

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIBATIV 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 be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

WARNING: FETAL RISK

See full prescribing information for complete boxed warning.

- Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. (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)

INDICATIONS AND USAGE

VIBATIV is a lipoglycopeptide antibacterial indicated for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive bacteria. (1.1)

DOSAGE AND ADMINISTRATION

- 10 mg/kg administered over 60 minutes by intravenous infusion once every 24 hours for 7 to 14 days. (2.1)
- Dosage adjustment in patients with renal impairment. (2.2):

Creatinine Clearance [#] (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

[#] As calculated using the Cockcroft-Gault formula (12.3)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Nephrotoxicity: New onset or worsening renal impairment has occurred. Monitor renal function in all patients. (5.3)
- Decreased efficacy with moderate/severe baseline renal impairment: Consider these data when selecting antibacterial therapy for patients with baseline CrCl ≤50 mL/min. (5.4)
- Infusion-related reactions: Administer VIBATIV over at least 60 minutes to minimize infusion-related reactions. (5.5)
- *Clostridium difficile*-associated disease: May range from mild diarrhea to fatal colitis. Evaluate if diarrhea occurs. (5.6)
- QTc prolongation: Avoid use in patients at risk. Use with caution in patients taking drugs known to prolong the QT interval. (5.8)
- Coagulation test interference: Telavancin interferes with some laboratory coagulation tests, including prothrombin time, international normalized ratio, and activated partial thromboplastin time. (5.9, 7.1)

ADVERSE REACTIONS

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 Astellas Pharma US, Inc. at 1-800-727-7003 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: 09/2009

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1 **FULL PRESCRIBING INFORMATION**

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3 **WARNING: FETAL RISK**

- 4 ▪ **Women of childbearing potential should have a serum pregnancy test prior to**
5 **administration of VIBATIV**
- 6 ▪ **Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient**
7 **outweighs the potential risk to the fetus**
- 8 ▪ **Adverse developmental outcomes observed in 3 animal species at clinically**
9 **relevant doses raise concerns about potential adverse developmental outcomes**
10 **in humans [see Warnings and Precautions (5.1), Use in Specific Populations (8.1)]**

11
12 **1 INDICATIONS AND USAGE**

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

19 **1.1 Complicated Skin and Skin Structure Infections**

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

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

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

31 **2 DOSAGE AND ADMINISTRATION**

32 **2.1 Complicated Skin and Skin Structure Infections**

33 The recommended dosing for VIBATIV is 10 mg/kg administered over a 60-minute period in
34 patients ≥18 years of age by intravenous infusion once every 24 hours for 7 to 14 days. The
35 duration of therapy should be guided by the severity and site of the infection and the
36 patient's clinical and bacteriological progress.

37 **2.2 Patients with Renal Impairment**

38 Because telavancin is eliminated primarily by the kidney, a dosage adjustment is required
39 for patients whose creatinine clearance is ≤50 mL/min, as listed in Table 1 [see *Clinical*
40 *Pharmacology* (12.3)].

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

Creatinine Clearance* (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

* As calculated using the Cockcroft-Gault formula [see *Clinical Pharmacology* (12.3)]

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

45 **2.3 Preparation and Administration**

46 250 mg vial: Reconstitute the contents of a VIBATIV 250 mg vial with **15** mL of 5% Dextrose
47 Injection, USP; Sterile Water for Injection, USP; or 0.9% Sodium Chloride Injection, USP.
48 The resultant solution has a concentration of 15 mg/mL (total volume of approximately
49 17.0 mL).

50 750 mg vial: Reconstitute the contents of a VIBATIV 750 mg vial with **45** mL of 5% Dextrose
51 Injection, USP; Sterile Water for Injection, USP; or 0.9% Sodium Chloride Injection, USP,
52 The resultant solution has a concentration of 15 mg/mL (total volume of approximately
53 50.0 mL).

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

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

57

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

59

60

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

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

71 Since no preservative or bacteriostatic agent is present in this product, aseptic technique
72 must be used in preparing the final intravenous solution. Studies have shown that the
73 reconstituted solution in the vial should be used within 4 hours when stored at room
74 temperature or within 72 hours under refrigeration at 2 to 8°C (36 to 46°F). The diluted
75 (dosing) solution in the infusion bag should be used within 4 hours when stored at room
76 temperature or used within 72 hours when stored under refrigeration at 2 to 8°C (36 to
77 46°F). However, the total time in the vial plus the time in the infusion bag should not exceed
78 4 hours at room temperature and 72 hours under refrigeration at 2 to 8°C (36 to 46°F).

79 VIBATIV is administered intravenously. Because only limited data are available on the
80 compatibility of VIBATIV with other IV substances, additives or other medications should not
81 be added to VIBATIV single-use vials or infused simultaneously through the same IV line. If
82 the same intravenous line is used for sequential infusion of additional medications, the line
83 should be flushed before and after infusion of VIBATIV with 5% Dextrose Injection, USP;
84 0.9% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP.

85 **3 DOSAGE FORMS AND STRENGTHS**

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

88 **4 CONTRAINDICATIONS**

89 None.

90 **5 WARNINGS AND PRECAUTIONS**

91 **5.1 Women of Childbearing Potential**

92 Women of childbearing potential should have a serum pregnancy test prior to administration
93 of VIBATIV. If not already pregnant, women of childbearing potential should use effective
94 contraception during VIBATIV treatment.

