

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

WARNINGS:

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

RECENT MAJOR CHANGES

Warnings and Precautions (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)

Creatinine Clearance ^a (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.

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-THRX (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: 06/2013

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FULL PRESCRIBING INFORMATION

WARNINGS

- Patients with pre-existing moderate/severe renal impairment ($\text{CrCl} \leq 50 \text{ mL/min}$) 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 ($\text{CrCl} \leq 50 \text{ mL/min}$) should be considered only when the anticipated benefit to the patient outweighs the potential risk [see *Warnings and Precautions (5.1)*].
- Nephrotoxicity: New onset or worsening renal impairment has occurred. Monitor renal function in all patients [see *Warnings and Precautions (5.3)*].
- Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV [see *Warnings and Precautions (5.4)*, *Use in Specific Populations (8.1)*].
- Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus [see *Warnings and Precautions (5.4)*, *Use in Specific Populations (8.1)*].
- Adverse developmental outcomes observed in 3 animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans [see *Warnings and Precautions (5.4)*, *Use in Specific Populations (8.1)*]

1 INDICATIONS AND USAGE

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 infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Combination therapy may be clinically indicated if the documented or presumed pathogens 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.

2.3 Patients with Renal Impairment

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

Table 1: Dosage Adjustment in Adult Patients with Renal Impairment

Creatinine Clearance ^a (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)

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

2.4 Preparation and Administration

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

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

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

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

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

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

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

114 **4 CONTRAINDICATIONS**

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

116 **5 WARNINGS AND PRECAUTIONS**

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

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

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

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

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

137

138 **5.3 Nephrotoxicity**

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

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

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

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

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

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

162 **5.5 Hypersensitivity Reactions**

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

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

169 **5.6 Infusion-Related Reactions**

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

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

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

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

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

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

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

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

197 **5.9 QTc Prolongation**

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

204 **5.10 Coagulation Test Interference**

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

211 Table 3: Coagulation Tests Affected and Unaffected by Telavancin

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

212
213 No evidence of increased bleeding risk has been observed in clinical trials with VIBATIV.
214 Telavancin has no effect on platelet aggregation. Furthermore, no evidence of
215 hypercoagulability has been seen, as healthy subjects receiving VIBATIV have normal
216 levels of D-dimer and fibrin degradation products.

217 **6 ADVERSE REACTIONS**

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

- 219 • Nephrotoxicity [see *Warnings and Precautions* (5.3)]
 - 220 • Infusion-related reactions [see *Warnings and Precautions* (5.5)]
 - 221 • *Clostridium difficile*-associated diarrhea [see *Warnings and Precautions* (5.6)]
- 222 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
223 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical
224 trials of another drug and may not reflect the rates observed in practice.

225 **6.1 Clinical Trials Experience**

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

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

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

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

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

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

	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.

HABP/VABP

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

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

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

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

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

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

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

Nephrotoxicity

Complicated Skin and Skin Structure Infections

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

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

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

Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia

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

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

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

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

303 **6.2 Postmarketing Experience**

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

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

312 **7 DRUG INTERACTIONS**

313 **7.1 Drug-Laboratory Test Interactions**

314 Effects of Telavancin on Coagulation Test Parameters

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

322

323 Urine Protein Tests

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

327 **8 USE IN SPECIFIC POPULATIONS**

328 **8.1 Pregnancy**

329 Teratogenic Effects: Pregnancy Category C

330 *Pregnancy Exposure Registry*

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

335 *Fetal Risk Summary*

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

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

342 *Clinical Considerations*

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

346 *Data*

347 Human Data

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

349

350

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 HABP/VABP patients treated with VIBATIV at a dose of 10 mg/kg once daily in
382 clinical trials of HABP/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)].

