PRODUCT MONOGRAPH

[Pr]VIBATIV™
Telavancin for injection

250 mg telavancin (as telavancin hydrochloride)/vial
750 mg telavancin (as telavancin hydrochloride)/vial

Antibiotic

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[Pr]VIBATIV™

Telavancin for injection (as telavancin hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients*
Intravenous infusion	Lyophilized powder for intravenous infusion 250 mg telavancin (as telavancin hydrochloride)/vial 750 mg telavancin (as telavancin hydrochloride)/vial	Hydroxypropylbetadex Mannitol

*see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section for a complete listing of non-medicinal ingredients.

INDICATIONS AND CLINICAL USE

VIBATIV (telavancin hydrochloride for injection) is a lipoglycopeptide antibiotic indicated for:

- The treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (methicillin-resistant and -susceptible strains (MRSA and MSSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group *(*including *S. anginosus, S. intermedius* and *S. constellatus)*, and *Enterococcus faecalis* (vancomycin-susceptible isolates only). Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative organisms.

- The treatment of adult patients with hospital-acquired bacterial pneumonia (HAP) and ventilator-associated bacterial pneumonia (VAP), known or suspected to be caused by susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant *S. aureus*).

VIBATIV has **not** been studied in patients with diabetic foot ulcers.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to telavancin. Once these results are available antimicrobial therapy should be adjusted accordingly. In the absence of such

data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. VIBATIV may be initiated as empiric therapy before the results of these tests are known.

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

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.

Geriatrics (≥ 65 years of age)
Evidence from clinical studies suggests that use in the geriatric population is associated with lower clinical success rates in cSSSI patients ≥ 65 years of age compared with those < 65 years of age. Overall, treatment-emergent adverse events occurred with similar frequencies in patients ≥ 65 and <65 years of age. In clinical studies of HAP/VAP patients, treatment-emergent adverse events as well as deaths and other serious adverse events occurred more often in patients ≥ 65 years of age than in those < 65 years of age in both treatment groups (see **WARNINGS AND PRECAUTIONS - Special Populations, Geriatrics**).

Because elderly patients are more likely to have decreased renal function, dosage adjustment for elderly patients should be based on renal function. Dosage adjustment is not required solely on the basis of age (see **DOSAGE AND ADMINISTRATION - Patients with Renal Impairment, ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics**).

Pediatrics (< 18 years of age)
The safety and effectiveness of VIBATIV in patients less than 18 years of age has not been established (see **WARNINGS AND PRECAUTIONS - Special Populations, Pediatrics**).

CONTRAINDICATIONS

VIBATIV (telavancin hydrochloride for injection) is contraindicated for use in patients who have known hypersensitivity to this drug or to other glycopeptides or to any ingredient in the formulation or component of the container (see **WARNINGS AND PRECAUTIONS – Immune**). For a complete listing of non-medicinal ingredients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Treatment of HAP/VAP in patients with pre-existing moderate to severe renal impairment (CrCl ≤50 mL/min) was associated with increased mortality observed versus vancomycin.**
- **Nephrotoxicity: new onset or worsening renal impairment has occurred. Monitor renal function in all patients.**
- **VIBATIV IS NOT RECOMMENDED for use in patients with severe renal impairment (CrCl < 30 mL/min), and in patients with end stage renal disease (ESRD) requiring hemodialysis (see WARNINGS AND PRECAUTIONS - Renal).**
- **Use of VIBATIV in patients with moderate renal impairment (CrCl 30 - 50 mL/min) should be considered only when the anticipated benefit to the patient outweighs the potential risk. A dosage adjustment is required in these patients and renal function (e.g. serum creatinine) should be monitored MORE FREQUENTLY in this group (see WARNINGS AND PRECAUTIONS – Renal).**
- **Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV.**
- **Developmental and reproductive toxicology studies in both rats and rabbits demonstrated a low incidence of limb defects (see TOXICOLOGY - Reproductive and Developmental Toxicology). There are no adequate and well-controlled studies in pregnant women with VIBATIV. VIBATIV should not be used during pregnancy unless the benefit to the mother outweighs the risk to the fetus.**

General

VIBATIV should be administered over a period of **not less** than 60 minutes to avoid infusion-related reactions. Rapid intravenous infusions of the glycopeptide class of antimicrobial agents, and VIBATIV, have been associated with "Red-man syndrome" like reactions including: flushing of the upper body, urticaria, pruritus, or rash. Stopping or slowing the infusion may result in cessation of these reactions (see **ADVERSE REACTIONS**).

As with other antibacterial drugs, use of VIBATIV may result in overgrowth of nonsusceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs during therapy, appropriate measures should be taken. Prescribing VIBATIV in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Due to the risk of teratogenicity, women of child-bearing potential who are given VIBATIV should either abstain from sexual activity or use double-barrier means of contraception while on VIBATIV. Drug interaction studies between VIBATIV and hormonal contraceptives have not been conducted.

VIBATIV contains hydroxypropylbetadex, a cyclodextrin. Cyclodextrins have been associated with nephrotoxicity. The use of other medications that contain a cyclodextrin at the same time as VIBATIV is not recommended.

Telavancin interferes with some laboratory coagulation tests, such as prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and activated clotting time (see **DRUG INTERACTIONS – Drug-Laboratory Interactions**).

Cardiovascular

In a Phase 1 thorough QT study involving healthy adult volunteers, doses up to 15 mg/kg VIBATIV prolonged the QTc interval (see **ACTION AND CLINICAL PHARMACOLOGY- Pharmacodynamics, Table 6**).

Patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy were not included in clinical trials of VIBATIV. There is limited clinical experience using VIBATIV in patients with known prolongation of the QTc interval, patients with hypokalemia, patients receiving Class 1A (e.g. quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents, or in other pro-arrhythmic conditions (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacodynamics**). It is expected that these patients may be more susceptible to drug-induced QT prolongation.

Many drugs that cause QT/QTc prolongation are suspected to increase the risk of a rare polymorphic ventricular tachyarrhythmia known as Torsades de pointes. Generally, the risk of Torsades de pointes increases with the magnitude of QT/QTc prolongation produced by the drug.

Pharmacokinetic studies between telavancin and drugs that prolong the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. It is recommended that VIBATIV be used with caution in patients taking concomitant medications with any risk of Torsades de pointes.

Ear and Labyrinth Disorders

Ototoxicity has not been studied in patients treated with VIBATIV. Pharmacological class related ototoxicity cannot be excluded in these patients. Ototoxicity has been reported with use of telavancin (see **ADVERSE REACTIONS**). Patients who develop signs and symptoms of impaired hearing or disorders of the inner ear during treatment with VIBATIV should be carefully evaluated and monitored.

Gastrointestinal

Clostridium difficile - associated disease (CDAD)

Clostridium difficile - associated disease (CDAD) has been reported with use of many antibacterial agents, including VIBATIV (see **ADVERSE REACTIONS**). CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over two months after the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases.

Hepatic

No dose adjustments are necessary for patients with mild to moderate hepatic insufficiency (Child-Pugh class A or B) (see **ACTION AND CLINICAL PHARMACOLOGY-Hepatic Insufficiency**). VIBATIV has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C).

Immune

Hypersensitivity
Drug hypersensitivity, rash hypersensitivity, allergic alveolitis and anaphylactic reaction has been reported in patients receiving VIBATIV. Before therapy is instituted, careful inquiry should be made to determine whether the patient had a previous hypersensitivity reaction to VIBATIV or glycopeptides (see **CONTRAINDICATIONS**). Hypersensitivity reactions may be more likely to occur in patients with a history of sensitivity to multiple allergens.

Renal

Treatment of HAP/VAP in patients with pre-existing moderate to severe renal impairment (CrCl ≤ 50 mL/min) was associated with increased mortality. In these patients, all-cause mortality within 28 days of starting treatment was 39% in the VIBATIV group, compared with 30% in the vancomycin group. All-cause mortality at 28 days in patients without pre-existing moderate to severe renal impairment (CrCl >50 mL/min) was 17% in the VIBATIV group and 18% in the vancomycin group (see **CLINICAL TRIALS**).

VIBATIV is associated with an increased risk of renal toxicity, primarily in patients receiving concomitant medications known to affect kidney function, or patients with baseline conditions known to predispose to kidney dysfunction.

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

Treatment of cSSSI in patients with severe renal impairment (CrCl ≤ 30 mL/min) or ESRD requiring hemodialysis was associated with decreased efficacy and increased incidences of renal adverse events, discontinuations due to adverse events and serious adverse events.

Renal function (e.g. serum creatinine) should be monitored in all patients receiving VIBATIV. Values should be obtained prior to initiation of treatment, during treatment (~day 3), at the end of therapy, **or more frequently as clinically indicated**. **If renal function deteriorates, the benefit of continuing VIBATIV versus discontinuing and initiating therapy with an alternative agent should be assessed** (see **DOSAGE AND ADMINISTRATION – Recommended Dose and Dosage Adjustment; WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests).**

VIBATIV IS NOT RECOMMENDED for use in patients with Severe Renal Impairment (CrCl <30 mL/min), and in patients with ESRD requiring hemodialysis. A dosage adjustment is required in patients with Moderate Renal Impairment (CrCl 30 – 50 mL/min) (see **DOSAGE AND ADMINISTRATION – Recommended Dose and Dosage Adjustment)**

Sexual Function/Reproduction

The effect of telavancin on testicular development and on sperm production and fertility in humans is unknown.

Chronic toxicity studies in adult rats given telavancin at doses up to 100 mg/kg/day (approximately equivalent to the human daily dose) for 6 weeks demonstrated a reduction in sperm number and motility that was reversible following an 8-week recovery period. Fertility studies in rats have shown that doses up to 100 mg/kg/day had no effect on fertility (see **TOXICOLOGY - Reproductive and Development Toxicology**).

Susceptibility/Resistance

Development of Drug Resistance Bacteria
Prescribing VIBATIV in the absence of' a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria."

Special Populations

Pregnant Women
There are no adequate and well-controlled studies of VIBATIV in pregnant women. The pregnancy status of women of child-bearing potential should be established prior to dosing with VIBATIV.

VIBATIV should not be used during pregnancy unless the benefit to the mother clearly outweighs the risk to the fetus (see **WARNINGS AND PRECAUTIONS**). Alternative therapies can be used before considering the use of VIBATIV in women of child-bearing potential.

In developmental and reproductive toxicology studies, the potential for telavancin to cause limb malformations was seen at near clinical exposure levels. In the rat study, in which dams were dosed

during the period of organogenesis at 50, 100, or 150 mg/kg/day, syndactyly (one fetus at 100 mg/kg/day) and brachymelia (one fetus each at 100 and 150 mg/kg/day) were noted. Also noted in the pre- and post-natal development rat study was one pup with transient, limited use of its forelimb from a dam that had received 150 mg/kg/day. In the rabbit study at doses up to 75 mg/kg/day, brachymelia and adactyly were noted in a single rabbit fetus whose dam had received 75 mg/kg/day. These effects occurred in animals exposed to approximately 1 to 2-fold the clinical dose based on AUC (see **TOXICOLOGY - Reproductive and Developmental Toxicology**).

Drug-drug interaction studies between VIBATIV and hormonal contraceptives were not conducted. Women of child-bearing potential who are given VIBATIV should either abstain from sexual activity or use double-barrier means of contraception.

Nursing Women
It is not known whether telavancin is excreted in human milk. Breast-feeding should be discontinued during treatment with VIBATIV.

Pediatrics (< 18 years of age)
The safety and effectiveness of VIBATIV in pediatric patients has not been established.

Geriatrics (≥ 65 years of age)
Of the 1,029 patients treated with VIBATIV at a dose of 10 mg/kg once daily in controlled clinical trials of cSSSI, 18% were ≥ 65 years of age and 9% were ≥ 75 years of age. In the Phase 3 clinical studies, lower clinical success rates were observed in cSSSI patients ≥ 65 years of age compared with those < 65 years of age. Overall, treatment-emergent adverse events occurred with similar frequencies in patients ≥ 65 and < 65 years of age. Of the 749 patients treated with VIBATIV at a dose of 10 mg/kg once daily in controlled clinical trials of HAP/VAP, 53% were ≥ 65 years of age and 31% were ≥ 75 years of age. Treatment-emergent adverse events as well as deaths and other serious adverse events occurred more often in patients ≥ 65 years of age than in those < 65 years of age in both treatment groups.

Telavancin is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function (see **WARNINGS AND PRECAUTIONS – Renal**).

Because elderly patients are more likely to have decreased renal function, dosage adjustment may be required. Dosage adjustment is not required solely on the basis of age (see **DOSAGE AND ADMINISTRATION - Recommended Dose and Dosage Adjustment; ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics**).

Monitoring and Laboratory Tests

Renal Function
VIBATIV is associated with an increased risk of renal toxicity, primarily in patients receiving concomitant medications known to affect kidney function, or patients with baseline conditions known to predispose to kidney dysfunction.

Renal function (e.g. serum creatinine) should be monitored in all patients receiving VIBATIV and more frequently in patients with moderate renal impairment (CrCl 30 –50 mL/min).

Values should be obtained prior to initiation of treatment, during treatment (~day 3), at the end of therapy, **or more frequently as clinically indicated. If renal function deteriorates, the benefit of continuing VIBATIV versus discontinuing and initiating therapy with an alternative agent should be assessed** (see **DOSAGE AND ADMINISTRATION – Recommended Dose and Dosage Adjustment; WARNINGS AND PRECAUTIONS - Renal**).

ADVERSE REACTIONS

Adverse Events Overview

A total of 1780 patients have received treatment with VIBATIV 10 mg/kg (or a dosage adjusted for renal insufficiency) in the efficacy and safety studies in cSSSI and HAP/VAP.

cSSSI

The most common adverse events in patients treated with VIBATIV in the cSSSI Phase 3 clinical studies were dysgeusia or taste disturbance (33%), nausea (22%), urine abnormality or foamy urine (12%), vomiting (11%), headache (9%), diarrhea (6%) and insomnia (5%). These events were generally mild to moderate in severity and transient in duration.

