [see *Warnings and Precautions* (5.7)]

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

227 **6.1 Clinical Trials Experience**

228 ***Complicated Skin and Skin Structure Infections***

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

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

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

245 Table 4 displays the incidence of treatment-emergent adverse drug reactions reported in
246 $\geq 2\%$ of patients treated with VIBATIV possibly related to the drug.

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

	VIBATIV (N=929)	Vancomycin (N=938)
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.

249

250 **HABP/VABP**

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

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

260 Table 5: 28-Day Mortality (Kaplan-Meier Estimates) Stratified by Baseline Creatinine
261 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)

262

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

269 Table 6 displays the incidence of treatment-emergent adverse drug reactions reported in
270 ≥ 5% of HABP/VABP patients treated with VIBATIV possibly related to the drug.

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

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

274

275 **Nephrotoxicity**

276 ***Complicated Skin and Skin Structure Infections***

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

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

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

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

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

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

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

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

306 **6.2 Postmarketing Experience**

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

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

315 **7 DRUG INTERACTIONS**

316 **7.1 Drug-Laboratory Test Interactions**

317 Effects of Telavancin on Coagulation Test Parameters

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

325 Urine Protein Tests

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

329 **8 USE IN SPECIFIC POPULATIONS**

330 **8.1 Pregnancy**

331 Teratogenic Effects: Pregnancy Category C

332 *Pregnancy Exposure Registry*

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

337 *Fetal Risk Summary*

338 All pregnancies have a background risk of birth defects (about 3%), pregnancy loss (about
339 15%), or other adverse outcomes regardless of drug exposure.

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

344 *Clinical Considerations*

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

348 *Data*

349 Human Data

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

351 Animal Data

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

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

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

366 **8.3 Nursing Mothers**

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

370 **8.4 Pediatric Use**

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

372 **8.5 Geriatric Use**

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

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

381 Of the 749 HAP/VABP patients treated with VIBATIV at a dose of 10 mg/kg once daily in
382 clinical trials of HAP/VABP, 397 (53%) were ≥ 65 years of age and 230 (31%) were
383 ≥ 75 years of age. Treatment-emergent adverse events as well as deaths and other serious

384 adverse events occurred more often in patients ≥ 65 years of age than in those < 65 years of
385 age in both treatment groups.

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

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

392 **8.6 Patients with Renal Impairment**

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

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

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

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

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

413 **8.7 Patients with Hepatic Impairment**

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

417 **10 OVERDOSAGE**

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

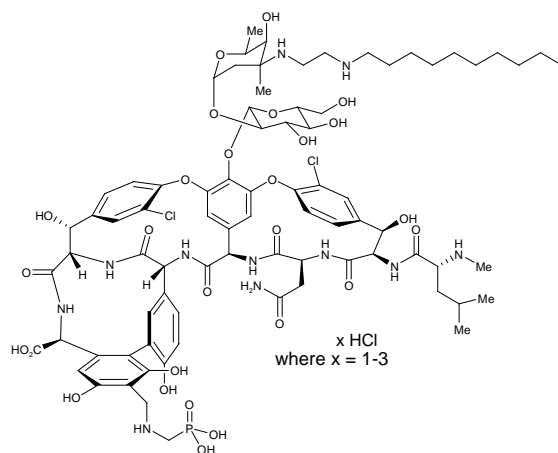
424 The clearance of telavancin by continuous venovenous hemofiltration (CVVH) was
425 evaluated in an *in vitro* study [see *Nonclinical Toxicology* (13.2)]. Telavancin was cleared by
426 CVVH and the clearance of telavancin increased with increasing ultrafiltration rate.
427 However, the clearance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

430 **11 DESCRIPTION**

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

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

436 Figure 1: Telavancin Hydrochloride



437

Telavancin hydrochloride

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

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

448 12 CLINICAL PHARMACOLOGY

449 12.1 Mechanism of Action

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

451 12.2 Pharmacodynamics

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

456 Cardiac Electrophysiology

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

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

	QTcF ¹ Change from Baseline	
	Mean (Upper 90% Confidence Limit ²) 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)

467 ¹ Fridericia corrected

468 ² Upper CL from a 2-sided 90% CI on difference from placebo (msec)
 469

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

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

486 12.3 Pharmacokinetics

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

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

	Single Dose (n=42)	Multiple Dose (n=36)
C _{max} (mcg/mL)	93.6 ± 14.2	108 ± 26
AUC _{0-∞} (mcg·hr/mL)	747 ± 129	-- ¹
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

¹ Data not available

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

494

495 Distribution

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

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

501 various times following administration of VIBATIV 10 mg/kg once daily for 3 days to healthy
502 adults. Telavancin concentrations in ELF and AM exceeded the MIC₉₀ for *S. aureus*
503 (0.5 mcg/mL) for at least 24 hours following dosing.