95 **5.2 Pregnancy**

96 Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs
97 the potential risk to the fetus. VIBATIV caused adverse developmental outcomes in 3 animal
98 species at clinically relevant doses. This raises concern about potential adverse
99 developmental outcomes in humans [*see Use in Specific Populations (8.1)*].

100 **5.3 Nephrotoxicity**

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

104 In 30/929 (3.1%) of VIBATIV-treated patients compared to 10/938 (1.1%) of vancomycin-
105 treated patients, renal adverse events indicative of renal impairment occurred, as defined by
106 the following terms: increased serum creatinine, renal impairment, renal insufficiency, and/or
107 renal failure. In 17 of the 30 VIBATIV-treated patients, these adverse events had not
108 completely resolved by the end of the trials, compared with 6 of the 10 vancomycin-treated
109 patients. Serious adverse events indicative of renal impairment occurred in 11/929 (1.2%) of
110 VIBATIV-treated patients compared to 3/938 (0.3%) of vancomycin-treated patients. Twelve
111 patients treated with VIBATIV discontinued treatment due to adverse events indicative of
112 renal impairment compared to 2 patients treated with vancomycin. Adverse events were
113 more likely to occur in patients with baseline comorbidities known to predispose patients to
114 kidney dysfunction (pre-existing renal disease, diabetes mellitus, congestive heart failure, or
115 hypertension). The renal adverse event rate was also higher in patients who received
116 concomitant medications known to affect kidney function (eg, non-steroidal anti-
117 inflammatory drugs, ACE inhibitors, and loop diuretics). Fifteen of 174 patients (8.6%)

118 ≥65 years of age had adverse events indicative of renal impairment compared to 16 of
119 755 patients (1.9%) <65 years of age [see Use in Specific Populations (8.5)].

120 Monitor renal function (i.e., serum creatinine, creatinine clearance) in all patients receiving
121 VIBATIV. Values should be obtained prior to initiation of treatment, during treatment (at 48-
122 to 72-hour intervals or more frequently, if clinically indicated), and at the end of therapy. If
123 renal function decreases, the benefit of continuing VIBATIV versus discontinuing and
124 initiating therapy with an alternative agent should be assessed [see Dosage and
125 Administration, Clinical Pharmacology (2.2)].

126 In patients with renal dysfunction, accumulation of the solubilizer hydroxypropyl-beta-
127 cyclodextrin can occur [see Patients with Renal Impairment (8.6) and Clinical Pharmacology
128 (12.3)].

129 **5.4 Decreased Efficacy with Moderate/Severe Baseline Renal Impairment**

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

135 Table 2: Clinical Cure by Baseline Renal Function

	VIBATIV % (n/N)	Vancomycin % (n/N)
ATe Population¹		
CrCl >50 mL/min	75.3% (565/750)	73.7% (575/780)
CrCl ≤50 mL/min	63.1% (70/111)	69.4% (75/108)
CE Population²		
CrCl >50 mL/min	87.0% (520/598)	85.9% (524/610)
CrCl ≤50 mL/min	67.4% (58/86)	82.7% (67/81)

136 ¹ All-treated population - includes all patients randomized, treated, and evaluated for efficacy

137 ² Clinically evaluable population

138 **5.5 Infusion-Related Reactions**

139 VIBATIV is a lipoglycopeptide antibacterial agent and should be administered over a period
140 of 60 minutes to reduce the risk of infusion-related reactions. Rapid intravenous infusions of
141 the glycopeptide class of antimicrobial agents can cause “Red-man Syndrome”-like

142 reactions including: flushing of the upper body, urticaria, pruritus, or rash. Stopping or
143 slowing the infusion may result in cessation of these reactions.

144 **5.6 Clostridium difficile-Associated Diarrhea**

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

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

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

159 **5.7 Development of Drug-Resistant Bacteria**

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

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

166 **5.8 QTc Prolongation**

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

173 **5.9 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 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 Xa tests	Thrombin time Whole blood (Lee-White) clotting time Ex vivo platelet aggregation Chromogenic factor Xa assay Functional (chromogenic) factor X assay Bleeding time D-dimer Fibrin degradation products

181

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

186 **6 ADVERSE REACTIONS**

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

- 188 • Nephrotoxicity [see *Warnings and Precautions (5.3)*]
- 189 • Infusion-related reactions [see *Warnings and Precautions (5.5)*]
- 190 • *Clostridium difficile*-associated diarrhea [see *Warnings and Precautions (5.6)*]

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

194 **6.1 Clinical Trials Experience**

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

199 In the cSSSI clinical trials, <1% (8/929) patients who received VIBATIV died and <1%
200 (8/938) patients treated with vancomycin died. Serious adverse events were reported in 7%
201 (69/929) of patients treated with VIBATIV and most commonly included renal, respiratory, or
202 cardiac events. Serious adverse events were reported in 5% (43/938) of vancomycin-treated
203 patients, and most commonly included cardiac, respiratory, or infectious events. Treatment
204 discontinuations due to adverse events occurred in 8% (72/929) of patients treated with
205 VIBATIV, the most common events being nausea and rash (~1% each). Treatment
206 discontinuations due to adverse events occurred in 6% (53/938) of vancomycin-treated
207 patients, the most common events being rash and pruritus (~1% each).