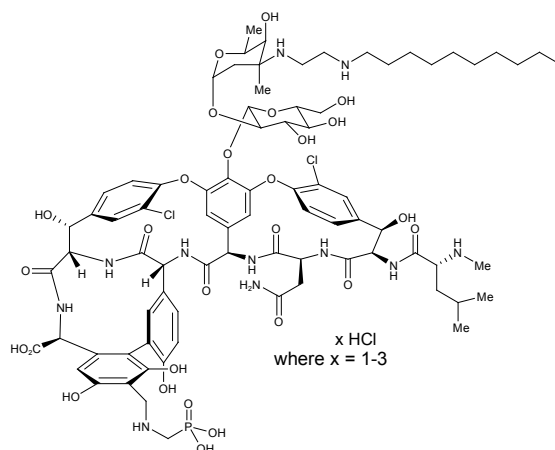
424 The clearance of telavancin by continuous venovenous hemofiltration (CVVH) was
425 evaluated in an in vitro study [see *Nonclinical Toxicology* (13.2)]. Telavancin was cleared by
426 CVVH and the clearance of telavancin increased with increasing ultrafiltration rate.
427 However, the clearance of 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 $C_{80}H_{106}C_{12}N_{11}O_{27}P \cdot xHCl$ (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

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

12.3 Pharmacokinetics

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

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

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

Distribution

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

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

501 adults. Telavancin concentrations in ELF and AM exceeded the MIC₉₀ for *S. aureus*
502 (0.5 mcg/mL) for at least 24 hours following dosing.

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

505 Metabolism

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

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

515 Excretion

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

519 Specific Populations

520 *Geriatric Patients*

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

525 *Pediatric Patients*

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

528 *Gender*

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

532 *Renal Impairment*

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

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

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

544 *Use actual body weight if < ideal body weight (IBW)
545 IBW (male) = 50 kg + 0.9 kg/cm over 152 cm height
546 IBW (female) = 45.5 kg + 0.9 kg/cm over 152 cm height

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

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

557 *Hepatic Impairment*

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

562 Drug Interactions

563 *In Vitro*

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

569 *Midazolam*

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

575 *Aztreonam*

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

581 *Piperacillin-tazobactam*

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

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

12.4 Microbiology

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

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

Mechanism of Action

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

Interactions with Other Antibacterial Drugs

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

Cross-Resistance

Some vancomycin-resistant enterococci have a reduced susceptibility to telavancin. There is 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 13 NONCLINICAL TOXICOLOGY

671 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

683 **13.2 Animal Toxicology and/or Pharmacology**

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

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

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

695 **14 CLINICAL TRIALS**

696 **14.1 Complicated Skin and Skin Structure Infections**

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

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

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

712 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

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

716 Table 12: Clinical Cure at Test-of-Cure in cSSSI Trials 1 and 2 – ATe and CE
717 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	74.7%	74.0%	0.7
	(309/426)	(307/429)	(-5.3, 7.2)	(342/458)	(356/481)	(-5.1, 6.5)
CE	84.3%	82.8%	1.5	83.9%	87.7%	-3.8
	(289/343)	(288/348)	(-4.3, 7.3)	(302/360)	(315/359)	(-9.2, 1.5)

718 ¹95% CI computed using a continuity correction

720 The cure rates by pathogen for the microbiologically evaluable (ME) population are
721 presented in [Table 13](#).

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

724

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

14.2 HABP/VABP

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

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

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

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

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

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

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

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%)	

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

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

777 **15 REFERENCES**

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783 Approved Standard – 11th ed. CLSI document M2-A11; CLSI, Wayne, PA.
784 19087-1898, 2012.

785 3. CLSI. Performance Standards for Antimicrobial Susceptibility Testing – 22nd
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788
789 **16 HOW SUPPLIED/STORAGE AND HANDLING**

790 • Cartons of 10 individually packaged 250 mg single-dose vials (NDC 52118-002-01)

791 • Cartons of 10 individually packaged 750 mg single-dose vials (NDC 52118-001-01)

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

794 **17 PATIENT COUNSELING INFORMATION**

795 *See Medication Guide.*

796 Use during Pregnancy and by Women of Childbearing Potential

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

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

802 • Have a pregnancy test prior to administration of VIBATIV

803 • If not pregnant, use effective contraceptive methods to prevent pregnancy during
804 VIBATIV treatment

805 • Notify their prescribing physician/ healthcare provider if they become pregnant during
806 VIBATIV treatment

807
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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842 Theravance, Inc.