In the combined Phase 3 clinical studies, of the patients treated with VIBATIV, 8% of patients discontinued treatment due to adverse events.

The most frequently reported treatment emergent adverse events resulting in discontinuation of study medication among patients treated with VIBATIV 10 mg/kg were nausea (1%), rash (0.8%), vomiting (0.7%), increased blood creatinine and osteomyelitis (0.6% each), acute renal failure (0.5%).

Serious adverse events were reported in 7% of patients treated with VIBATIV. Twenty-six patients (2%) in the VIBATIV group experienced at least one possibly/probably related serious adverse event. The most frequently reported treatment emergent adverse events in patients treated with VIBATIV were renal failure acute and myocardial infarction (0.4% each), anaemia, drug hypersensitivity, mental status changes and renal insufficiency (0.3% each).

Nine patients who received VIBATIV died (one patient received 7.5 mg/kg, eight patients received 10 mg/kg).

HAP/VAP

The most common adverse events in patients treated with VIBATIV in the HAP/VAP Phase 3 clinical studies were diarrhea (11%), constipation (9%), anemia (9%), hypokalemia (8%), hypotension (6%), peripheral edema (5%), nausea (5%), vomiting (5%), insomnia (5%), acute renal failure (5%) and decubitus ulcer (5%). The frequencies of these events were similar in vancomycin-treated patients.

In the combined Phase 3 clinical studies, 8% of patients treated with VIBATIV discontinued treatment due to adverse events versus 5% of patients who received vancomycin. The most frequently reported treatment emergent adverse events resulting in discontinuation of study medication among patients treated with VIBATIV were renal failure acute (1%), electrocardiogram QT corrected interval prolonged (1%), blood creatinine increased (<1%), and sepsis (<1%).

Serious adverse events were reported in 31% of patients treated with telavancin compared with 26% of patients who received vancomycin. A total of 23 telavancin-treated patients (3%) experienced at least one possibly/probably related SAE compared with 17 vancomycin-treated patients (2%). The most frequently reported serious adverse event was septic shock (4% of patients in both treatment groups). Multi-organ failure, renal failure acute, and sepsis were observed in slightly more (1% absolute difference) telavancin-treated patients than vancomycin-treated patients.

Twenty percent of patients who received VIBATIV died during the studies, compared with 19% of patients who received vancomycin.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Most Common Clinical Trial Adverse Drug Reactions (occurring at a rate of ≥ 1%)

cSSSI

Clinical and pharmacology studies enrolled a total of 3277 patients, who were treated with either VIBATIV (N=1697), or a comparator (N= 1580), primarily vancomycin, for up to 14 days, with the comparator dose adjusted as per study institution guidelines.

The most common adverse reactions in patients treated with VIBATIV in the clinical pharmacology studies were dysgeusia (taste disturbance) (53%), urine abnormality (foamy urine) (15%), headache (15%), nausea (13%), and somnolence (8%).

In the efficacy and safety studies in cSSSI, 1221 patients were treated with VIBATIV, (N=1029 treated with the recommended dosage of 10 mg/kg; N=192 treated with 7.5 mg/kg). In these same efficacy and safety studies in cSSSI, 1222 patients were treated with comparator antibiotic (N=1195 treated with vancomycin; N=27 treated with an antistaphylococcal penicillin).

Table 1 displays the incidence of adverse reactions considered possibly or probably related to study drug through the follow-up (Test of Cure) visit, reported in ≥ 1% of the patients treated for up to 14 days with VIBATIV or comparator in the ATLAS 1 and ATLAS 2 Phase 3 clinical studies (see **CLINICAL TRIALS**). These events were generally mild to moderate in severity and transient in duration. Less than 0.5% of VIBATIV- or comparator-treated patients experienced severe nausea or vomiting.

Table 1: Incidence of Related Treatment Emergent Adverse Reactions (%) Reported in ≥ 1% of VIBATIV- or Comparator- Treated Patients in cSSSI Phase 3 ATLAS 1 and ATLAS 2 Clinical Studies

	VIBATIV N=929 (%)	Comparator N=938 (%)
Any event	583 (63%)	484 (52%)
Blood and lymphatic system disorders	6 (<1%)	11 (1%)
Cardiac disorders	17 (2%)	11 (1%)
Gastrointestinal disorders	290 (31%)	207 (22%)
abdominal pain	5 (<1%)	16 (2%)
constipation	40 (4%)	17 (2%)
diarrhea	53 (6%)	60 (6%)
dry mouth	12 (1%)	15 (2%)
dyspepsia	14 (2%)	13 (1%)
nausea	208 (22%)	109 (12%)
vomiting	104 (11%)	58 (6%)
General disorders and administration site conditions	115 (12%)	104 (11%)
fatigue	27 (3%)	20 (2%)
infusion site pain	8 (<1%)	14 (1%)
infusion site phlebitis	8 (<1%)	10 (1%)
infusion site pruritus	6 (<1%)	11 (1%)
rigors	29 (3%)	11 (1%)
Immune system disorders	10 (1%)	10 (1%)
Infections and infestations	36 (4%)	35 (4%)
vaginal mycosis	9 (<1%)	10 (1%)
Investigations	37 (4%)	37 (4%)
alanine aminotransferase increased	6 (<1%)	12 (1%)
aspartate aminotransferase increased	6 (<1%)	10 (1%)
blood creatinine increased	11 (1%)	4 (<1%)
Metabolism and nutrition disorders	47 (5%)	38 (4%)
anorexia	14 (2%)	9 (<1%)
decreased appetite	20 (2%)	15 (2%)
Musculoskeletal and connective tissue disorders	21 (2%)	20 (2%)
Nervous system disorders	362 (39%)	147 (16%)
dizziness	35 (4%)	29 (3%)
dysgeusia	306 (33%)	60 (6%)
headache	82 (9%)	64 (7%)
Psychiatric disorders	56 (6%)	45 (5%)
insomnia	43 (5%)	32 (3%)
Renal and urinary disorders	138 (15%)	38 (4%)
urine abnormality (foamy urine)	115 (12%)	26 (3%)
Reproductive system and breast disorders	13 (1%)	15 (2%)

Table 1: Incidence of Related Treatment Emergent Adverse Reactions (%) Reported in ≥ 1% of VIBATIV- or Comparator- Treated Patients in cSSSI Phase 3 ATLAS 1 and ATLAS 2 Clinical Studies

	VIBATIV N=929 (%)	Comparator N=938 (%)
Respiratory, thoracic and mediastinal disorders	33 (4%)	22 (2%)
Skin and subcutaneous tissue disorders	113 (12%)	184 (20%)
erythema	5 (<1%)	11 (1%)
hyperhidrosis	10 (1%)	7 (<1%)
pruritus	54 (6%)	146 (16%)
rash	36 (4%)	34 (4%)
Vascular disorders	18 (2%)	27 (3%)
flushing	7 (<1%)	15 (2%)

In the Phase 3 clinical studies, the combined total adverse reactions associated with renal dysfunction and elevated serum creatinine levels, was 3% of patients treated with VIBATIV and 1% of patients treated with comparator. Thirteen VIBATIV-treated patients (1.4%) and two comparator-treated patients (0.2%) experienced a renal adverse event that was assessed as possibly/probably related to study medication and that resulted in early discontinuation.

Renal adverse events observed with VIBATIV-treated and comparator-treated patients were generally reversible and occurred more often in patients with impaired renal function or who were receiving concomitant medications known to adversely affect kidney function.

HAP/VAP

Table 2 displays the incidence of most common treatment emergent adverse drug reactions reported in ≥ 1% of HAP/VAP patients treated with VIBATIV or vancomycin, as judged by the investigator to be possibly or probably related to the study medication.

Table 2: Incidence of Related Treatment Emergent Adverse Reactions (%) Reported in ≥ 1% of VIBATIV- or Vancomycin- Treated Patients in HAP/VAP Phase 3 ATTAIN 1 and ATTAIN 2 Clinical Studies

	VIBATIV (N=751)	Vancomycin* (N=752)
Any Event	212 (28)	174 (23)
Gastrointestinal Disorders		
Diarrhea	33 (4)	23 (3)
Nausea	17 (2)	11 (1)
Vomiting	14 (2)	7 (< 1)
Investigations		
Alanine Aminotransferase Increased	12 (2)	12 (2)
Aspartate Aminotransferase Increased	11 (1)	11 (1)
Blood Creatinine Increased	12 (2)	7 (< 1)

Electrocardiogram QT Corrected Interval Prolonged	8 (1)	3 (< 1)
Renal and Urinary Disorders		
Renal Failure Acute	17 (2)	10 (1)
Skin and Subcutaneous Tissue Disorders		
Rash	12 (2)	10 (1)

* Includes 20 patients who received an antistaphylococcal penicillin instead of vancomycin

In the Phase 3 clinical studies, 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 treated patients experienced at least one serious renal adverse event. Renal adverse events resulted in discontinuation of study medication in 14 VIBATIV-treated patients (2%) and 7 vancomycin-treated patients (1%) (see **WARNINGS AND PRECAUTIONS – Renal**).

Increases in serum creatinine to 1.5 times baseline occurred more frequently among VIBATIV-treated patients (16%) compared with vancomycin-treated patients (10%) (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests**).

Forty-four of 399 (11.0%) VIBATIV-treated patients ≥ 65 years of age had adverse events indicative of renal impairment compared with 30 of 352 patients (8%) < 65 years of age (see **WARNINGS AND PRECAUTIONS – Special Populations**).

Less Common Clinical Trial Adverse Drug Reactions (occurring at a rate of ≥ 0.1% to < 1%)

(as judged by the investigator to be possibly or probably related to VIBATIV)

The following less common adverse drug reactions were infrequently reported (≥ 0.1 to < 1%) in patients receiving VIBATIV in the cSSSI or HAP/VAP Phase 3 clinical studies:

- **Blood and lymphatic system disorders:** anaemia, coagulopathy, disseminated intravascular coagulation, eosinophilia, leukaemoid reaction, leukocytosis, leukopenia, secondary anaemia, thrombocythaemia, thrombocytopenia.

- **Cardiac disorders:** angina pectoris, arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, cardiac failure congestive, cardio-respiratory arrest, conduction disorder, myocardial infarction, myocardial ischaemia, palpitation, sinus tachycardia, supraventricular extrasystoles, tachycardia, ventricular arrhythmia, ventricular extrasystoles, ventricular tachycardia.

- **Ear and labyrinth disorders:** deafness, tinnitus, vertigo.

- **Eye disorders:** blepharospasm, conjunctivitis, eye irritation, keratoconjunctivitis sicca, vision blurred.

- **Endocrine disorders:** hypothyroidism.

- **Gastrointestinal disorders:** abdominal pain, colitis, constipation, diarrhea, dry mouth, duodenal ulcer, dyspepsia, gastric ulcer haemorrhage, gastrointestinal haemorrhage, gastrooesophageal reflux disease, haematemesis, hypoaesthesia oral, loose stools, lower gastrointestinal haemorrhage, mouth ulceration, stomatitis, stools watery.

- **General disorders and administration site conditions:** asthenia, fatigue, feeling abnormal, infusion related reaction, infusion site erythema, infusion site oedema, infusion site pain, injection site bruising, injection site haemorrhage, injection site phlebitis, injection site pruritus, injection site thrombosis, lethargy, malaise, localised oedema, mucosal inflammation, non-cardiac chest pain, oedema peripheral, pyrexia, red man syndrome, rigors, venipuncture site haemorrhage.

- **Hepatobiliary disorders:** hepatic function abnormal, hepatitis, hepatitis cholestatic.

- **Immune system disorders:** hypersensitivity.

- **Infections and infestations:** candidiasis, candiduria, catheter sepsis, clostridium colitis, fungal skin infection, oesophageal candidiasis, oral candidiasis, oral fungal infection, pneumonia, rash pustular, respiratory moniliasis, sepsis, urinary tract infection, vaginal candidiasis.

- **Injury, poisoning and procedural complications:** blister, postoperative haematoma.

- **Investigations:** activated partial thromboplastin time prolonged, alanine aminotransferase abnormal or increased, aspartate aminotransferase abnormal or increased, bacteria stool identified, band neutrophil count increased, blood alkaline phosphatase increased, blood bilirubin increased, blood cortisol decreased, blood in stool, blood lactate dehydrogenase increased, blood magnesium decreased, blood potassium decreased, blood pressure increased, blood urea increased, coagulation factor decreased, electrocardiogram QT corrected interval prolonged, gamma-glutamyltransferase increased, heart rate irregular, international normalised ratio increased, lymphocyte count increased, neutrophil count decreased, neutrophil count increased, platelet count decreased, platelet count increased, prothrombin time prolonged, urine output decreased, white blood cell count decreased, white blood cell count increased, white blood cells urine positive.

- **Metabolism and nutrition disorders:** anorexia, decreased appetite, diabetes mellitus, dehydration, fluid overload, hyperglycaemia, hyperkalaemia, hypoglycaemia, hypokalaemia, hyponatraemia, hypomagnesaemia, metabolic acidosis.

- **Musculoskeletal and connective tissue disorders:** arthralgia, arthritis, back pain, muscle cramp, muscle spasms, myalgia, neck pain, pain in extremity, pain in jaw, sensation of heaviness.

- **Nervous system disorders:** burning sensation, dizziness, dysgeusia, headache, hyperreflexia, hypertonia, hypogeusia, migraine, ischaemic stroke, paraesthesia, parosmia, polyneuropathy, somnolence.

- **Psychiatric disorders:** agitation, anxiety, confusional state, depression, hallucination, insomnia, libido decreased, mental status changes, panic attack, psychotic disorder, restlessness, sleep disorder.

- **Renal and urinary disorders:** acute prerenal failure, anuria, azotaemia, dysuria, haematuria, nocturia, oliguria, pollakiuria, polyuria, proteinuria, pyuria, renal failure acute, renal failure chronic, renal impairment, renal insufficiency, renal tubular acidosis, urinary incontinence, urine odour abnormal.