208 The most common adverse reactions occurring in ≥10% of VIBATIV-treated patients
209 observed in the VIBATIV Phase 3 cSSSI trials were taste disturbance, nausea, vomiting,
210 and foamy urine.

211 Table 4 displays the incidence of treatment-emergent adverse drug reactions reported in
212 >2% of patients treated with VIBATIV possibly related to the drug (including those reactions
213 known to occur with other glycopeptide antibacterial agents).

214 Table 4: Incidence of Treatment-emergent Adverse Drug Reactions Reported in ≥2%
215 of VIBATIV or Vancomycin Patients Treated in Trial 1 and Trial 2

	VIBATIV (N=929)	Vancomycin (N=938)
Body as a Whole		
Rigors	4%	2%
Generalized pruritus	3%	6%
Digestive System		
Nausea	27%	15%
Vomiting	14%	7%
Diarrhea	7%	8%
Abdominal pain	2%	2%

	VIBATIV (N=929)	Vancomycin (N=938)
Metabolic and Nutritional		
Decreased appetite	3%	2%
Nervous System		
Taste disturbance ¹	33%	7%
Dizziness	6%	6%
Renal System		
Foamy urine	13%	3%
Skin and Appendages		
Pruritus	6%	13%
Rash	4%	5%
Other		
Infusion site pain	4%	4%
Infusion site erythema	3%	3%

¹ Described as a metallic or soapy taste.

216

217 7 DRUG INTERACTIONS

218 7.1 Drug-Laboratory Test Interactions

219 Effects of Telavancin on Coagulation Test Parameters

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

227 Urine Protein Tests

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

231 **8 USE IN SPECIFIC POPULATIONS**

232 **8.1 Pregnancy**

233 Teratogenic effects: Pregnancy Category C

234 *Pregnancy Exposure Registry*

235 There is a pregnancy registry that monitors pregnancy outcomes in women exposed to
236 VIBATIV during pregnancy. Physicians are encouraged to register pregnant patients, or
237 pregnant women may enroll themselves in the VIBATIV pregnancy registry by calling 1-888-
238 658-4228.

239 *Fetal Risk Summary*

240 All pregnancies have a background risk of birth defects (about 3%), pregnancy loss (about
241 15%), or other adverse outcomes regardless of drug exposure.

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

246 *Clinical Considerations*

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

250 *Data*

251 Human Data

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

253 Animal Data

254 In embryo-fetal development studies in rats, rabbits, and minipigs, telavancin demonstrated
255 the potential to cause limb and skeletal malformations when given intravenously during the
256 period of organogenesis at doses up to 150, 45 or 75 mg/kg/day, respectively. These doses
257 resulted in exposure levels approximately 1- to 2-fold the human exposure (AUC) at the
258 maximum clinical recommended dose. Malformations observed at <1% (but absent or at
259 lower rates in historical or concurrent controls), included brachymelia (rats and rabbits),
260 syndactyly (rats, minipigs), adactyly (rabbits), and polydactyly (minipigs). Additional findings

261 in rabbits included flexed front paw and absent ulna, and in the minipigs included misshapen
262 digits and deformed front leg. Fetal body weights were decreased in rats.

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

268 **8.3 Nursing Mothers**

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

272 **8.4 Pediatric Use**

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

274 **8.5 Geriatric Use**

275 Of the 929 patients treated with VIBATIV at a dose of 10 mg/kg once daily in clinical trials of
276 cSSSI, 174 (18.7%) were ≥ 65 years of age and 87 (9.4%) were ≥ 75 years of age. In the
277 cSSSI trials, lower clinical cure rates were observed in patients ≥ 65 years of age compared
278 with those < 65 years of age. Overall, treatment-emergent adverse events occurred with
279 similar frequencies in patients ≥ 65 (75% of patients) and < 65 years of age (83% of patients).
280 Fifteen of 174 (8.6%) patients ≥ 65 years of age treated with telavancin had adverse events
281 indicative of renal impairment compared to 16 of 755 (1.9%) patients < 65 years of age [see
282 *Warnings and Precautions (5.3), Clinical Trials (14.1)*].

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

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

289 **8.6 Patients with Renal Impairment**

290 The cSSSI trials included patients with normal renal function and patients with varying
291 degrees of renal impairment. Patients with underlying renal dysfunction or risk factors for
292 renal dysfunction had a higher incidence of renal adverse events [see *Warnings and*
293 *Precautions (5.3)*]. Patients with creatinine clearance ≤ 50 mL/min also had lower clinical
294 cure rates. Consider these data when selecting antibacterial therapy in patients with
295 baseline moderate/ severe renal impairment (CrCl ≤ 50 mL/min).

296 Dosage adjustment is required in patients with ≤ 50 mL/min renal impairment [see *Dosage*
297 *and Administration (2.2)*]. There is insufficient information to make specific dosage
298 adjustment recommendations for patients with end-stage renal disease (CrCl < 10 mL/min),
299 including patients receiving hemodialysis [see *Overdosage (10)*, *Clinical Pharmacology*
300 *(12.3)*].

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

305 **8.7 Patients with Hepatic Impairment**

306 The cSSSI trials included patients with normal hepatic function and with hepatic impairment.
307 No dosage adjustment is recommended in patients with mild or moderate hepatic
308 impairment [see *Clinical Pharmacology (12.3)*].