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

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

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

VIBATIV can cause serious side effects, including:

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

What is VIBATIV?

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

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

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

Who should not take VIBATIV?

Do not take VIBATIV if you:

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

What should I tell my healthcare provider before receiving VIBATIV?

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

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

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

Especially tell your healthcare provider if you take:

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

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

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

How will I receive VIBATIV?

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

What are the possible side effects of VIBATIV?

VIBATIV may cause serious side effects, including:

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

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

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

The most common side effects of VIBATIV include:

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

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

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

How should I store VIBATIV?

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

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

General Information about the safe and effective use of VIBATIV.

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

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

For more information, go to www.vibativ.com or call 1-855-MED-THRX (1-855-633-8479).

What are the ingredients in VIBATIV?

Active ingredient: telavancin hydrochloride

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

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

Manufactured for:

Theravance, Inc.

South San Francisco, CA 94080

VIBATIV® is a registered trademark of Theravance, Inc.

Revised: 06/2013

Initial approval 9/2009

Most recent modification 6/2013

**NDA 22-110 and NDA 22-407 VIBATIV[®]
(telavancin) for injection
[Lipoglycopeptide]**

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

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the VIBATIV REMS are:

- A. To inform healthcare professionals (HCP) about the increased risk of mortality associated with VIBATIV in patients with pre-existing creatinine clearance of ≤ 50 mL/min being treated for hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP)
- B. To avoid unintended exposure of pregnant women to VIBATIV through:
 - Educating healthcare professionals 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 Females of Reproductive Potential (FRP)
 - Informing HCPs that FRP, including those being treated in the outpatient setting, should be counseled about pregnancy prevention and use of effective contraception during VIBATIV use

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each VIBATIV prescription in accordance with 21 CFR 208.24.

The Medication Guide is part of the REMS and is appended.

B. Communication Plan

Theravance will implement the following elements of a communication plan:

1. **A Dear Healthcare Provider (DHCP) Letter** will be sent within 60 days, and again at 6 months, 1 and 2 years of approval, of the most recent REMS modification. The letter will be sent through either hardcopy mailings by U.S. mail or email to healthcare professionals likely to prescribe or dispense VIBATIV. This includes, but is not limited to healthcare professionals who practice in: hospitals, infectious disease,

emergency medicine, critical care, general surgery, obstetrics and gynecology, family practice and outpatient infusion centers. Subsequent letters will be sent to any new health care provider that was not initially sent the appended DHCP letter. The DHCP Letter will be distributed with the VIBATIV Package Insert and Medication Guide.

- a. The letter will be available via a link from the VIBATIV website at www.vibativ.com and as well as from the medical information department for a period of one year after the approval of the most recent modification of the REMS. The letter will include Pregnancy Registry Information.
- b. The Dear HCP Letter will be sent to the leadership of the following professional organizations with a request that these organizations disseminate the content of the letter to their professional membership:
 - 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
 - American College of Chest Physicians
 - American College of Obstetrics and Gynecology
 - Outpatient Parenteral Antimicrobial Therapy
 - American Medical Association
 - American Hospital Association
 - Federation of American Hospitals
 - American Society of Health-System Pharmacists
 - American College of Clinical Pharmacists
 - Society of Infectious Disease Pharmacists
 - American College of Clinical Pharmacists
 - American Pharmacists Association
 - Premier
2. 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.
3. Providers that have an email address on file will receive the DHCP Letter via email. If the intended recipient does not open the DHCP Letter within 10 days, 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.
4. The DHCP letter will be provided to MedWatch at the same time it is provided to the professional organizations.

The DHCP Letter is part of the REMS and is appended.

C. Timetable for Submission of Assessments

Theravance will submit REMS Assessments to FDA at 18 months, 3 years, and 7 years following the approval date of the most recent modification of the REMS (6/2013).

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 FDA on or before the due date.