- **Reproductive system and breast disorders:** erectile dysfunction, genital pruritus female, menorrhagia, oedema genital, pelvic pain, postmenopausal haemorrhage, scrotal oedema, testicular pain, testicular swelling.

- **Respiratory, thoracic and mediastinal disorders:** acute pulmonary oedema, acute respiratory failure, alveolitis allergic, bronchospasm, choking sensation, cough, dry throat, dyspnoea, epistaxis, haemoptysis, hiccups, hydrothorax, hypoxia, lung infiltration, nasal congestion, nasopharyngeal disorder, pharyngolaryngeal pain, pleuritic pain, tachypnoea.

- **Skin and subcutaneous tissue disorders:** acne, angioneurotic oedema, cold sweat, decubitus ulcer, dermatitis, dermatitis allergic, dyshidrosis, erythema, exanthem, face oedema, hyperhidrosis, pruritus, pruritus generalised, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash pruritic, skin atrophy, urticaria.

- **Vascular disorders:** hot flush, hypertension, hypotension, thrombophlebitis superficial.

Abnormal Hematologic and Clinical Chemistry Findings

cSSSI

In the cSSSI Phase 3 clinical studies, the percentage of patients with normal baseline serum creatinine who experienced an increase in creatinine (maximum value ≥ 2.0 mg/dL) was 2.9% in VIBATIV-treated patients and 0.5% in comparator-treated patients. A total of 1.2% of VIBATIV-treated patients and 0.4% of comparator-treated patients had increases in creatinine that were considered to be an adverse event that was related to study medication. Increases in serum creatinine that were observed with VIBATIV-treated and comparator-treated patients were generally reversible and occurred more often in patients with impaired renal function or who were receiving concomitant medications known to adversely affect kidney function.

In the cSSSI Phase 3 clinical studies, the percentage of patients with normal baseline ALT who experienced an increase ≥ 3 times the upper limit of normal (ULN) was 2% in VIBATIV-treated patients and 4% in comparator-treated patients. The percentage of patients with normal baseline AST who experienced an increase ≥ 3 times ULN was 2% in VIBATIV-treated patients and 3% in comparator-treated patients. There were no patients with AST or ALT increase ≥ 3 times ULN and concurrent bilirubin increase ≥ 1.5 times ULN.

HAP/VAP
In HAP/VAP Phase 3 clinical studies, the percentage of patients with normal baseline serum creatinine at the start of treatment who experienced an increase in creatinine (maximum value ≥ 1.5 mg/dL and at least a 50% increase from baseline) was 14% of VIBATIV-treated patients and 9% of vancomycin-treated patients. In addition, the percentage of patients who had a maximum increase in serum creatinine of ≥ 1.25 times their baseline value was also higher in the VIBATIV group (45%) compared to the vancomycin group (34%). The number of patients with a ≥ 50% decrease from a normal baseline CrCl value was similar between the two groups, with 47 (15%) VIBATIV-treated patients and 50 (16%) vancomycin-treated patients experiencing such a decrease. The proportion of patients with an abnormal baseline CrCl value who had an on-treatment value ≤ 50% of baseline was greater in the VIBATIV group than the vancomycin group (15% vs. 8%).

Post-Market Adverse Drug Reactions

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

Serious hypersensitivity reactions have been reported after first or subsequent doses of VIBATIV, including anaphylactic reactions. It is unknown if patients with hypersensitivity reactions to vancomycin will experience cross-reactivity to VIBATIV (see **CONTRAINDICATIONS**).

DRUG INTERACTIONS

Overview

The inhibitory activity of telavancin against the following CYP 450 enzymes was evaluated in human liver microsomes: CYP 1A2, 2C9, 2C19, 2D6, and 3A4/5. Telavancin inhibited CYP 3A4/5 at potentially clinically relevant concentrations. A clinical study using multiple doses of telavancin with the probe substrate midazolam was conducted to further evaluate this effect. Telavancin had no effect on the pharmacokinetic disposition of midazolam.

Pharmacokinetic studies with telavancin and drugs that prolong the QTc interval have not been performed. There is limited clinical experience using VIBATIV in patients with known prolongation of the QTc interval, patients with hypokalemia, patients receiving Class 1A (e.g. quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents, or in other pro-arrhythmic conditions (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacodynamics**). It is recommended that VIBATIV be used with caution in patients taking concomitant medications that could be implicated in QT/QTc prolongation and/or Torsades de pointes.

Drug-Drug Interactions

Drug-drug interaction studies were performed with telavancin and other antibiotics that are likely to be co-administered:

- **Aztreonam**: Co-administration of telavancin and aztreonam had no effect on the pharmacokinetics of either antibiotic.
- **Piperacillin-tazobactam**: Co-administration of telavancin and piperacillin-tazobactam had no effect on the pharmacokinetics of any of the antibiotics.

In vitro investigations demonstrated no antagonism between telavancin and other antibacterial drugs including 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.

Aztreonam, piperacillin-tazobactam and metronidazole were used as concomitant antimicrobials in the Phase 3 HAP/VAP studies for the treatment of infections caused by Gram-negative pathogens, and the AEs associated with these drugs appeared to be additive to the AEs of telavancin and vancomycin. This trend was also apparent with the concomitant use of imipenem, fentanyl, and furosemide. Notably, piperacillin-tazobactam use was associated with a higher incidence of acute renal failure in both treatment groups.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Coagulation Testing

Although telavancin does not interfere with coagulation, it interfered with certain tests used to monitor coagulation (see Table 3), when conducted using samples drawn 0-18 hours after VIBATIV administration for patients being treated every 24 hours. Blood samples for these tests should be collected just prior to the patient's dose of VIBATIV and at least 18 hours after the VIBATIV dose.

Telavancin does not interfere with certain coagulation tests (see Table 3). Therefore, when these tests are utilized, samples can be collected at any time following VIBATIV administration.

Table 3: Coagulation Tests Affected and Unaffected by VIBATIV

Affected by VIBATIV	Unaffected by VIBATIV

Table 3: Coagulation Tests Affected and Unaffected by VIBATIV

Affected by VIBATIV	Unaffected by VIBATIV
• 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

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

Urinary Protein Tests

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

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dosing for VIBATIV is 10 mg/kg administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to 14 days (cSSSI) or for 7 to 21 days (***HAP/VAP)***. The duration of therapy should be guided by the severity and site of the infection and the patient's clinical and bacteriological progress.

Patients with Renal Impairment

A dosage adjustment is required for patients with creatinine clearance of 30 - 50 mL/min, as listed in Table 4 to achieve comparable exposure levels to patients with normal renal function (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics**). Intermittent hemodialysis does not remove clinically significant quantities of telavancin.

Table 4: Dosage Adjustment in Adult Patients with Renal Impairment

Creatinine Clearance* (mL/min)	VIBATIV Dose and Dosage Interval
> 50	10 mg/kg every 24 hours
30 – 50	7.5 mg/kg every 24 hours

*As calculated using the Cockroft-Gault formula (see **ACTION AND CLINICAL PHARMACOLOGY-Special Populations and Conditions**)

VIBATIV IS NOT RECOMMENDED for use in patients with Severe Renal Impairment (CrCl <30 mL/min), and in patients with ESRD requiring hemodialysis (see **WARNINGS**

AND PRECAUTIONS – Renal).

VIBATIV is associated with an increased risk of renal toxicity, primarily in patients receiving concomitant medications known to affect kidney function, or patients with baseline conditions known to predispose to kidney dysfunction.

Renal function (e.g. serum creatinine) should be monitored in all patients receiving VIBATIV. Values should be obtained prior to initiation of treatment, during treatment (~day 3), at the end of therapy, or **MORE FREQUENTLY in patients with Moderate Renal Impairment (CrCl 30 – 50 mL/min). If renal function deteriorates, the benefit of continuing VIBATIV versus discontinuing and initiating therapy with an alternative agent should be assessed.**

Patients with Hepatic Impairment
No dose adjustments are necessary for patients with mild to moderate (Child-Pugh class A or B) hepatic insufficiency (see **ACTION AND CLINICAL PHARMACOLOGY-**
Special Populations and Conditions). VIBATIV has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C).
Geriatrics (≥ 65 years of age)
Dosage adjustment is not required solely based on age. Because elderly patients are more likely to have decreased renal function, dosage adjustment for elderly patients should be based on renal function (see **DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics**).

Pediatrics (< 18 years of age)
No dosage recommendations can be made as the safety and efficacy of VIBATIV has not been established in this population.

Administration

Reconstitution
The contents of a VIBATIV 250 mg vial or a VIBATIV 750 mg vial must be reconstituted with 5% Dextrose Injection solution for injection, Sterile Water for Injection, or 0.9% Sodium Chloride for Injection to achieve a concentration of 15 mg/mL. Please see Table 5 below.

Table 5: Preparation of the Patient Infusion Solution

Product Strength	Vial Size	Diluents	Volume of Diluent to Add to Vial	Nominal Concentration per mL
250 mg	30 mL	5% Dextrose Injection, USP; or Sterile Water for Injection, USP; or 0.9% Sodium Chloride Injection, USP	15 mL	15 mg/mL*
750 mg	50 mL		45 mL	15 mg/mL*

* further dilute to a final dosing solution concentration of 0.6 to 8 mg/mL, as described below.

Reconstitution time is generally under two minutes but in rare occasions can take up to 10 minutes. Mix thoroughly to reconstitute. 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 solution.

The reconstituted VIBATIV solution should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion. Discard the vial if the vacuum did not pull the diluent into the vial.

Dilution
The reconstituted VIBATIV solution must be further diluted into 100 mL to 250 mL of the appropriate infusion solution to a final dosing solution 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. Do not shake the final infusion. The dosing solution should be administered by intravenous infusion over a period of 60 minutes.

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

Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparing the final intravenous solution (see **STORAGE AND STABILITY**).
VIBATIV may be administered intravenously through a dedicated line or through a Y-site. 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.

OVERDOSAGE

No cases of overdose have been reported. In the event of overdosage, supportive care is advised with maintenance of glomerular filtration and careful monitoring of renal function. Telavancin is minimally cleared by hemodialysis (see **ACTION AND CLINICAL PHARMACOLOGY - Special Populations**).

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Telavancin is a semisynthetic, lipoglycopeptide antibiotic (see **MICROBIOLOGY**). Telavancin's bactericidal activity results from a multifunctional mechanism of action that contributes to a low potential for selection of resistant mutants of Gram-positive bacteria. The multifunctional mechanism of action of telavancin includes:

1. Inhibition of bacterial cell wall synthesis, and
2. Disruption of the functional integrity of the bacterial membrane.

In vitro studies have shown that telavancin inhibits cell wall biosynthesis by binding to late-stage peptidoglycan precursors, including lipid II, which prevents both the polymerization of precursor into peptidoglycan and subsequent cross-linking events. Telavancin also binds to bacterial membranes and causes membrane depolarization and increased membrane permeability. Collectively these actions of telavancin result in inhibition of peptidoglycan, protein, RNA, and lipid syntheses, and lead to bacterial cell death.

Pharmacodynamics

Cardiac Electrophysiology

Table 6 shows the results of a Phase 1 randomized, placebo-controlled and active-controlled, parallel group study conducted to examine potential effects of telavancin on the QT interval in 160 healthy adult male and female volunteers. Moxifloxacin 400 mg once daily was used as the positive control in this study. The study analysis indicates that administration of telavancin is associated with a greater QT/QTc prolongation than placebo, yet a shorter prolongation than moxifloxacin. There was no evidence that telavancin affected other components of the ECG including PR interval, QRS duration, heart rate, and ECG morphology or interpretation (see **WARNINGS AND PRECAUTIONS- Cardiovascular**). The summary of post-dose changes in QTc interval following administration of telavancin is shown in Table 6.

Table 6: Summary of Post-Dose Changes in QTc Interval (Corrected Using Fridericia's Correction Formula) in a Phase 1 Study with Healthy Volunteers

	Placebo n=39	**Moxifloxacin 400 mg n=39**	**VIBATIV 7.5 mg/kg n=39**	**VIBATIV 15 mg/kg n=34**
Mean Change from Baseline to Day 3, msec:				
Least-squares Mean, ± standard error (Range in msec)	-1.1 ±1.36 (-24 to 18)	8.1 ±1.39 (-12 to 28)	3.0 ±1.37 (-14 to 20)	3.4 ±1.51 (-12 to 29)
Outliers, number (%) of subjects	5 (12.8)	15 (38.5)	10 (25.6)	7 (20.6)
QTcF ≥ 500 msec	0	0	0	0
QTcF increase from baseline ≥ 30 msec	5 (13)	15 (39)	10 (26)	7 (21)
New abnormal U-wave	0	0	0	0

In addition to the Phase 1 QTc study, which was specifically designed to evaluate QTc prolongation in healthy adults, ECGs were performed periodically during the Phase 3 VIBATIV clinical program to monitor QTc intervals. Patients with congenital long QT syndrome, baseline QTc > 500 msec, uncompensated heart failure, and severe left ventricular hypertrophy were not included in the cSSSI and HAP/VAP clinical studies.

In the cSSSI Phase 3 studies, 11/929 (1%) patients treated with VIBATIV (10 mg/kg) and 5/938 (0.5%) patients treated with the comparator had a > 60 msec change from baseline in QTc. One patient treated with VIBATIV and two patients treated with the comparator had a QTc greater than 500 msec. Approximately 35% of the cSSSI patients assessed in the cSSSI Phase 3 studies had risk factors for QT interval prolongation (e.g., hypokalemia, congestive heart failure, or taking medications known to prolong the QTc interval).

In the Phase 3 HAP/VAP studies, the incidence of QTc prolongation > 60 msec or mean value > 500 msec was 8% (52/631 patients) in the VIBATIV group and 7% (48/641 patients) in the

vancomycin group. Many of the HAP patients had either pre-existing cardiac conditions at baseline and/or abnormal baseline ECG findings.