309 **10 OVERDOSAGE**

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

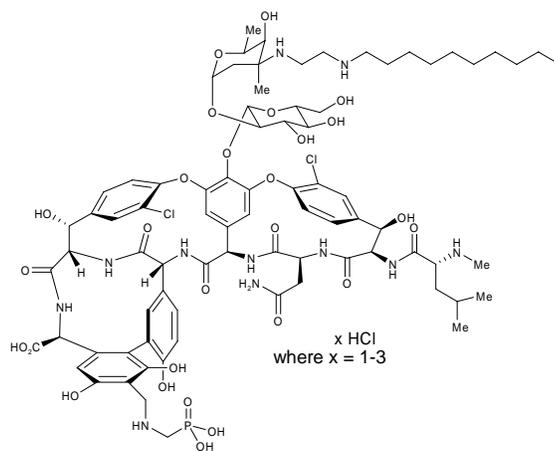
316 The clearance of telavancin by continuous venovenous hemofiltration (CVVH) was
317 evaluated in an in vitro study [see *Nonclinical Toxicology (13.2)*]. Telavancin was cleared by
318 CVVH and the clearance of telavancin increased with increasing ultrafiltration rate.
319 However, the clearance of telavancin by CVVH has not been evaluated in a clinical study;

320 thus, the clinical significance of this finding and use of CVVH to treat an overdose is
321 unknown.

322 11 DESCRIPTION

323 VIBATIV contains telavancin hydrochloride, a lipoglycopeptide antibacterial that is a
324 synthetic derivative of vancomycin. The chemical name of telavancin hydrochloride is
325 vancomycin,N3''-[2-(decylamino)ethyl]-29-[[[(phosphono-methyl)-amino]-methyl]-
326 hydrochloride. Telavancin hydrochloride has the following chemical structure:

327 Figure 1: Telavancin Hydrochloride



328 **Telavancin hydrochloride**

329 Telavancin hydrochloride is an off-white to slightly colored amorphous powder with the
330 empirical formula $C_{80}H_{106}C_{12}N_{11}O_{27}P \cdot xHCl$ (where $x = 1$ to 3) and a free-base molecular
331 weight of 1755.6. It is highly lipophilic and slightly soluble in water.

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

339 **12 CLINICAL PHARMACOLOGY**

340 **12.1 Mechanism of Action**

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

342 **12.2 Pharmacodynamics**

343 The antimicrobial activity of telavancin appears to best correlate with the ratio of area under
344 the concentration-time curve to minimal inhibitory concentration (AUC/MIC) for
345 *Staphylococcus aureus* based on animal models of infection. An exposure-response
346 analysis of 2 cSSSI clinical trials supports the dose of 10 mg/kg every 24 hours.

347 Cardiac Electrophysiology

348 The effect of telavancin on cardiac repolarization was assessed in a randomized,
349 double-blind, multiple-dose, positive-controlled, and placebo-controlled, parallel study
350 (n=160). Healthy subjects received VIBATIV 7.5 mg/kg, VIBATIV 15 mg/kg, positive control,
351 or placebo infused over 60 minutes once daily for 3 days. Based on interpolation of the data
352 from VIBATIV 7.5 mg/kg and 15 mg/kg, the mean maximum baseline-corrected, placebo-
353 corrected QTc prolongation at the end of infusion was estimated to be 12-15 msec for
354 VIBATIV 10 mg/kg and 22 msec for the positive control (Table 5). By 1 hour after infusion
355 the maximum QTc prolongation was 6-9 msec for VIBATIV and 15 msec for the positive
356 control.

357 Table 5: 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)

358 ¹ Fridericia corrected

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

360 ECGs were performed prior to and during the treatment period in patients receiving VIBATIV
361 10 mg/kg in 3 studies to monitor QTc intervals. In these trials, 214 of 1029 (21%) patients
362 allocated to treatment with VIBATIV and 164 of 1033 (16%) allocated to vancomycin
363

364 received concomitant medications known to prolong the QTc interval and are known to be
 365 associated with definite or possible risk of torsades de pointes. The incidence of QTc
 366 prolongation >60 msec was 1.5% (15 patients) in the VIBATIV group and 0.6% (6 patients)
 367 in the vancomycin group. Nine of the 15 VIBATIV patients received concomitant medications
 368 known to prolong the QTc interval and definitely or possibly associated with a risk of
 369 torsades de pointes, compared with 1 of the 6 patients who received vancomycin. A similar
 370 number of patients in each treatment group (<1%) who did not receive a concomitant
 371 medication known to prolong the QTc interval experienced a prolongation >60 msec from
 372 baseline. In a separate analysis, 1 patient in the VIBATIV group and 2 patients in the
 373 vancomycin group experienced QTc >500 msec. No cardiac adverse events were ascribed
 374 to prolongation of the QTc interval.

375 12.3 Pharmacokinetics

376 The mean pharmacokinetic parameters of telavancin (10mg/kg) after a single and multiple
 377 60-minute intravenous infusions (10 mg/kg every 24 hours) are summarized in [Table 6](#).