504 Concentrations of telavancin in skin blister fluid were 40% of those in plasma
505 (AUC_{0-24hr} ratio) after 3 daily doses of 7.5 mg/kg VIBATIV in healthy young adults.

506 Metabolism

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

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

516 Excretion

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

520 Specific Populations

521 *Geriatric Patients*

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

526 *Pediatric Patients*

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

529 *Gender*

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

533 *Renal Impairment*

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

541 Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault
542 formula:

543

$$544 \quad \text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{ideal body weight (kg)}^* \{ \times 0.85 \text{ for female patients} \}}{545 \quad [72 \times \text{serum creatinine (mg/dL)}]}$$

546 *Use actual body weight if < ideal body weight (IBW)

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

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

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

553 Following a single intravenous dose of VIBATIV 7.5 mg/kg, the clearance of hydroxypropyl-
554 beta-cyclodextrin was reduced in subjects with renal impairment, resulting in a higher
555 exposure to hydroxypropyl-beta-cyclodextrin. In subjects with mild, moderate, and severe

556 renal impairment, the mean clearance values were 38%, 59%, and 82% lower, respectively,
557 compared with subjects with normal renal function. Multiple infusions of VIBATIV may result
558 in accumulation of hydroxypropyl-beta-cyclodextrin.

559 *Hepatic Impairment*

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

564 Drug Interactions

565 *In Vitro*

566 The inhibitory activity of telavancin against the following CYP 450 enzymes was evaluated in
567 human liver microsomes: CYP 1A2, 2C9, 2C19, 2D6, and 3A4/5. Telavancin inhibited CYP
568 3A4/5 at potentially clinically relevant concentrations. Upon further evaluation in a Phase 1
569 clinical trial, telavancin was found not to inhibit the metabolism of midazolam, a sensitive
570 CYP3A substrate (see below).

571 *Midazolam*

572 The impact of telavancin on the pharmacokinetics of midazolam (CYP 3A4/5 substrate) was
573 evaluated in 16 healthy adult subjects following administration of a single dose of VIBATIV
574 10 mg/kg, intravenous midazolam 1 mg, and both. The results showed that telavancin had
575 no impact on the pharmacokinetics of midazolam and midazolam had no effect on the
576 pharmacokinetics of telavancin.

577 *Aztreonam*

578 The impact of telavancin on the pharmacokinetics of aztreonam was evaluated in 11 healthy
579 adult subjects following administration of a single dose of VIBATIV 10 mg/kg, aztreonam
580 2 g, and both. Telavancin had no impact on the pharmacokinetics of aztreonam and
581 aztreonam had no effect on the pharmacokinetics of telavancin. No dosage adjustment of
582 telavancin or aztreonam is recommended when both drugs are coadministered.

583 *Piperacillin-tazobactam*

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

590 **12.4 Microbiology**

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

597 Although telavancin is approximately 90% protein bound, the presence of human serum or
598 human serum albumin has minimal impact on the *in vitro* activity of telavancin against
599 staphylococci, streptococci, and vancomycin-susceptible enterococci.

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 Cross-Resistance

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

613 Antibacterial Activity

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

617 Facultative Gram-Positive Microorganisms

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

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

629 Facultative Gram-Positive Microorganisms

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

634 Susceptibility Test Methods

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

640 *Dilution technique*

641 Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations
642 (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial
643 compounds. The MICs should be determined using a standardized procedure [see

644 *References (15)*. Standardized procedures are based on a dilution method (broth or agar)
 645 or equivalent with standardized inoculum concentrations and standardized concentrations of
 646 telavancin powder. The MIC values should be interpreted according to the criteria provided
 647 in Table 9.

648 *Diffusion technique*

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

655 Table 9: Susceptibility Interpretive Criteria for Telavancin

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

¹ 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.

656

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

660 *Quality Control*

661 Standardized susceptibility test procedures require the use of laboratory control
 662 microorganisms to monitor the performance of the supplies and reagents used in the assay,

663 and the techniques of the individuals performing the test. Standard telavancin powder
664 should provide the range of values noted in Table 10.