Pharmacokinetics

The mean pharmacokinetic parameters of telavancin (10mg/kg) after a single and multiple 60-minute intravenous infusions (10 mg/kg every 24 hours) are summarized in Table 7. Telavancin pharmacokinetics are linear following single doses from 5 to 12.5 mg/kg and multiple doses of 7.5 to 15 mg/kg administered once daily for 7 days with an infusion duration of 60 minutes. Steady-state concentrations are achieved by the third daily dose. Maximal telavancin concentrations (C_{max}) observed at the end of infusion are followed by rapid decrease in concentration (approximately 50 % in 4 hours supporting rapid distribution into surrounding tissue). The median intercompartmental clearance (Q) is 4.93 L/h. This rapid distributive phase is followed by a slow elimination phase with a mean estimated half-life of 8.1 hours. Telavancin is eliminated primarily by the kidney. Mean plasma clearance of telavancin which did not change with repeated administration in healthy subjects ranged from 13.1 to 13.9 mL/hr/kg.

Table 7: Pharmacokinetic Parameters of Telavancin in Healthy Adults

Parameter	Single Dose / 10 mg/kg n = 42	Multiple Dose / 10 mg/kg n = 36
C_{max} (mcg/mL)	94 ± 14	108 ± 26
C_{min} (mcg/mL)	--	8.6 ± 2.8
$AUC_{0-\infty}$ (mcg·h/mL)	747 ± 129	--
AUC_{0-24h} (mcg·h/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
MRT (hr)	10.8 ± 2.1	10.2 ± 1.9
V_{ss} (mL/kg)	145 ± 23	133 ± 24

C_{max} = maximum plasma concentration; C_{min} = steady-state plasma concentration at 24 hours; AUC = area under concentration-time course; $t_{1/2}$ = terminal elimination half-life; Cl = clearance; MRT = mean residence time; V_{ss} = apparent volume of distribution at steady state.

Absorption
Absorption is not relevant since VIBATIV is administered intravenously.

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 insufficiency or moderate hepatic impairment.

Concentrations of telavancin in skin blister fluid (SBF) were 40% of those in plasma (AUC_{0-24hr} ratio) after three daily doses of 7.5 mg/kg telavancin via a 60 minute infusion once daily for 3 days in healthy young adults. Maximum concentrations of telavancin obtained 9.3 hours post start of infusion are reflective of the large intercompartmental clearance with distribution to surrounding tissues. C_{max}, t_{max}, AUC, $t_{1/2}$ and SBF/plasma ratios can be found in Table 8. Plasma and skin blister trough concentrations with SBF/plasma ratios are listed in Table 9.

Table 8: Pharmacokinetic Parameters of Telavancin in Plasma and Skin Blister Fluid on Day 3 Following Intravenous Administration to Healthy Subjects at a Dose of 7.5 mg/kg via a 60-minute Infusion Once Daily for 3 days

Parameter	Plasma*	Skin Blister Fluid* (SBF)
N	8	8
C_{max} (mcg/mL)	84.8 ± 5.3	16.0 ± 2.0
T_{max} (hr)	1.0 ± 0.0	9.3 ± 2.4
AUC_0-24 (mcg.hr/mL)	604 ± 83	241 ± 33
T1/2 (hr)	6.26 ± 0.78	6.91 ± 0.53[1]
C_{max} Ratio (SBF/plasma)	0.189 ± 0.030	
AUC Ratio (SBF/plasma)	0.403 ± 0.058	
% Penetration	40.3 ± 5.8	

[1]n=5

* The maximum MIC for recent clinical isolates of *Staphylococcus aureus*, including methicillin-resistant strains, is 0.25 mcg/mL and the MIC_{90} for such strains of *Staphylococcus aureus* is 0.5 mcg /mL.

Table 9: Trough Concentrations of Telavancin in Plasma and Skin Blister Fluid (SBF) Following Intravenous Administration to Healthy Subjects at a Dose of 7.5 mg/kg via a 60-minute Infusion for 3 Days

Parameter	Plasma* (mcg/mL)	Skin Blister Fluid* (mcg/mL)	SBF/Plasma ratio
N	8	8	8
Day 3, pre-dose	4.61 ± 1.17	3.55 ± 0.95	0.787 ± 0.176
Day 3, 24 hr post-initiation of 3rd infusion	4.92 ± 1.58	3.90 ± 1.24	0.816 ± 0.182

* The maximum MIC for recent clinical isolates of *S. aureus*, including methicillin-resistant strains, is 0.25 µg/mL and the MIC_{90} for such strains of *Staphylococcus aureus* (0.5µg/mL).

(Values are presented as mean ± SD)

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 telavancin 10 mg/kg once daily for 3 days to healthy adults. Telavancin concentrations in ELF and AM exceeded the MIC_{90} for *S. aureus* (0.5 µg/mL) for at least 24 hours following dosing. The highest concentration of telavancin in ELF was found at 8 hours (~3.7 mcg/mL); concentrations averaged 1.8 mcg/mL at 12 hours and ~1 mcg/mL at 24 hours. There were substantially higher concentrations of telavancin in AM than in ELF at all time points, and the ratio of drug concentration in AM to plasma rose in the 12 to 24 hours after dosing. Plasma, AM and ELF concentrations with AM/Plasma and ELF/Plasma ratios are listed in Table 10.

Table 10: Concentration of Telavancin in Plasma, Alveolar Macrophages (AM), and Epithelial Lining Fluid (ELF) After Intravenous Administration to Healthy Subjects at a Dose of 10 mg/kg via a 60-minute Infusion Given Once Daily for 3 Days by Bronchoscopy Time Point

Time Point (hr)	N	Concentration of Telavancin (µg/mL)*			Ratio	
		Plasma	AM	ELF	AM/Plasma	ELF/Plasma
4	5	56.0 ± 4.5	21.0 ± 16.6	2.75 ± 0.61	0.360 ± 0.261	0.050 ± 0.014
8	5	38.6 ± 7.5	19.0 ± 16.8	3.73 ± 1.28	0.490 ± 0.442	0.098 ± 0.035
12	5	22.9 ± 4.8	45.0 ± 22.4	1.77 ± 0.45	1.93 ± 0.73	0.082 ± 0.036
24	5	7.3 ± 2.01	42.0 ± 31.4	0.89 ± 1.03	6.67 ± 5.34	0.121 ± 0.135

*The MIC_{90} for recent clinical isolates of *S. aureus*, including methicillin-resistant strains, is 0.5 mcg/mL.

The effects of repeated dosing of telavancin on tissue accumulation were evaluated in female rats following intravenous administration at 100 mg/kg/day. Liver and kidney tissue concentrations of telavancin increased with number of doses administered and had not reached the steady-state after 14 doses. The estimated half-life of telavancin in liver and kidney tissues was 10.5 days and 14 days, respectively. It was estimated that 50-70 days of repeated dosing would be required to reach steady-state in liver and kidneys.

In a human mass balance study, there was some evidence that daily administration of telavancin for a period of 14 days could produce some accumulation based on the observed terminal half-life for ^{14}C-telavancin radioactivity of 96.2 hrs.

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

In a mass balance study in male subjects using radiolabeled telavancin, three hydroxylated metabolites were identified with the predominant metabolite accounting for < 10% of the radioactivity in urine and < 2% of the radioactivity in plasma. The metabolic pathway for telavancin has not been identified.

Excretion
Renal excretion is the major route of elimination for telavancin in humans. After infusion of radiolabeled telavancin (10 mg/kg over 60 min) in healthy young adults, approximately 76% of the administered dose was recovered from urine and less than 1% of the dose was recovered from feces (collected for up to 9 days), based on total radioactivity. Telavancin is mainly excreted unchanged accounting for approximately 82% of the total amount recovered over 48 hours in urine.

Special Populations and Conditions

Pediatric Population (<18 years of age)
The pharmacokinetics of telavancin in patients less than 18 years of age have not been established.

Geriatric Population (≥ 65 years of age)
Age alone did not have a clinically meaningful impact on the pharmacokinetics of telavancin based on a population pharmacokinetic analysis and a composite analysis of Phase 1 studies. No dosage adjustment is required based on age.

Gender
Gender alone did not have clinically meaningful impact on the pharmacokinetics of telavancin, based on a population pharmacokinetic analysis and Phase 1 studies. No dosage adjustment is required based on gender.

Race
The pharmacokinetics of telavancin based on race have not been established.

Hepatic Insufficiency
The pharmacokinetics of telavancin were not altered to a clinically significant extent in subjects with moderate hepatic insufficiency (n= 8, Child-Pugh B) compared to healthy subjects matched for gender, age, and weight following a dose of 10 mg/kg by 60 min infusion. No adjustment of dosage is recommended for patients with mild or moderate (Child-Pugh class A or B) hepatic impairment. The pharmacokinetics of telavancin have not been evaluated in patients with severe (Child-Pugh class C) hepatic impairment.

Renal Insufficiency
In a study of 27 subjects with varying degrees of renal function receiving a single dose of 7.5 mg/kg telavancin by 60 min infusion, the plasma clearance of telavancin was reduced and the systemic exposure was increased with decreasing renal function (Table 11).

In subjects with moderate renal insufficiency (CrCl 30 - 50 mL/min), clearance of telavancin was reduced by approximately 21% and $AUC_{0-\infty}$ was increased by approximately 30%. In subjects with creatinine clearance < 30 mL/min, including patients with ESRD on hemodialysis, the clearance of telavancin was reduced by approximately 50% and $AUC_{0-\infty}$ was approximately doubled. Telavancin was not cleared to a clinically significant degree by hemodialysis. The effects of peritoneal dialysis have not been studied.

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

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

*Use actual body weight if less than ideal body weight (IBW), IBW (male) = 50 kg + 0.9 kg/cm over 152 cm height, IBW (female) = 45.5 kg + 0.9 kg/cm over 152 cm height

Table 11: Mean ± SD Telavancin Pharmacokinetic Parameters in Subjects with Varying Degrees of Renal Function Given a Single 7.5 mg/kg Dose of Telavancin by 60 min Infusion

Parameter	Degree of Renal Impairment				
	Normal n=6	Mild n=6	Moderate n=6	Severe n=4	ESRD [a] n=6
CrCl (ml/min) [b]	93.8 ± 10.8	64.1 ± 9.7	40.3 ± 7.0	21.0 ± 6.3	10.4 ± 4.3
C_{max} (mcg/ml)	70.6 ± 11.2	65.9 ± 2.7	65.8 ± 12.1	71.8 ± 7.1	52.1 ± 10.1
T_{max} (hr)	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0
AUC_{0-48t} (mcg·h/mL)	554 ± 92	608 ± 81	683 ± 169	1060 ± 70	898 ± 264
$AUC_{0-\infty}$ (mcg·hr/ml)	560 ± 93	633 ± 101	721 ± 200	1220 ± 120	1010 ± 341
% increase in $AUC_{0-\infty}$ compared to normal	0	13 ± 18	29 ± 36	118 ± 21	79 ± 61
$t_{1/2}$ (hr)	6.9 ± 0.6	9.6 ± 2.9	10.6 ± 2.4	14.5 ± 1.3	11.8 ± 2.8
CL (mL/hr/kg)	14 ± 2	12 ± 2	11 ± 3	6 ± 1	8 ± 3
V_{ss} (mL/kg)	131 ± 16	157 ± 19	156 ± 24	136 ± 10	157 ± 27

[a] ESRD= End-stage renal disease maintained on haemodialysis; dose was given on a dialysis day
[b] Baseline mean creatinine clearance

STORAGE AND STABILITY

Stability and Storage Recommendations

VIBATIV in its original package should be stored refrigerated at 2°C to 8°C.

Storage of Reconstituted Product Concentrate and Diluted Product

Studies have shown that the reconstituted solution is stable in the vial for up to 12 hours at room temperature (25 °C) or 7 days under refrigeration at 2°C to 8°C. The diluted (dosing) solution is also stable in the infusion bag for 12 hours at room temperature (25°C) or 7 days under refrigeration at 2°C to 8°C. However, the total time in the vial plus the time in the IV bag should not exceed 12 hours at room temperature (25°C) and 7 days under refrigeration (2°C to 8°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

VIBATIV is available in 250 mg or 750 mg glass vials.

VIBATIV is a sterile, white to pale pink lyophilized powder containing telavancin hydrochloride (equivalent to either 250 mg or 750 mg of telavancin as the free base). The inactive ingredients are hydroxypropylbetadex (hydroxypropyl-beta-cyclodextrin) (2500 mg per 250 mg telavancin or 7500 mg per 750 mg telavancin), mannitol (312.5 mg per 250 mg telavancin or 937.5 mg per 750 mg telavancin), and sodium hydroxide and hydrochloric acid used in minimal quantities for pH adjustment.