378 Table 6: Pharmacokinetic Parameters of Telavancin in Healthy Adults, 10 mg/kg

	Single Dose	Multiple Dose
	(n=42)	(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		

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

383

384 Distribution

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

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

390 Metabolism

391 No metabolites of telavancin were detected in in vitro studies using human liver microsomes,
392 liver slices, hepatocytes, and kidney S9 fraction. None of the following recombinant CYP
393 450 isoforms were shown to metabolize telavancin in human liver microsomes: CYP 1A2,
394 2C9, 2C19, 2D6, 3A4, 3A5, 4A11. The clearance of telavancin is not expected to be altered
395 by inhibitors of any of these enzymes.

396 In a mass balance study in male subjects using radiolabeled telavancin, 3 hydroxylated
397 metabolites were identified with the predominant metabolite (THR-651540) accounting for
398 <10% of the radioactivity in urine and <2% of the radioactivity in plasma. The metabolic
399 pathway for telavancin has not been identified.

400 Excretion

401 Telavancin is primarily eliminated by the kidney. In a mass balance study, approximately
402 76% of the administered dose was recovered from urine and <1% of the dose was
403 recovered from feces (collected up to 216 hours) based on total radioactivity.

404 Specific Populations

405 *Geriatric Patients*

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

410

411 *Pediatric Patients*

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

414 *Gender*

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

418 *Renal Impairment*

419 The pharmacokinetics of telavancin were evaluated in subjects with normal and subjects
420 with varying degrees of renal impairment following administration of a single dose of
421 telavancin 7.5 mg/kg (n=28). The mean AUC_{0-∞} values were approximately 13%, 29%, and
422 118% higher for subjects with CrCl >50 to 80 mL/min, CrCl 30 to 50 mL/min, and
423 CrCl ≤30 mL/min, respectively, compared to subjects with normal renal function. Dosage
424 adjustment is required in patients with CrCl ≤50 mL/min [see *Dosage and Administration*
425 (2.2)].

426 Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault
427 formula:

$$428 \quad \text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{ideal body weight (kg)}^* \{ \times 0.85 \text{ for female patients} \}}{[72 \times \text{serum creatinine (mg/dL)}]}$$

429

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

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

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

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

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

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

443 *Hepatic Impairment*

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

448 Drug Interactions

449 *In Vitro*

450 The inhibitory activity of telavancin against the following CYP 450 enzymes was evaluated in
451 human liver microsomes: CYP 1A2, 2C9, 2C19, 2D6, and 3A4/5. Telavancin inhibited CYP
452 3A4/5 at potentially clinically relevant concentrations. Upon further evaluation in a Phase 1
453 clinical trial, telavancin was found not to inhibit the metabolism of midazolam, a sensitive
454 CYP3A substrate (see below).

455 *Midazolam*

456 The impact of telavancin on the pharmacokinetics of midazolam (CYP 3A4/5 substrate) was
457 evaluated in 16 healthy adult subjects following administration of a single dose of VIBATIV
458 10 mg/kg, intravenous midazolam 1 mg, and both. The results showed that telavancin had
459 no impact on the pharmacokinetics of midazolam and midazolam had no effect on the
460 pharmacokinetics of telavancin. Therefore, telavancin is unlikely to alter the
461 pharmacokinetics of drugs metabolized by the CYP450 system to a clinically significant
462 degree.

463 *Aztreonam*

464 The impact of telavancin on the pharmacokinetics of aztreonam was evaluated in 11 healthy
465 adult subjects following administration of a single dose of VIBATIV 10 mg/kg, aztreonam
466 2 gm, and both. Telavancin had no impact on the pharmacokinetics of aztreonam and
467 aztreonam had no effect on the pharmacokinetics of telavancin. No dosage adjustment of
468 telavancin or aztreonam is recommended when both drugs are coadministered.

469 *Piperacillin-tazobactam*

470 The impact of telavancin on the pharmacokinetics of piperacillin-tazobactam was evaluated
471 in 12 healthy adult subjects following administration of a single dose of VIBATIV 10 mg/kg,
472 piperacillin-tazobactam 4.5 g, and both. Telavancin had no impact on the pharmacokinetics
473 of piperacillin-tazobactam and piperacillin-tazobactam had no effect on the
474 pharmacokinetics of telavancin. No dosage adjustment of telavancin or piperacillin-
475 tazobactam is recommended when both drugs are coadministered.

476 **12.4 Microbiology**

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

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

486 Mechanism of Action

487 Telavancin inhibits bacterial cell wall synthesis by interfering with the polymerization and
488 cross-linking of peptidoglycan. Telavancin binds to the bacterial membrane and disrupts
489 membrane barrier function.

490 Interactions with Other Antibacterials

491 In vitro investigations demonstrated no antagonism between telavancin and amikacin,
492 aztreonam, cefepime, ceftriaxone, ciprofloxacin, gentamicin, imipenem, meropenem,
493 oxacillin, piperacillin/tazobactam, rifampin, and trimethoprim/sulfamethoxazole, when tested
494 in various combinations against telavancin susceptible staphylococci, streptococci, and
495 enterococci. This information is not available for other bacteria.

496

497

498 Cross-Resistance

499 Some vancomycin-resistant enterococci have a reduced susceptibility to telavancin. There is
500 no known cross-resistance between telavancin and other classes of antibiotics.