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

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

	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration (mcg/mL)	Disk Diffusion Zone Diameter (mm)
<i>Enterococcus faecalis</i> ATCC 29212	0.12-0.5	Not applicable
<i>Staphylococcus aureus</i> ATCC 29213	0.12-1	Not applicable
<i>Staphylococcus aureus</i> ATCC 25923	Not applicable	16-20
<i>Streptococcus pneumoniae</i> ATCC 49619 ¹	0.004-0.03	17-24

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

670

671 13 NONCLINICAL TOXICOLOGY

672 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

684 **13.2 Animal Toxicology and/or Pharmacology**

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

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

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

696 **14 CLINICAL TRIALS**

697 **14.1 Complicated Skin and Skin Structure Infections**

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

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

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

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

	VIBATIV (N=884)¹	Vancomycin (N=910)¹
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%)

¹ Includes all patients randomized, treated, and evaluated for efficacy

714

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

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

	Trial 1			Trial 2		
	VIBATIV	Vancomycin	Difference	VIBATIV	Vancomycin	Difference
	% (n/N)	% (n/N)	(95% CI)¹	% (n/N)	% (n/N)	(95% CI)¹
ATe	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)
CE	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)

720 ¹95% CI computed using a continuity correction

721

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

724 Table 13: Clinical Cure Rates at the Test-of-Cure for the Most Common Pathogens in
 725 cSSSI Trials 1 and 2 – ME Population¹

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

¹ 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).

726

727 In the two cSSSI trials, clinical cure rates were similar across gender and race. Clinical cure
 728 rates in the VIBATIV clinically evaluable (CE) population were lower in patients ≥65 years of
 729 age compared with those <65 years of age. A decrease of this magnitude was not observed
 730 in the vancomycin CE population. Clinical cure rates in the VIBATIV CE population
 731 <65 years of age were 503/581 (87%) and in those ≥65 years were 88/122 (72%). In the
 732 vancomycin CE population clinical cure rates in patients <65 years of age were 492/570
 733 (86%) and in those ≥65 years was 111/137 (82%). Clinical cure rates in the VIBATIV-treated
 734 patients were lower in patients with baseline CrCl ≤50 mL/min compared with those with
 735 CrCl >50 mL/min. A decrease of this magnitude was not observed in the vancomycin-treated
 736 patients [see *Warnings and Precautions (5.2)*].

737 **14.2 HABP/VABP**

738 Adult patients with hospital-acquired and ventilator-associated pneumonia were enrolled in
 739 two randomized, parallel-group, multinational, multicenter, double-blinded trials of identical
 740 design comparing VIBATIV (10 mg/kg IV every 24 hours) with vancomycin (1 g IV every
 741 12 hours) for 7 to 21 days. Vancomycin dosages could be adjusted for body weight and/or
 742 renal function per local guidelines. Patients could receive concomitant aztreonam or

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

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

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

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

		Trial 1		Trial 2	
		VIBATIV	Vancomycin	VIBATIV	Vancomycin
All Patients	Mortality ^a	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 ^a	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 ^a	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)	

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

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

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

	Trial 1		Trial 2	
	VIBATIV	Vancomycin	VIBATIV	Vancomycin
AT ^a	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 ^b	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%)	

776 ^aAll-Treated (AT) Population: Patients who received at least one dose of study medication

777 ^bClinically Evaluable (CE) Population: Patients who were clinically evaluable
778

779 **15 REFERENCES**

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- 784 2. CLSI. Performance Standards for Antimicrobial Disk Susceptibility Tests, Approved
785 Standard – 11th ed. CLSI document M2-A11; CLSI, Wayne, PA. 19087-1898, 2012.
- 786 3. CLSI. Performance Standards for Antimicrobial Susceptibility Testing – 22nd
787 Informational Supplement. CLSI document M100-S22, CLSI, Wayne, PA. 19087-1898,
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789
790 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

795 **17 PATIENT COUNSELING INFORMATION**

796 *See Medication Guide.*

797 Use During Pregnancy and By Women of Childbearing Potential

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

- 801 • Be informed about the potential risk of fetal harm if VIBATIV is used during
802 pregnancy
- 803 • Have a pregnancy test prior to administration of VIBATIV
- 804 • If not pregnant, use effective contraceptive methods to prevent pregnancy during
805 VIBATIV treatment
- 806 • Notify their prescribing physician/ healthcare provider if they become pregnant during
807 VIBATIV treatment

808
809 Pregnancy Registry

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

814 Diarrhea

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

820 Correct Use of Antibacterial Drugs

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

829 Common Adverse Effects

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

836 **Manufactured for:**

837 Theravance, Inc.
838 South San Francisco, CA 94080

839 US Patent Nos. 6,635,618 B2; 6,858,584 B2; 6,872,701 B2; 7,008,923 B2; 7,208,471 B2;
840 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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