The reconstituted solution of VIBATIV is a clear, colorless to pale pink solution and has a pH of 4.5 (4.0 - 5.0). VIBATIV does not contain any preservative agents.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Telavancin hydrochloride

Chemical name: vancomycin, N3''-[2-(decylamino)ethyl]-29 – [[(phosphonomethyl)amino]methyl]-hydrochloride

Molecular formula: $C_{80}H_{106}C_{l2}N_{11}O_{27}P$• x HCl (where x = 1 - 3)

Molecular mass: 1755.63 (free base),
1792.10 - 1865.02 (salt form)

Structural formula:

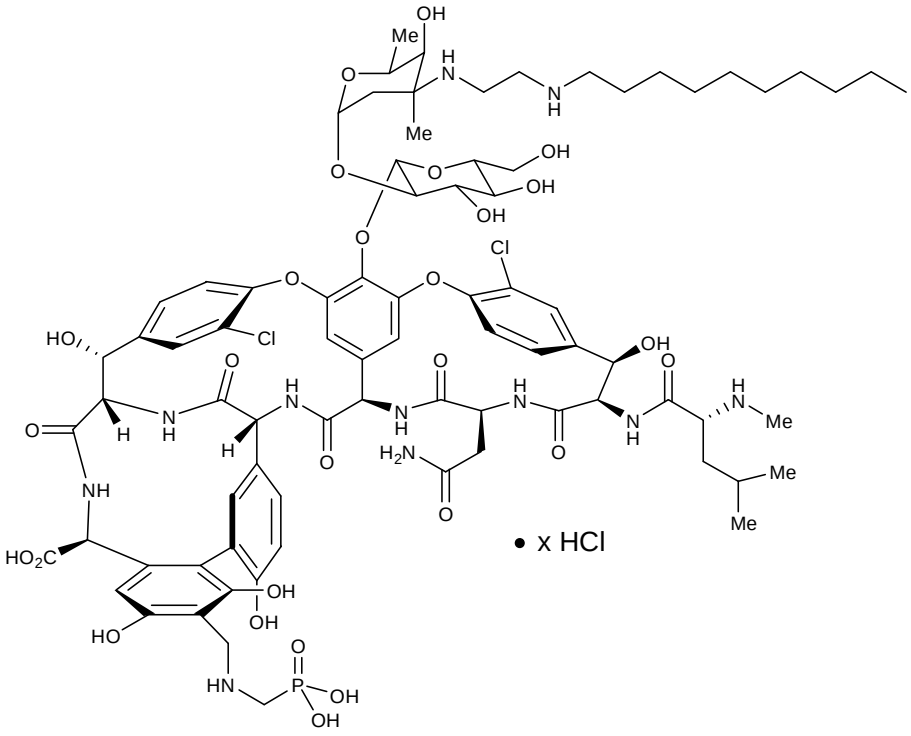

Figure 1: Structural formula of telavancin hydrochloride

Physicochemical properties

Description:	Telavancin hydrochloride is an amorphous material, confirmed by powder X-ray diffraction. No crystalline forms have been observed.
Solubility:	It is sparingly soluble in sterile Water for Injection (pH 2) and dimethyl sulfoxide (DMSO), slightly soluble in sterile Water for Injection (pH 4), methyl alcohol, and propylene glycol and very slightly soluble in absolute ethyl alcohol, polyethylene glycol 300 and acetonitrile.

CLINICAL TRIALS

VIBATIV has **not** been studied in patients with diabetic foot ulcers, ischemic ulcers/wounds, necrotizing fasciitis, gas gangrene, burns involving > 20% of body surface area or third degree/full-thickness in nature, prosthetic materials, osteomyelitis, endocarditis, mediastinitis or other deep site tissue infection (other than skin and skin structure infection).

Complicated Skin and Skin Structure Infections (cSSSI)

Study Demographics and Trial Design

Adult patients with clinically documented complicated skin and skin structure infections (cSSSI) were enrolled in two large, randomized, multicenter, double-blinded studies (ATLAS 1 and ATLAS 2). These two studies were identical in design and are presented in Tables 12 and 13.

Table 12: Phase 3 Clinical Studies for cSSSI - Study Demographics and Trial Design

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female/ Male)
ATLAS 1	Double-blind, randomized, active controlled comparison study of VIBATIV and vancomycin to treat cSSSI	VIBATIV Arm: 10 mg/kg/day, IV, (7-14 days) Vancomycin Arm: 1 g/12 hours, IV (7-14 days)	VIBATIV: (426) Vancomycin: (429)	VIBATIV: 49 years (18 - 96) Vancomycin: 48 years (17 – 90)	VIBATIV: 46%/54% Vancomycin: 42%/58%
ATLAS 2	Double-blind, randomized, active controlled comparison study of VIBATIV and vancomycin to treat cSSSI	VIBATIV Arm: 10 mg/kg/day, IV, (7-14 days) Vancomycin Arm: 1 g/12 hours, IV (7-14 days)	VIBATIV: (502) Vancomycin: (510)	VIBATIV: 49 years (18 – 95) Vancomycin: 50 years (18 – 91)	VIBATIV: 43%/57% Vancomycin: 39%/61%

Table 13: Summary of Baseline Characteristics of Patients in Pooled ATLAS 1 and ATLAS 2 Trials – All Treated (AT) Population

Baseline Characteristics	VIBATIV N=928 (%)	Vancomycin N=939 (%)
Mean Weight	86.7 kg	85.3 kg
Obese (BMI > 30) (%)	38%	39%
Renal Function		
CrCl 30 - 50 mL / min	8%	9%
CrCl < 30 mL / min	4%	3%
Diabetic	25%	25%
Race		
White	78%	77%
Black	14%	14%
Asian	5%	6%
Primary Diagnosis		
Major Abscess	42%	43%
Deep/Extensive Cellulitis	36%	38%

Table 13: Summary of Baseline Characteristics of Patients in Pooled ATLAS 1 and ATLAS 2 Trials – All Treated (AT) Population

Baseline Characteristics	VIBATIV N=928 (%)	Vancomycin N=939 (%)
Wound Infection	16%	13%
Infected Ulcer	5%	5%
Infected Burn (less than 20% BSA)	2%	<1%

Study Results

Clinical cure rates in ATLAS 1 and ATLAS 2 are displayed for the All Treated (AT) and Clinically Evaluable (CE) populations in Table 14.

Table 14: **Clinical Cure at Test-of-Cure in AT and CE Populations**

Patient Population	ATLAS 1			ATLAS 2		
	VIBATIV % (n/N)	Vancomycin % (n/N)	Difference (95% CI)	VIBATIV % (n/N)	Vancomycin % (n/N)	Difference (95% CI)
AT population	75.8% (323 / 426)	74.8% (321 / 429)	1.0 (-4.8 , 6.8)	77.1% (387 / 502)	73.7% (376 / 510)	3.4 (-1.9, 8.7)
CE population	87.9% (304 / 346)	86.5% (302 / 349)	1.3 (-3.6 , 6.3)	88.7% (354 / 399)	87.6% (346 / 395)	1.1 (-3.4 , 5.6)

Table 15 displays key pre-specified efficacy endpoints from the combined patient population from ATLAS 1 and ATLAS 2.

Table 15: Summary of Clinical, Microbiological and Overall Therapeutic Responses in ATLAS 1 and ATLAS 2 Combined

	VIBATIV	Vancomycin
Clinical Cure in CE Patients	88.3% (658/745)	87.1% (648/744)
	95% CI (-2.1% to 4.6%)	
Overall Therapeutic Response in ME Patients	88.6% (467/527)	86.2% (462/536)
	95% CI (-1.6% to 6.4%)	
Clinical Cure in MRSA ME Patients	90.6% (252/278)	86.4% (260/301)
	95% CI (-1.1% to 9.3%)	
Microbiological Eradication in MRSA ME Patients	89.9% (250/278)	85.4% (257/301)
	95% CI (-0.9% to 9.8%)	
Overall Therapeutic Response in MRSA ME Patients	89.9% (250/278)	84.7% (255/301)
	95% CI (-0.3% to 10.5%)	
Microbiological Eradication in MSSA ME Patients	89.0% (161/181)	87.5% (154/176)
	95% CI (-5.3% to 8.1%)	
Overall Therapeutic Response in MSSA ME Patients	87.8% (159/181)	85.8% (151/176)
	95% CI (-5.0% to 9.1%)	

The cure rates by pathogen for the ME population are presented in Table 16.

Table 16: Clinical Cure Rates at the Test-of-Cure for the Most Common Pathogens ATLAS 1 and ATLAS 2 Combined – ME Population

Pathogens	VIBATIV % (n/N)	Vancomycin % (n/N)
Staphylococcus aureus (All)	89.9% (410 / 456)	86.9% (411 / 473)
Staphylococcus aureus (MRSA)	90.6% (252 / 278)	86.4% (260 / 301)
Staphylococcus aureus (MSSA)	88.4% (160 / 181)	87.5% (154 / 176)
Streptococcus pyogenes	91.3% (21 / 23)	92.0% (23 / 25)
Enterococcus faecalis (vancomycin-susceptible isolates)	92.6% (25 / 27)	82.4% (28 / 34)
Streptococcus agalactiae	78.9% (15 / 19)	89.5% (17 / 19)
Streptococcus anginosus Group	100.0% (11 / 11)	100.0% (8 / 8)

Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia (HAP/VAP)

Study Demographics and Trial Design

Adult patients with hospital-acquired and ventilator-associated pneumonia were enrolled in two randomized, parallel-group, multinational, multicenter, double-blinded trials of identical design (ATTAIN 1 and ATTAIN 2) 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 as per local guidelines. Patients could receive concomitant aztreonam or metronidazole for suspected Gram-negative and anaerobic infection, respectively. The addition of piperacillin/tazobactam was also permitted for coverage of Gram-negative organisms if resistance to aztreonam was known or suspected. Patients with known or suspected infections due to methicillin-resistant *Staphylococcus aureus* were enrolled in the studies.

Of the patients enrolled across both trials, 64% were male and 70% were white. The mean age was 63 years. At baseline, more than 50% were admitted to an intensive care unit, about 23% had chronic obstructive pulmonary disease, about 29% had ventilator-associated pneumonia and about 6% had bacteremia. Demographic and baseline characteristics were generally well-balanced between treatment groups; however, there were differences between ATTAIN 1 and ATTAIN 2 with respect to a baseline history of diabetes mellitus (31% in ATTAIN 1, 21% in ATTAIN 2) and baseline renal insufficiency (CrCl ≤50 mL/min) (36% in ATTAIN 1, 27% in ATTAIN 2). The demographics and trial designs are presented in Tables 17 and 18.

Table 17: Phase 3 Clinical Studies for HAP/VAP- Study Demographics and Trial Design – AT Population

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female/ Male)
ATTAIN 1	Double-blind, randomized, active controlled comparison study of VIBATIV and vancomycin to treat HAP/VAP due to Gram-positive pathogens with a focus on infections due to MRSA	VIBATIV Arm: 10 mg/kg/day, IV, (7-21 days) Vancomycin Arm: 1 g/12 hours, IV (7-21 days)	VIBATIV: (372) Vancomycin: (374)	VIBATIV: 63 years (44 - 82) Vancomycin: 64 years (47 – 81)	VIBATIV: 37%/63% Vancomycin: 43%/57%

Table 17: Phase 3 Clinical Studies for HAP/VAP- Study Demographics and Trial Design – AT Population

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female/ Male)
ATTAIN 2	Double-blind, randomized, active controlled comparison study of VIBATIV and vancomycin to treat HAP/VAP due to Gram-positive pathogens with a focus on infections due to MRSA	VIBATIV Arm: 10 mg/kg/day, IV, (7-21 days) Vancomycin Arm: 1 g/12 hours, IV (7-21 days)	VIBATIV: (377) Vancomycin: (380)	VIBATIV: 61 years (43 – 79) Vancomycin: 62 years (44 – 81)	VIBATIV: 33%/67% Vancomycin: 33%/67%

Table 18: Summary of Baseline Characteristics of Patients in Pooled Trials ATTAIN 1 and ATTAIN 2 – AT Population

Baseline Characteristics	**VIBATIV N=749 (%)**	**Vancomycin N=754 (%)**
Mean Weight	72 kg	71 kg
Obese (BMI > 30 kg/m^2) (%)	17%	17%
Baseline Renal Status		
CrCl ≤ 50 mL / min	34%	33%
Acute Renal Failure	10%	8%
Hemodialysis	2%	2%
Diabetes	27%	25%
Race		
White	69%	70%
Black	3%	3%
Asian	23%	24%
ICU at Baseline	58%	58%
Type of Pneumonia		
VAP	29%	28%
Late VAP (≥ 4 Days on Ventilation at Diagnosis)	25%	23%
PaO2/FiO2 (Mean ± SD)	254 ±142.4	244 ± 125.3
NON-VAP	71%	72%

Study Results

The protocol-specified primary efficacy analysis was to evaluate clinical noninferiority of VIBATIV compared to vancomycin, with respect to Clinical Response at the TOC assessment (7 to 14 days after the last dose of study drug), employing a prospectively determined noninferiority margin (the "Δ") of 20% and a post-hoc noninferiority margin of 14%. Clinical Response was determined by resolution of signs and symptoms, no further antibacterial therapy for HAP/VAP after end-of-treatment, and improvement or no progression of baseline radiographic findings. In this analysis, the CE and AT analysis populations were considered co-primary.

ATTAIN 1 and ATTAIN 2 demonstrated that VIBATIV 10 mg/kg administered intravenously every 24 hours for 7 to 21 days was non-inferior to vancomycin in treatment of patients with HAP/VAP caused by susceptible strains of Gram-positive pathogens (Table 19).

Table 19: Clinical Cure Rates in ATTAIN 1 and ATTAIN 2 – AT and CE Populations

	ATTAIN 1		ATTAIN 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%)	

[a]All-Treated (AT) Population: Patients who received at least one dose of study medication
[b]Clinically Evaluable (CE) Population: Patients who were clinically evaluable

All-cause mortality was also evaluated because there is historical evidence of treatment effect for this endpoint. This was a protocol pre-specified secondary endpoint. The overall 28-day all-cause mortality outcomes in the group of patients who had at least one baseline Gram-positive respiratory pathogen are shown in Table 20. This group of patients included those who had mixed Gram-positive/Gram negative infections.

Table 20: All-Cause Mortality at Day 28 in Patients with at least One Baseline Gram Positive Pathogen

		ATTAIN 1		ATTAIN 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%)	

[a]Mortality 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.

All-cause mortality in patients with pre-existing moderate to severe renal impairment (CrCl ≤ 50 mL/min) was 39% in the VIBATIV group, compared with 30% in the vancomycin group. All-cause mortality in patients without pre-existing severe renal impairment (CrCl > 50 mL/min) was 17% in the VIBATIV group and 18% in the vancomycin group. **VIBATIV should only be considered for use in patients with moderate renal impairment (CrCl 30 - 50 mL/min) when the anticipated benefit to the patient outweighs the potential risk** (see **WARNINGS AND PRECAUTIONS- Renal**).