501 Antibacterial Activity

502 Telavancin has been shown to be active against most isolates of the following
503 microorganisms both in vitro and in clinical infections as described in the Indications and
504 Usage section [see *Indications and Usage (1.1)*]:

505 Facultative Gram-Positive Microorganisms

506 *Staphylococcus aureus* (including methicillin-resistant isolates)
507 *Streptococcus pyogenes*
508 *Enterococcus faecalis* (vancomycin-susceptible isolates only)
509 *Streptococcus agalactiae*
510 *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and
511 *S. constellatus*)

512 Greater than 90% of the following microorganisms exhibit an in vitro MIC less than or equal
513 to the telavancin-susceptible breakpoint for organisms of similar genus shown in [Table 7](#).
514 The safety and effectiveness of telavancin in treating clinical infections due to these
515 microorganisms have not been established in adequate and well-controlled clinical trials.

516 Facultative Gram-Positive Microorganisms

517 *Enterococcus faecium* (vancomycin-susceptible isolates only)
518 *Staphylococcus haemolyticus*
519 *Streptococcus dysgalactiae* subsp. *equisimilis*
520 *Staphylococcus epidermidis*

521 Susceptibility Test Methods

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

527

528 *Dilution technique*

529 Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations
 530 (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial
 531 compounds. The MICs should be determined using a standardized procedure [see
 532 *References (15)*]. Standardized procedures are based on a dilution method (broth or agar)
 533 or equivalent with standardized inoculum concentrations and standardized concentrations of
 534 telavancin powder. The MIC values should be interpreted according to the criteria provided
 535 in [Table 7](#).

536 *Diffusion technique*

537 Quantitative methods that require measurement of zone diameters also provide reproducible
 538 estimates of the susceptibility of bacteria to antimicrobial compounds. One such
 539 standardized procedure requires the use of standardized inoculum concentrations [see
 540 *References (15)*]. This procedure uses paper disks impregnated with 30 mcg of telavancin
 541 to test the susceptibility of microorganisms to telavancin. The disk diffusion interpretive
 542 criteria are provided in [Table 7](#).

543 Table 7: Susceptibility Interpretive Criteria for Telavancin

	Susceptibility Interpretive Criteria ¹					
	Minimal 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</i> group	≤ 0.12	--	--	≥ 15	--	--
<i>Enterococcus faecalis</i> (vancomycin-susceptible isolates only)	≤ 1	--	--	≥ 15	--	--

544 1 The current absence of resistant isolates precludes defining any results other than "susceptible"
 545 Isolates yielding results other than susceptible should be subjected to additional testing

546 A report of "susceptible" indicates that the antimicrobial is likely to inhibit growth of the
 547 pathogen if the antimicrobial compound in the blood reaches the concentrations usually
 548 achievable.

549

550 *Quality Control*

551 Standardized susceptibility test procedures require the use of laboratory control
552 microorganisms to monitor the performance of the supplies and reagents used in the assay,
553 and the techniques of the individuals performing the test. Standard telavancin powder
554 should provide the range of values noted in [Table 8](#).

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

558 Table 8: Acceptable Quality Control Ranges for Telavancin to be used in Validation of
559 Susceptibility Test Results

	Acceptable Quality Control Ranges	
	Minimal 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*

560 **13 NONCLINICAL TOXICOLOGY**

561 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

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

573 **13.2 Animal Toxicology and/or Pharmacology**

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

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

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

585 **14 CLINICAL TRIALS**

586 **14.1 Complicated Skin and Skin Structure Infections**

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

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

599 The ATe population consisted of 1,794 patients. Of these, 1,410 (78.6%) patients were
 600 clinically evaluable (CE). Patients with demographic and baseline characteristics were
 601 well-balanced between treatment groups and are presented in Table 9.

602 Table 9: Baseline Infection Types in Patients in 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

603 The primary efficacy endpoints in both trials was the clinical cure rates at a follow-up (Test of
 604 Cure) visit in the ATe and CE populations. Clinical cure rates in Trials 1 and 2 are displayed
 605 for the ATe and CE population in [Table 10](#).

606 Table 10: Clinical Cure at Test-of-Cure in Trials 1 and 2 - ATe and CE 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%	71.6%	0.9 (-5.3, 7.2)	74.7%	74.0%	0.7 (-5.1, 6.5)
	(309/426)	(307/429)		(342/458)	(356/481)	
CE	84.3%	82.8%	1.5 (-4.3, 7.3)	83.9%	87.7%	-3.8 (-9.2, 1.5)
	(289/343)	(288/348)		(302/360)	(315/359)	

607 ¹95% CI computed using a continuity correction

608
 609 The cure rates by pathogen for the microbiologically evaluable (ME) population are
 610 presented in [Table 11](#).

611 Table 11: Clinical Cure Rates at the Test-of-Cure for the Most Common Pathogens in
 612 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)

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

613

614 In

615 rates in the telavancin clinically evaluable (CE) population were lower in patients ≥ 65 years
616 of age compared to those < 65 years of age. A decrease of this magnitude was not observed
617 in the vancomycin CE population. Clinical cure rates in the telavancin CE population
618 < 65 years of age were 503/581 (86.6%) and in those ≥ 65 years were 88/122 (72.1%). In the
619 vancomycin CE population clinical cure rates in patients < 65 years of age were 492/570
620 (86.3%) and in those ≥ 65 years was 111/137 (82.0%). Clinical cure rates in the telavancin-
621 treated patients were lower in patients with baseline CrCl ≤ 50 mL/min compared to those
622 with CrCl > 50 mL/min. A decrease of this magnitude was not observed in the vancomycin-
623 treated patients [see *Warnings and Precautions (5.4)*].