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacokinetics

The pharmacokinetics of telavancin has been evaluated in mice, rats, dogs, and monkeys. The intravenous single dose pharmacokinetics of telavancin (10 mg/kg) in mice, rats, dogs, and monkeys were characterized by clearance (CL) of 0.101, 0.051, 0.065, and 0.058 L/h/kg, respectively. An apparent Vd_{ss} for these same species were of 0.15, 0.10, 0.14, 0.17 L/kg and the elimination t1/2 values were 1.2, 1.3, 1.4, and 2.3 hours, respectively. In mice and rats, exposures increased linearly with dose over a dose range of 1.0 to 25 mg/kg. In dogs, a linear increase in systemic exposure was also noted over a dose range of 12.5 to 50 mg/kg. In mice and rats, CL decreased with increasing dose. Repeat, daily IV administration of telavancin to rats and dogs for 13 weeks resulted in increases in AUC values of 1.47 to 1.16 fold compared with AUC values after a single dose. No sex related differences in pharmacokinetics were observed.

The effect of repeated dosing of telavancin on tissue accumulation and clearance was evaluated in female rats following intravenous administration at 100 mg/kg/day (see Table 21). Liver and kidney tissue concentrations of telavancin increased with number of doses administered and had not reached the steady-state after 14 doses. The estimated half-life of telavancin in liver and kidney tissues was 10.5 days and 14 days, respectively. It was estimated that 50-70 days of repeated dosing would be required to reach steady-state in liver and kidneys. Therefore, the retention of telavancin in tissues could potentially result in higher systemic exposures following long term repeated dosing in rats. The tissue distribution of [14C] telavancin-derived radioactivity was evaluated in rats and dogs and is summarized in Table 22.

Table 21: Tissue Concentration in Liver and Kidneys Following Repeated Dosing of VIBATIV at 100 mg/kg in Female Rats

Dosing Day	**Concentration (mcg/g)**	
Tissue	Liver	Kidney
Day 1	166 ± 24	265 ± 52
Day 3	531 ± 50	524 ± 83
Day 7	864 ± 154	837 ± 101
Day 10	1048 ± 159	969 ± 126
Day 14	1548 ± 324	1303 ± 184
Recovery		
Day 21	1193 ± 107	920 ± 149
Da7 28	616 ± 295	661 ± 107

Table 22: Tissue Concentration Based on the Total Radioactivity 24 Hours After Intravenous Administration of ^{14}C-Telavancin to Male Animals at a Dose of 25 mg/kg

	Tissue Distribution - Rat	**Tissue Distribution - Dog**
Brain	0.17	0.18
CSF	0.01	0.036
Eye	1.01	0.40
Feces	42.83	19.9
Heart	1.72	2.09
Kidney	66.38	33.7
Large Intestine	4.76	4.94

Table 22: Tissue Concentration Based on the Total Radioactivity 24 Hours After Intravenous Administration of ^{14}C-Telavancin to Male Animals at a Dose of 25 mg/kg

	Tissue Distribution - Rat	Tissue Distribution - Dog
Liver	45.58	39.5
Lung	5.14	7.15
Marrow	14.81	0.10
Mesenteric LN	11.10	15.5
Muscle	1.06	0.79
Pancreas	2.51	2.82
Plasma	0.76	1.72
Prostate	4.07	2.85
Skin	4.48	1.68
Small Intestine	6.34	6.91
Spleen	19.93	16.1
Stomach	3.98	2.99
Testes	2.13	1.52
Thymus	7.67	7.77
Thyroid	5.17	3.81
Urine	293.8	359
White Fat	0.32	0.99

Data are expressed as mcg-equivalent telavancin per gram.

Plasma protein binding (primarily to albumin) ranged from 93.8 – 96.2%, 93.4 – 95.6%, and 91.5 – 94.3% over telavancin concentrations of 0.1 to 100 mcg/mL in the mouse, rat, and dog.

The metabolism of IV administered telavancin was evaluated in rats and dogs. In rats, recovery of ^{3}H in the urine ranged from 61.2 to 80.4% of the injected dose with only 3.5 to 16.2% of the urine ^{3}H associated with telavancin metabolites. In dogs, 83.1 to 86.9% of the injected radioactivity was recovered in the urine with less than half the radioactivity being associated with metabolites of telavancin. The metabolism of telavancin was not characterized in mice or monkeys.

Pharmacodynamics

In general, telavancin as IV infusion had no untoward pharmacologic effects on the CNS, cardiovascular, or respiratory systems. Telavancin was associated with mild, reversible immunomodulatory effects that were generally deemed to be not of clinical significance but it did have reversible effects on the male reproductive system. The findings from these studies were consistent with the results from the more detailed safety pharmacology and toxicology studies performed with telavancin.

Central Nervous and Respiratory Systems

Rats were administered a single, IV, bolus dose of telavancin at dosages of 0, 12.5, 25, or 50 mg/kg and Irwin observations were performed at 5, 15, 30, 60, and 120 minutes post dose. No neurobehavioral findings were observed at any dose tested. Respiratory safety pharmacology was performed in anesthetized dogs administered telavancin at a dose of 25 or 50 mg/kg. Telavancin had no effect on peak inspiratory flow (PIF), peak expiratory flow (PEF), minute volume, tidal volume, or respiratory rate. Administration of telavancin did not elicit any toxicologically significant effects on either the CNS or respiratory systems in rats or dogs at the dosages administered.

Cardiovascular System
The effects of IV administration of telavancin on the cardiovascular system were evaluated in dogs. Dogs were anesthetized, instrumented, and allowed to stabilize for 30 minutes before telavancin was infused over a 2 hour period at doses of 25 or 50 mg/kg. Arterial blood pressure (systolic, diastolic, and mean), heart rate, electrocardiogram (ECG), femoral blood flow, and left ventricular dP/dt were monitored 10 and 20 minutes before dosing (baseline) and again at 5, 10, 20, 30, 60, 90, 120, 150, 180, and 210 minutes post dose. There were no telavancin related effects on ECG, including QT interval, at any dosage. Similarly, telavancin, at doses up to 50 mg/kg, had no effect on arterial pressure, left ventricular dP/dt, or femoral arterial blood flow. In conscious telemetered dogs, administration of telavancin at doses up to 100 mg/kg/day for four consecutive days resulted in no treatment related effects on heart rate, blood pressure (systolic, diastolic, or mean), or ECG parameters (RR, PR, QRS, QT, or QTc intervals).

Other Systems
The effect of telavancin on the immune system was assessed in rats. Rats were intravenously infused with telavancin (12.5 to 100 mg/kg, IV) over 30 minutes daily for six weeks. Minimal to mild, reversible alterations in immune system parameters were noted at the 50 and 100 mg/kg/day dose level including an increase in the total lymphocyte count without a shift in lymphocyte populations. Mild reversible effects on the T-cell dependent antigen response were also noted. Telavancin (50 or 100 mg/kg/day) also increased phagocytic activity by macrophages but decreased the respiratory burst. These data indicate that telavancin was associated with mild, reversible, and probably not clinically relevant immunomodulatory effects *in vivo*.

The effect of telavancin on the male reproductive system was evaluated in rats. Male rats were administered telavancin at 12.5 to 100 mg/kg/day for six weeks. Telavancin at doses of 50 or 100 mg/kg/day resulted in sloughed testicular germ cells in the epididymis, decreased sperm count, motility, and increased frequency of abnormal sperm morphology. All of these effects were reversible.

Human Pharmacology

Pharmacokinetics
Telavancin pharmacokinetics are linear and do not change with time at single doses from 1 to 15 mg/kg and following multiple doses of 7.5 to 15 mg/kg administered once daily for 7 days. Steady-state concentrations are achieved by the third daily dose. There is no significant plasma accumulation of telavancin on multiple-dose administration; plasma concentrations are comparable following single doses and at steady state in subjects with normal renal function.

Telavancin is not extensively metabolized, with elimination of unchanged drug primarily in the urine. No metabolites of telavancin were detected in *in vitro* studies using human liver microsomes, liver slices, hepatocytes, kidney S9 fraction, and incubations with any of the following recombinant CYP isoforms: CYP 1A2, 2C9, 2C19, 2D6, 3A4, 3A5, 4A11. The clearance of telavancin is not expected to be altered by inhibitors of any of these enzymes. The primary metabolite of telavancin is the hydroxylated metabolite, AMI-11352, which is 10-fold less microbiologically active than telavancin. In plasma of patients with normal renal function, the AUC of AMI-11352 is 1-3% of the AUC of telavancin. About 5% of the dose is recovered in the urine as AMI-11352. The metabolic route to AMI-11352 and 2 additional minor hydroxylated

metabolites is unknown. Following single doses of telavancin, plasma concentrations of AMI-11352 rise slowly, peaking between 10 and 20 hours after the telavancin dose and exhibiting a very slow apparent rate of elimination, despite having a more rapid renal clearance rate than telavancin. A process impurity, AMI-999, is also found in small quantities (AUC 1.5% or less of the telavancin AUC) in plasma and urine and is rapidly eliminated from plasma.

Telavancin is excreted primarily by the kidney, with approximately 70-80% of the dose excreted in the urine. In the ^{14}C-study, intact telavancin accounted for approximately 82% of the total amount recovered in the urine from 0-48 hours after dosing. Renal clearance of telavancin is approximately 75% of plasma clearance.

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 insufficiency or moderate hepatic impairment.

Age and gender did not affect the pharmacokinetics of telavancin to a clinically relevant degree. No dose adjustment is required based on age or gender. The pharmacokinetics of telavancin are not altered in patients with moderate hepatic insufficiency (Child-Pugh Class B). No dose adjustment is required for mild and moderate hepatic impairment. The pharmacokinetics of telavancin have not been evaluated in patients with severe hepatic impairment. Telavancin has not been studied in children.

Plasma concentrations of telavancin were elevated consequent to reduced clearance of telavancin in subjects with renal impairment. Because renal excretion is the primary route of elimination, dosage adjustment based on relative AUCs and $t_{½}$ is necessary in patients with moderate to severe renal insufficiency ($CrCl \leq 50$ mL/min). Telavancin is not removed from plasma to a significant degree by intermittent hemodialysis. Telavancin has not been studied in patients receiving peritoneal dialysis (see **ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions**).

In vitro studies using human microsomes demonstrated that telavancin inhibits to some degree CYP3A4, including midazolam 1'-hydroxylation at 14 mcM, a concentration approximating free telavancin concentrations at C_{max}. In human liver microsomes CYPs 1A2, 2C9, 2C19, 2D6 were inhibited at even higher concentrations than CYP 3A4/5. In a clinical study, multiple doses of telavancin had no effect on the pharmacokinetic disposition of midazolam; therefore, effects on other CYPs are not expected. Another study evaluated potential interactions with aztreonam and piperacillin/tazobactam which are also renally excreted. The dispositions of telavancin and aztreonam or telavancin and piperacillin/tazobactam were not altered within either pair of treatments.

MICROBIOLOGY

Telavancin demonstrates *in vitro* activity against a broad range of clinically relevant Gram-positive bacterial pathogens, including isolates resistant to oxacillin/methicillin, linezolid, clindamycin, trimethoprim/sulfamethoxazole, or fluoroquinolones; and staphylococci non-susceptible to daptomycin or with reduced susceptibility to vancomycin.

Telavancin exerts rapid, concentration-dependent, bactericidal activity against Gram-positive organisms *in vitro*, as demonstrated by time-kill assays and MBC/MIC ratios (minimum bactericidal concentration/minimum inhibitory concentration) using broth dilution methodology. *In vitro* studies further demonstrated telavancin's prolonged postantibiotic effect, ranging up to 6.5 hours against *S. aureus* and other Gram-positive pathogens.

Telavancin decreased bacterial load in an *in vitro* model of biofilm infection with *S. aureus* or *S. epidermidis*. *In vivo* studies in soft-tissue models of infection demonstrated that immune status has little effect on the activity of telavancin. The clinical significance of these findings is not known.

Interactions with other Antibiotics

Antagonism was not observed between telavancin and other commonly used antibacterial drugs *in vitro*. Synergy against *S. aureus*, including methicillin-resistant strains, was observed with some β−lactam agents, including imipenem.

Development of Resistance

Telavancin exhibits a low potential for resistance development. No specific mechanism of resistance to telavancin has been identified among target organisms. In both clinical trials and clinical use, telavancin resistance in *S. aureus* is rare.

Cross-Resistance

Some VanA-type vancomycin-resistant enterococci have reduced susceptibility to telavancin. Non-VanA-type vancomycin-resistant enterococci are susceptible to telavancin. There is no known cross-resistance between telavancin and other classes of antibiotics.

Susceptibility Testing Methods

Susceptibility testing by broth dilution methods requires the use of telavancin powder. When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a broth dilution method or equivalent with standardized inoculum concentrations and standardized concentrations of telavancin powder. The test method treats telavancin as a water-insoluble agent. Dimethyl sulfoxide is used as solvent and diluent, and the cation-adjusted Mueller Hinton Broth test medium

is supplemented with polysorbate 80 to a final concentration of 0.002%. Telavancin should not be tested by the agar dilution method. The MIC values should be interpreted according to the criteria provided in Table 23.

Table 23: Susceptibility Interpretive Criteria for Telavancin

Pathogen	Susceptibility Interpretive Criteria					
	Minimal inhibitory concentration (mcg/mL)			Disk diffusion zone diameter (mm)		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Staphylococcus aureus (methicillin-susceptible and methicillin-resistant)	≤ 0.12	--[c]	--[c]	≥ 15	--[c]	--[c]
Streptococcus spp. other than *S. pneumoniae* and *S. anginosus* group	≤ 0.12[a]	--[c]	--[c]	≥ 15[b]	--[c]	--[c]
Streptococcus anginosus group	≤ 0.06	--[c]	--[c]	≥ 15	--[c]	--[c]
Enterococcus faecalis (vancomycin-susceptible only)	≤ 0.25	--[c]	--[c]	≥ 15	--[c]	--[c]

[a] The MIC interpretive criteria for *Streptococcus spp.* other than *S. pneumoniae* are applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth supplemented with 2-5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20 to 24 hours.
[b] The zone diameter interpretive criteria for *Streptococcus* spp. other than *S. pneumoniae* are applicable only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood inoculated with a direct colony suspension and incubated in 5% CO2 at 35°C for 20 to 24 hours.
[c] The current absence of data on telavancin-resistant isolates precludes defining any categories other than "Susceptible." Isolates yielding test results suggestive of a "nonsusceptible" category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg of telavancin to test the susceptibility of microorganisms to telavancin. The disk diffusion interpretive criteria are provided in Table 23.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone, which prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; and other therapy should be selected.

Quality Control

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standard telavancin powder should provide the range of values noted in Table 24. Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Table 24: Acceptable Quality Control Ranges for Telavancin to Be Used in Validation of Susceptibility Test Results

Strain	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration (MIC in mcg/mL)	Disk Diffusion (zone diameter in mm)
Enterococcus faecalis ATCC 29212	0.03 – 0.12	Not applicable
Staphylococcus aureus ATCC 29213	0.03 – 0.12	Not applicable
Staphylococcus aureus ATCC 25923	Not applicable	16-20
Streptococcus pneumoniae ATCC 49619[a]	0.004-0.015[b]	17-24[c]

[a] This organism may be used for validation of susceptibility test results when testing *Streptococcus spp*. other than *S. pneumoniae*.
[b] This quality control range for *S. pneumoniae* is applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth supplemented with 2-5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20 to 24 hours.
[c] This quality control zone diameter range is applicable only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood inoculated with a direct colony suspension and incubated in 5% CO2 at 35°C for 20 to 24 hours.

Table 25: *In vitro* Activities of Telavancin Against Organisms for Which VIBATIV Has Demonstrated Clinical Efficacy[a]

Organisms	Number of Isolates	MIC (µg/mL)		
		Range	50%[b]	90%[c]
Enterococcus faecalis, VSE	905	≤ 0.015-0.5	0.12	0.12
Staphylococcus aureus, MRSA[d]	3528	≤ 0.015-8	0.06	0.06
Staphylococcus aureus, MSSA	4105	≤ 0.015-0.25	0.03	0.06
Streptococcus anginosus (All)	87	≤ 0.015-0.06	0.03	0.03
Streptococcus agalactiae (All)	393	≤ 0.015-0.12	0.06	0.12
Streptococcus pyogenes (All)	511	≤ 0.015-0.12	0.03	0.06

[a] Studies included are: Bridging Study, Phase 3 cSSSI Clinical Isolate Retest Data, Phase 3 HAP Clinical Isolate Retest Data, 2011 Telavancin International Surveillance Study (Revised Methods).
[b] 50%: Lowest telavancin concentration required to inhibit 50% of the test isolates (MIC_{50}).
[c] 90%: Lowest telavancin concentration required to inhibit 90% of the test isolates (MIC_{90}).
[d] Includes VISA (n=16) and VRSA (n=6) isolates.

Table 26: *In vitro* Activities of Telavancin Against Recent Clinical Isolates Performed with Reference Methods, However Clinical Efficacy Has Not Yet Been Demonstrated[a]

Organisms	Number of Isolates	MIC (mcg/mL)		
		Range	50%[b]	90%[c]
Enterococcus faecium, VSE	274	≤ 0.015-0.12	0.03	0.06
Staphylococcus epidermidis (All)[d]	401	≤ 0.015-0.25	0.06	0.06
Staphylococcus epidermidis, MRSE	315	≤ 0.015-0.25	0.06	0.06
Staphylococcus haemolyticus (All)	82	≤ 0.015-0.12	0.06	0.06
Streptococcus constellatus (All)	40	≤ 0.015-0.03	0.03	0.03
Streptococcus intermedius (All)	17	≤ 0.015-0.06	0.03	0.06
Streptococcus pneumoniae (All)	2266	≤ 0.004-0.06	≤ 0.015	≤ 0.015
Streptococcus spp Group G	101	≤ 0.015-0.12	0.03	0.06
Streptococcus dysgalactiae subsp equisimilis (All)	90	≤ 0.015-0.12	0.03	0.06

[a]Studies included are: Bridging Study, Phase 3 cSSSI Clinical Isolate Retest Data, Phase 3 HAP Clinical Isolate Retest Data, 2011 Telavancin International Surveillance Study (Revised Methods).
[b]50%: Lowest telavancin concentration required to inhibit 50% of the test isolates (MIC_{50}).
[c]90%: Lowest telavancin concentration required to inhibit 90% of the test isolates (MIC_{90}).
[d]Includes 9 vancomycin-intermediate isolates and 37 teicoplanin-nonsusceptible isolates.

TOXICOLOGY

Genotoxicity and Carcinogenesis

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

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

Reproductive and Developmental Toxicology

Telavancin did not affect the fertility or reproductive performance of adult male rats (exposed to telavancin up to 100 mg/kg/day for at least 4 weeks prior to mating) or female rats (exposed to telavancin up to 150 mg/kg/day for at least 2 weeks prior to mating).

Male rats given telavancin (50 or 100 mg/kg/day) for 6 weeks, at exposures similar to those measured in clinical studies, displayed altered sperm parameters that were reversible following an 8-week recovery period. Following 13-weeks of treatment, reversible, minimal to slight testicular degeneration was noted in rats but not in dogs. No testicular degeneration or hypospermatogenesis was observed in dogs administered telavancin (up to 100 mg/kg/day) for 13 weeks.

In developmental and reproductive toxicology studies, telavancin demonstrated the potential to cause skeletal malformations in rabbits and limb malformations (brachymelia, syndactyly) in rats, rabbits, and minipigs. In the rat study, in which dams were dosed during the period of

organogenesis at 50, 100 or 150 mg/kg/day, syndactyly (one fetus at 100 mg/kg/day) and brachymelia (one fetus each at 100 and 150 mg/kg/day) were noted. Also noted in the pre- and post-natal development rat study was one pup with transient, limited use of its forelimb from a dam that had received 150 mg/kg/day. In the rabbit study at doses up to 75 mg/kg/day, brachymelia and adactyly were noted in a single rabbit fetus whose dam had received 75 mg/kg/day. These effects occurred in animals exposed to approximately 1 to 2-fold the clinical dose based on AUC.

In the rat embryo-fetal development study, dilatation of the lateral ventricles of the brain was observed in the high dose group (systemic exposure 2-fold the clinical dose based on AUC). However, in the pre- and postnatal development study, there were no effects found on reflex, locomotor activity, learning, and memory of the offspring.

Long-Term Toxicology

Two weeks administration of telavancin in rats produced minimal renal tubular vacuolization with no changes in BUN or creatinine. These effects were not seen in studies conducted in dogs for similar duration. Four weeks of treatment resulted in reversible elevations in BUN and/or creatinine in association with renal tubular degeneration that further progressed following 13 or 26 weeks of treatment. These effects occurred at exposures (based on AUCs) that were similar to those measured in clinical studies.

Six weeks of telavancin exposure resulted in increased ALT and AST in dogs, which increased further following 13 weeks of exposure. Dogs showed minimal to slight hepatocellular degeneration necrosis at the 13 week timepoint. In rats exposed to telavancin for 13 weeks, similar changes in liver enzymes and hepatocellular findings were observed. These effects occurred in both rats and dogs at exposures that were approximately 1.5 to 2-fold higher than the clinical exposure, based on AUC.

Other Toxicology Studies

Six weeks of daily administration of telavancin to rats was associated with minimal to mild, reversible alterations in immune system parameters at the 50 and 100 mg/kg/day dose level. These findings included: an increase in the total lymphocyte count without a shift in lymphocyte populations, mild reversible effects on the T-cell dependent antigen response, as well as increased phagocytic activity by macrophages but decreased respiratory burst. These findings were considered mild, reversible, and probably not a clinically relevant immunomodulatory effect.

The potential effects of continuous renal replacement therapies (CRRT), i.e., continuous venovenous hemodialysis (CVVHD) and continuous venovenous hemofiltration (CVVH), on the clearance of telavancin were examined in an *in vitro* model using bovine blood. Telavancin was substantially cleared by CRRT and clearance increased with increasing filtration rate.

Table 27: Tabulated Overview of Key Toxicology Studies

Study Number	Species/Strain/No. per group and Gender	Method of Administration (Vehicle/ Formulation)	Doses (mg/kg)	Noteworthy Findings
Single-Dose 01-001-11	Mouse/ Crl:CD-1® (ICR) 5 M and 2 or 5 F	IV (bolus)/ HP-β-CD in 5% w/v dextrose	25, 35, 50, 100	Treatment-related mortality: all mice (3/3 M and 2/2 F) given 100 mg/kg died within 1 hr post dosing. Treatment-related clinical signs: decreased activity, staggered gait, prostration, dyspnea, gasping, noted in mice given 100 mg/kg. Similar clinical signs in F given 50 mg/kg but signs resolved by Study Day 2. Decreased activity noted in M (50 mg/kg) and F (35 mg/kg) up to 30 min post dosing. Minimal lethal dose 100 mg/kg for both sexes.
Single-Dose 01-001-12	Rat/Crl:CD® (SD)IGS 5 M and 5 F	IV (bolus)/ HP-β-CD in 5% w/v dextrose	25, 50, 100, or 150	Treatment-related mortality: 1 M given 100 mg/kg and 2 M given 150 mg/kg found dead on Study Day 2. Treatment-related clinical signs: Decreased activity and/or dyspnea in M given 50 mg/kg, both M and F given 100 or 150 mg/kg. Signs had resolved 30 min post dosing (50 or 100 mg/kg) and by Study Day 2 (150 mg/kg). Minimal lethal dose 100 mg/kg/ for M and >150 mg/kg for F.
Repeat-Dose 01-001-09 2-week GLP rat	Rat/ Crl:CD® (SD)IGS 15M, 15F	Intravenous (2-hour infusion) Placebo: HP-β-CD Diluent: 5% w/v dextrose	6.25, 12.5, 25	No effects on hematology, coagulation, clinical chemistry, or urine chemistry test results. Administration of telavancin associated with increased incidences of granular casts and positive urine occult blood tests on Day 15 for males at 25 mg/kg/day. At the terminal sacrifice, renal tubular vacuolation present in animals given placebo control and at 25 mg/kg/day. Mean severity scores for finding in males receiving 25 mg/kg/day of telavancin slightly increased over placebo-controls. Renal vacuolation present in recovery animals; however, severity score similar between the 25 mg/kg/day and placebo-control animals. No-Observed-Adverse-Effect Level: 12.5 mg/kg/day

Table 27: Tabulated Overview of Key Toxicology Studies (Continued)

Study Number	Species/Strain/No. per group and Gender	Method of Administration (Vehicle/ Formulation)	Doses (mg/kg)	Noteworthy Findings
Repeat-Dose 01-001-10 2-week GLP dog	Dog/Beagle 6M, 6F	Intravenous (2-hour infusion) Placebo: HP-β-CD Diluent: 5% w/v dextrose	6.25, 12.5, 25	No effects on hematology, coagulation, clinical chemistry, or urine chemistry test results. No macroscopic/microscopic alterations that could be attributed to telavancin or placebo control. No-Observed-Adverse-Effect Level: 25 mg/kg/day
Repeat-Dose 02-001-01 4-Week GLP Rat	Rat/ Crl:CD® (SD)IGS 15M, 15F	Intravenous (30 minute infusion) Placebo: HP-β-CD Diluent: 5% w/v dextrose	12.5, 25, 50	Administration of telavancin associated with minimally increased urea nitrogen and creatinine at 50 mg/kg/day. Effects reversible following the 4-week recovery period. Minimal and reversible, focal or multifocal renal tubular degeneration in males and females at 25 and 50 mg/kg/day. Diffuse renal cortical tubular vacuolation in males and females given the placebo, or telavancin at all dose levels; this latter finding attributed to HP -β-CD in the placebo and not completely reversed by end of the 4-week recovery period. No-Observed-Adverse-Effect Level: 12.5 mg/kg/day
Repeat-Dose 02-003-01 4-Week GLP Dog	Dog/Beagle 6M, 6F	Intravenous (30 minute infusion) Placebo: HP-β-CD Diluent: 5% w/v dextrose	12.5, 25, 50	Transitory effects characteristic of histamine-mediated reactions noted and most prominent at 50 mg/kg/day. Findings not considered deleterious to the longer term clinical condition of the animals. Slight increases in blood urea nitrogen, serum creatinine and urinary volumes observed at 50 mg/kg/day and associated with minimal, multifocal renal cortical tubular dilatation at the end of the treatment period. Renal tubular dilatation reversible at the end of the 4-week recovery period. No-Observed-Adverse-Effect Level: 25 mg/kg/day
Repeat-Dose 02-001-06 13-Week GLP Rat	Rat/ Crl:CD® (SD)IGS 18M, 18F	Intravenous (30 minute infusion) Placebo: HP-β-CD	12.5, 50, 100	Administration of telavancin resulted in effects on kidney, liver and testes as well as systemic macrophage hypertrophy/hyperplasia. Clinical pathology findings considered related to kidney and liver injury included increases in urea nitrogen, and creatinine, and ALT

Table 27: Tabulated Overview of Key Toxicology Studies (Continued)

Study Number	Species/Strain/No. per group and Gender	Method of Administration (Vehicle/ Formulation)	Doses (mg/kg)	Noteworthy Findings
		Diluent: 5% w/v dextrose		and AST noted in placebo and with greater severity at doses of 50 and 100 mg/kg/day. Clinical pathology effects generally reversible following the 4-week recovery period. The only effect exhibiting minimal or no evidence of reversibility was higher creatinine for males at 50 or 100 mg/kg/day and females at 100 mg/kg/day. Telavancin administered at doses of 50 and/or 100 mg/kg/day associated with increased severity of placebo-related histopathological effects including renal tubular degeneration, hepatocellular degeneration, seminiferous tubule degeneration and systemic macrophage hypertrophy/hyperplasia. Telavancin-related changes in the kidney, liver, and testes displayed evidence of reversibility following the 4-week recovery period. In contrast, systemic macrophage hypertrophy/hyperplasia at the end of the recovery period was inconsistent and variable across tissues/sexes, suggestive of a much slower recovery for these effects. No-Observed-Adverse-Effect Level: 12.5 mg/kg/day
Repeat-Dose 02-003-05 13-Week GLP Dog	Dog/Beagle 6M, 6F	Intravenous (1-hour infusion) Placebo: HP-β-CD Diluent: 5% w/v dextrose	12.5, 25, 100	Clinical signs indicative of a reaction to treatment were transitory, characteristic of histamine-mediated reactions and noted in the 100 mg/kg/day dose group. Reactions initially required diphenhydramine to moderate their severity: intervention generally not required beyond Day 20 of the study. Histamine-mediated reactions not deleterious to the longer term clinical condition of the animals. Administration of telavancin resulted in effects on kidney and liver as well as systemic macrophage hypertrophy/hyperplasia. Elevations in ALT, AST and ALKPHOS were observed at 100 mg/kg/day starting at week 6 of the study. The hepatic enzyme changes were consistent with slight hepatocellular degeneration/necrosis in this group. These findings were partially