624

625 **15 REFERENCES**

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- 630 2. CLSI. Performance Standards for Antimicrobial Disk Susceptibility Tests, Approved
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635

636 16 HOW SUPPLIED/STORAGE AND HANDLING

637 • Cartons of 10 individually packaged 250 mg single-dose vials (NDC 0469-3525-30)

638 • Cartons of 10 individually packaged 750 mg single-dose vials (NDC 0469-3575-50)

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

641 17 PATIENT COUNSELING INFORMATION

642 *See Medication Guide.*

643 Use during Pregnancy and by Women of Childbearing Potential

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

647 • Be informed about the potential risk of fetal harm if VIBATIV is used during
648 pregnancy

649 • Have a pregnancy test prior to administration of VIBATIV

650 • If not pregnant, use effective contraceptive methods to prevent pregnancy during
651 VIBATIV treatment

652 • Notify their prescribing physician/ healthcare provider if they become pregnant during
653 VIBATIV treatment

654

655 Pregnancy Registry

656 There is a pregnancy registry that monitors pregnancy outcomes in women exposed to
657 VIBATIV during pregnancy. Physicians are encouraged to register pregnant patients, or
658 pregnant women may enroll themselves in the pregnancy registry by calling 1-888-658-
659 4228.

660

661

662 Diarrhea

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

668 Correct Use of Antibacterial Drugs

669 Patients should be counseled that antibacterial drugs including VIBATIV should only be
670 used to treat bacterial infections. They do not treat viral infections (eg, the common cold).
671 When VIBATIV is prescribed to treat a bacterial infection, patients should be told that
672 although it is common to feel better early in the course of therapy, the medication should be
673 taken exactly as directed. Skipping doses or not completing the full course of therapy may:
674 (1) decrease the effectiveness of immediate treatment, and (2) increase the likelihood that
675 the bacteria will develop resistance and will not be treatable by VIBATIV or other
676 antibacterial drugs in the future.

677 Common Adverse Effects

678 Patients should be informed about the common adverse effects of VIBATIV including taste
679 disturbance, nausea, vomiting, headache, and foamy urine. Patients should be instructed to
680 inform their healthcare provider if they develop any unusual symptom, or if any known
681 symptom persists or worsens. Patients should be instructed to inform their healthcare
682 provider of any other medications they are currently taking with VIBATIV, including
683 over-the-counter medications.

684 **Manufactured for:**

685 Theravance, Inc.
686 South San Francisco, CA 94080

687 **Marketed by:**

688 Astellas Pharma US, Inc.
689 Deerfield, IL 60015

690 US Patent Nos. 6,635,618 B2; 6,858,584 B2; 6,872,701 B2; 7,008,923 B2; 7,208,471 B2;
691 7,351,691 B2; 7,531,623 B2; and 7,544,364 B2

692 VIBATIV is a trademark of Astellas Pharma Inc.

693

MEDICATION GUIDE

VIBATIV (vy-'ba-tiv) (telavancin) for injection

Read this Medication Guide before you start taking VIBATIV and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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

VIBATIV may harm your unborn baby. Women who can become pregnant should have a blood pregnancy test before taking VIBATIV.

- Talk to your healthcare provider if you are pregnant or plan to become pregnant. Your healthcare provider will decide if VIBATIV is the right medicine for you
- Do not become pregnant while taking VIBATIV. Women who can become pregnant should use effective birth control (contraception) while taking VIBATIV
- If you get pregnant while taking VIBATIV, tell your healthcare provider right away
- If you become pregnant while taking VIBATIV, talk to your healthcare provider about taking part in the VIBATIV Pregnancy Registry. This is a study to learn how VIBATIV affects pregnancy and babies. You can enroll in this registry by calling 1- 888-658-4228

What is VIBATIV?

VIBATIV is a prescription antibiotic medicine used in adults, alone or with other medicines to treat certain types of germs (bacteria) that cause serious skin infections.

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

What should I tell my healthcare provider before taking VIBATIV?

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

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

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

Especially tell your healthcare provider if you take:

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

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

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

How will I receive VIBATIV?

- VIBATIV is injected into your vein (IV infusion) by your healthcare provider slowly over 1 hour, 1 time a day, for 7 to 14 days.
- Do not stop taking VIBATIV unless your healthcare provider tells you to even if you feel better.
- It is important that you receive **all of your VIBATIV doses**. Do not skip any doses.
- If you miss a dose or stop taking VIBATIV before getting all of your doses, contact your healthcare provider right away.
- If you skip doses or stop treatment too soon, the germs (bacteria) may grow again and VIBATIV may not work.
- Your healthcare provider will do tests before you start and while you take VIBATIV.

What are the possible side effects of VIBATIV?

VIBATIV may cause serious side effects, including:

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

- **Kidney problems**
- **Infusion-related reactions.** Infusion-related reactions can include: red color (flushing) to your upper body, hives (raised bumps), itching or rash if VIBATIV is given too fast
- **Intestine infection.** Intestine infections can cause diarrhea or bloody stools, stomach cramps, and a fever. These infections can happen 2 or more months after you stop taking VIBATIV
- **Irregular heartbeat.**
- **Changes in blood and urine test.** Tell your healthcare provider if you plan to have any test of your blood or urine while taking VIBATIV

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

The most common side effects of VIBATIV include:

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

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

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

How should I store VIBATIV?

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

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

General Information about the safe and effective use of VIBATIV.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VIBATIV for a condition for which it is not prescribed. Do not give VIBATIV to other people, even if they have the same symptoms that you have. It may harm them.

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

For more information, go to www.vibativ.com or call 1-800-727-7003.

What are the ingredients in VIBATIV?

Active ingredient: telavancin hydrochloride

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

Manufactured for:

Theravance, Inc.
South San Francisco, CA 94080

Marketed by:

Astellas Pharma US, Inc.
Deerfield, IL 60015

VIBATIV is a trademark of Astellas Pharma Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration
August 2009

NDA 22-110 VIBATIV™ (telavancin)

[Lipoglycopeptide]

**Theravance, Inc.
901 Gateway Boulevard, South San Francisco, CA 94080
[650-808-6076]**

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goal of the VIBATIV REMS is to avoid unintended exposure of pregnant women to VIBATIV by:

- Educating healthcare professionals (HCPs) and patients on the potential risk of fetal developmental toxicity if women are exposed to VIBATIV while pregnant.
- Informing HCPs that a serum pregnancy test should be performed before initiating therapy with VIBATIV in women of childbearing potential.
- Informing HCPs that women of childbearing potential, including those being treated in the outpatient setting, should be counseled about pregnancy prevention and use of effective contraception during VIBATIV use.
- Informing HCPs and patients about the Pregnancy Registry for patients exposed to VIBATIV during pregnancy.

II. REMS ELEMENTS

A. Medication Guide

Theravance will ensure that a Medication Guide will be distributed with each VIBATIV prescription in accordance with 21 CFR 208.24. VIBATIV is packaged as a single unit of use and the Medication Guide is inserted inside the carton.

Additional copies of the Medication Guide will also be available via sales and/or clinical representatives, the product website, and by request at 1-800-727-7003.

Please see appended Medication Guide.

B. Communication Plan

In accordance with FDCA 505-1(e)(3), Theravance will implement a communication plan to targeted healthcare providers and pharmacists to support the implementation of the VIBATIV REMS. The communication plan consists of the following:

1. A Dear Healthcare Provider (HCP) Letter describing the fetal effects of VIBATIV seen in animals and pregnancy prevention measures. The letter will include Pregnancy Registry Information. The letter will be accompanied by the VIBATIV Package Insert (PI) and the Medication Guide.
2. The Dear HCP Letter will be distributed to targeted HCPs and pharmacists at the specified timeframes:
 - a. Prior to commercial distribution
 - b. 6 months after product approval
 - c. 1 and 2 years after product approval
3. The Dear HCP Letter will be distributed either through hardcopy mailings by U.S. mail or email to reach the target audience. The letter will also be available on the product website. The website will also include information about the Pregnancy Registry and the toll-free number to call to enroll in the Registry.

The email will target physicians based on the American Medical Association database. The email distribution list for other healthcare providers will be based on other databases and secured through a private contractor.

Providers that have an email address on file will receive the Dear HCP Letter via email. If the intended recipient does not open the Dear HCP Letter within 72 hours, the materials will be distributed hardcopy via U.S. mail. The healthcare providers on the target audience list who do not have an email on file will receive a hardcopy via U.S. mail.

All distributions, hardcopy and electronic will include the designation "Important Drug Warning" according to 21 CFR 200.5.

4. The Dear HCP Letter will be sent to the following targeted Healthcare Providers:

Physician Groups

Infectious Disease
Emergency Medicine
Critical Care Medicine
Hospitalist
General Surgery
Obstetrics and Gynecology
Family Practice

Other Healthcare Professionals

Health System Pharmacists / Hospital Pharmacists
Outpatient Infusion Providers

Organizational Headquarters

Infectious Disease Society of America
American College of Emergency Physicians

Society of Critical Care Medicine
 Society of Hospital Medicine
 Surgical Infection Society
 American Thoracic Society (critical care)
 American College of Chest Physicians (critical care)
 American College of Obstetrics and Gynecology
 American Society of Health System Pharmacists
 Society of Infectious Disease Pharmacists
 American College of Clinical Pharmacists
 Outpatient Parenteral Antimicrobial Therapy
 American Medical Association

The Dear HCP Letter will be distributed with the VIBATIV Package Insert and Medication Guide.

Please see appended Dear HCP Letter.

C. Elements to Assure Safe Use

VIBATIV can be approved without any elements to assure safe use.

D. Implementation System

VIBATIV can be approved without any elements to assure safe use, therefore an implementation system is not required.

E. Timetable for Submission of Assessments

Theravance will submit REMS Assessments at 18 months, 3 years, and 7 years following the approval of the REMS (see table below). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Theravance will submit each assessment so that it will be received by the FDA on or before the due date.

Timetable for Submission of Assessments	
Assessment	Month/Year of Submission
1 st Assessment (18 months from approval)	March 2011
2 nd Assessment (3 years from approval)	September 2012
3 rd Assessment (7 years from approval)	September 2016

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22110	ORIG-1	THERAVANCE INC	TELAVANCIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDWARD M COX
09/11/2009