Table 27: Tabulated Overview of Key Toxicology Studies (Continued)

Study Number	Species/Strain/No. per group and Gender	Method of Administration (Vehicle/ Formulation)	Doses (mg/kg)	Noteworthy Findings
				reversible after 28-days recovery. Slight increases in urea nitrogen, serum creatinine and urinary volumes observed at 100 mg/kg/day starting at week 6 of the study and associated with renal tubular dilation and/or degeneration/necrosis. Renal pathology associated with administration of the placebo with effects being more severe at 100 mg/kg/day. Both clinical and anatomic findings showed evidence of reversibility. No-Observed-Adverse-Effect Level: 25 mg/kg/day
Repeat-Dose 03-001-07 26-Week GLP Rat	Rat/ Crl:CD® (SD)IGS 18M, 18F	Intravenous (30 minute infusion) Placebo: HP-β-CD Diluent: 5% w/v dextrose	6.25, 12.5, 50	Clinical pathology findings considered related to kidney injury included increases in urea nitrogen and creatinine at a dose of 50 mg/kg/day. There were also a higher incidence of granular casts in the urine sediment in both males and females at this dose. These renal findings were reversible. AST and ALT were minimal to mild; both findings were fully reversible following the 4-week recovery period. Microscopic findings included renal tubular vacuolation of diffuse cortical tubular epithelial cells, renal tubular dilation/casts, vacuolation of the eipdidymal epithelial cells, vacuolation of epithelioid venules (ileum), and macrophage hypertrophy/hyperplasia. These findings were also present with placebo but they were more severe and occurred more frequently with telavancin administration. Findings unique to the telavancin group were low-grade renal proximal tubular degeneration and macrophage hypertrophy/hyperplasia (bone marrow, spleen, thymus, and duodenum). Histologic findings showed no or partial recovery at the end of the 4-week recovery period. No-Observed-Adverse-Effect Level: 12.5 mg/kg/day

Table 27: Tabulated Overview of Key Toxicology Studies (Continued)

Study Number	Species/Strain/No. per group and Gender	Method of Administration (Vehicle/ Formulation)	Doses (mg/kg)	Noteworthy Findings
Genotoxicity				
Reverse Mutation 01-001-03	Bacterial cells *(S. typhimurium and E. coli)*	*In vitro*	0.333-5000 mcg/plate	Negative
Reverse Mutation 02-001-08	Bacterial cells *(S. typhimurium and E. coli)*	*In vitro*	1.0 to 5000 mcg/plate	Negative
Chromosomal Aberration 01-001-04	Human Lymphocytes	*In vitro*	3 hrs w/o activation: 207 to 1750 mcg/mL. 19 hrs w/o activation: 104 to 1230 mcg/mL 3 hrs w activation: 207 to 603, 207 to 861 mcg/mL.	Negative
Micronucleus Assay 01-001-05	Mouse/Crl:CD-1® (ICR) 6M, 6F Polychromatic erythrocytes	Intravenous (slow bolus)	12.5, 25, 50	Negative
Reproductive and Developmental Toxicity				
Fertility and Early Embryonic Development 02-001-05	Rat/ Crl:CD® (SD)IGS 20M, 20F	Intravenous (slow bolus) Placebo: HP-β-CD Diluent: 5% w/v dextrose	Males: 50, 75, 100 Females: 50, 100, 150	Compound-related changes in male reproductive organ weights included lower epididymis weights (left and right, weighed separately) at doses ≥50 mg/kg/day, and relative (to body wt.) testis weights at doses ≥50 mg/kg/day. Estrous cycle unaffected by treatment.

Table 27: Tabulated Overview of Key Toxicology Studies (Continued)

Study Number	Species/Strain/No. per group and Gender	Method of Administration (Vehicle/ Formulation)	Doses (mg/kg)	Noteworthy Findings
				No compound-related effects on pregnancy rates, fetal viability at time of cesarean section, or live fetuses in any of the dose groups. No effects on number of corpora lutea, implantation sites, or resorptions. No compound-related effects on pre- or postimplantation loss. Decreases in mean sperm motility and mean epididymal sperm counts, as well as increases in the percentage of sperm with abnormal morphology. No-Observed-Adverse-Effect Level: Male reproductive system <50 mg/kg/day; Male fertility 100 mg/kg/day; Female fertility 150 mg/kg/day; Early embryogenesis 150 mg/kg/day.
Embryo Fetal Development 02-001-04	Rat/ Crl:CD® (SD)IGS 25F	Intravenous (slow bolus) Placebo: HP-β-CD Diluent: 5% w/v dextrose	50, 100, 150	Cesarean section parameters unaffected by treatment. All dams had viable fetuses. No early deliveries or abortions. Pre- and postimplantation loss similar across treatment groups. Covariate-adjusted mean fetal weights significantly lower than diluent control at doses of 100 and 150 mg/kg/day. Fetal external malformations included brachymelia (one fetus each dose at 100 and 150 mg/kg/day out of 332 and 322, respectively) were observed. Syndactyly was observed in one fetus at 100/kg/day dose level. Dilatations of the lateral ventricles of the brain were observed at the 150 mg/kg/day dose level (incidence above historical controls). Maternal No-Observed-Adverse-Effect Level: 150 mg/kg/day Developmental (fetal) No-Observed-Adverse-Effect Level: 50 mg/kg/day
Embryo Fetal Development 02-001-15	Rabbit/ Hra(NZW)SPF 20F	Intravenous (slow bolus) Placebo: HP-β-CD Diluent: 5% w/v	0, 60 75,	Pregnancy rates similar for all dose groups. Cesarean section data unremarkable, and mean fetal weights were similar across treatment groups. Fetal external malformations observed in two fetuses at

Table 27: Tabulated Overview of Key Toxicology Studies (Continued)

Study Number	Species/Strain/No. per group and Gender	Method of Administration (Vehicle/ Formulation)	Doses (mg/kg)	Noteworthy Findings
		dextrose		75 mg/kg/day and included flexed front paws, brachymelia, adactyly, gastroschisis, and umbilical hernia. Treatment-related skeletal malformations noted at 75 mg/kg/day consisting of absent ulna, major fusion of the sternebrae, adactyly and vertebral anomaly with/without associated rib anomaly. Maternal No-Observed-Adverse-Effect Level: 60 mg/kg/day Developmental (fetal) No-Observed-Adverse-Effect Level: 60 mg/kg/day
Embryo Fetal Development 05-013-04	Pregnant Minipig/ Göttingen SPF 14F	Intravenous (slow bolus) Placebo: HP-β-CD Diluent: 5% w/v dextrose	0, 25, 50, 75	Increased incidence of limb malformations was seen at the 25 and 50 mg/kg dose level. Similar finding were not seen at the 75 mg/kg/day dose. These data suggest that the limb malformations may possibly be related to telavancin administration. Maternal No-Observed-Adverse-Effect Level: 75 mg/kg/day These data suggest that the observed limb malformations may possibly be related to telavancin administration.
Effects on Pre- and Postnatal Development 02-001-07	Rat/ Crl:CD®(SD)IGS BR	Intravenous (slow bolus) Placebo: HP-β-CD Diluent: 5% w/v dextrose	50, 100, 150	Compound-related necropsy findings in F_0 dams included pale kidneys in the placebo-control group and all telavancin-treated groups; finding was more severe at 150 mg/kg/day. Telavancin-related increases in the number of F0 dams with stillborn pups and the total numbers of stillborn pups per group increased with dose and were above historic control ranges at 150 mg/kg/day. Covariate-adjusted mean F1 pup weights lower than both diluent and placebo controls at 150 mg/kg/day were considered secondary to maternal toxicity. Minimal increases in mean days to F_1 pup vaginal opening was observed at 150 mg/kg/day compared to the D5W control. A singe F1 pup in the 150-mg/kg/day group was observed to have limited use of a forelimb during the lactation period. There were no compound-related effects on reproductive performance or fertility of F1 males and females or the viability of

Table 27: Tabulated Overview of Key Toxicology Studies (Continued)

Study Number	Species/Strain/No. per group and Gender	Method of Administration (Vehicle/ Formulation)	Doses (mg/kg)	Noteworthy Findings
				the F2 pups.
Repeat-Dose (Gondal Toxicity) 03-001-04 6-Week GLP Rat	Rat/ Crl:CD® (SD)IGS 20M	Intravenous (slow bolus) Placebo: HP-β-CD Diluent: 5% w/v dextrose	12.5, 25, 50, 100	Sloughed testicular germ cells in epididymides and vacuolated macrophages in testes, (reversible) in placebo and at 50 and 100 mg/kg/day. Epididymal epithelial vacuolation in placebo and at 100 mg/kg/day. After recovery period, epididymal epithelial vacuolation increased in severity and was noted in the lower dose groups. Decreased sperm motility and decreased epididymal sperm count, as well as increased abnormal sperm morphology was observed at 50 and 100 mg/kg/day. Motility, count and morphology recovered after 8 weeks.
Other Toxicology Studies				
Repeated-Dose (Immunotoxicity) 04-001-06 6-Week GLP Rat	Rat/ Crl:CD® (SD)IGS Test Groups: 15 M, 15F Immunomodulatory Control: 10M, 10F	Intravenous (30 minute infusion) Placebo: HP-β-CD Diluent: 5% w/v dextrose	12.5, 50, 100	Telavancin administration (50 and 100 mg/kg/day) resulted in minimal to mild increases in the total lymphocyte count without a shift in lymphocyte populations, mild reversible effects on the T-cell dependent antigen response, as well as increased macrophage phagocytic activity but a decreased respiratory burst activity. No-Observed-Adverse-Effect Level: 12.5 mg/kg/day

M: Males F: Females IV: Intravenous ND: Not Determined HP-β-CD: Hydroxypropyl-β-cyclodextrin

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PART III: CONSUMER INFORMATION

PrVIBATIV™
Telavancin for injection (as telavancin hydrochloride)

This leaflet is part III of a three-part "Product Monograph" published when VIBATIV was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VIBATIV. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
The active ingredient in VIBATIV is telavancin hydrochloride. Telavancin is a lipoglycopeptide antibiotic. It can kill certain types of bacteria. VIBATIV can be used to treat infections of the skin or infections in the tissues beneath the skin that are caused by bacteria susceptible to telavancin. VIBATIV can also be used to treat hospital acquired pneumonia (infection of the lungs) or ventilator associated pneumonia caused by certain types of bacteria susceptible to telavancin.

Depending on the type of bacteria causing your infection, your doctor may also prescribe other antibiotics while you are treated with VIBATIV.

Antibacterial drugs like VIBATIV treat only bacterial infections. They do not treat viral infections. Although you may feel better early in treatment, VIBATIV should be used exactly as directed. Misuse or overuse of VIBATIV could lead to the growth of bacteria that will not be killed by VIBATIV (resistance). This means that VIBATIV may not work for you in the future. Do not share your medicine.

What it does:
Telavancin prevents the bacteria from multiplying by stopping the formation of new bacterial cell walls and interfering with the bacteria's cell membrane. The cell wall and membrane are important components of bacteria. This prevents the bacteria from functioning and causes it to die.

When it should not be used:
- If you are allergic to VIBATIV or any of its ingredients. (See what the nonmedicinal ingredients are below)

What the medicinal ingredient is:
- Telavancin hydrochloride

What the important nonmedicinal ingredients are:
- Hydroxypropyl-beta-cyclodextrin (hydroxypropyl betadex)
- Mannitol
- Sodium hydroxide
- Hydrochloric acid

What dosage forms it comes in:
VIBATIV (telavancin for injection) is available as a sterile powder for injection containing 250 mg or 750 mg of telavancin per glass vial (as telavancin hydrochloride).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
- **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 is not recommended for use in patients with severe kidney impairment or in patients with end stage kidney disease requiring hemodialysis.**
- **If you have moderate kidney impairment, your doctor will adjust your dose and monitor your kidney function more frequently.**
- **VIBATIV may harm your unborn baby. Women who can become pregnant should have a blood pregnancy test before receiving VIBATIV.**
- **Animal studies have shown a low incidence of fetal limb defects. There are no adequate studies in pregnant women. VIBATIV should not be used in pregnancy unless the doctor decides the benefits outweigh the risks.**

BEFORE you use VIBATIV talk to your doctor or pharmacist if:
- You are suffering from other infections
- You have heart abnormalities such as congenital long QT syndrome, and heart arrhythmia (irregular heartbeat)
- You are suffering from heart disorders such as uncompensated heart failure, or severe left ventricular hypertrophy
- You are suffering from an HIV infection
- You are due to undergo treatment with chemotherapy
- You have experienced skin reactions to other glycopeptides
- You are suffering from a kidney disorder
- You are suffering from severe liver disorder
- You are taking other antibiotics. While antibiotics including VIBATIV fight certain bacteria, other bacteria and fungi may continue to grow. This is called overgrowth. Your doctor will monitor you for any potential infections and treat you if necessary
- You are using other medicines that contain a cyclodextrin. VIBATIV contains hydroxypropylbetadex, a cyclodextrin. Cyclodextrins have been associated with nephrotoxicity (kidney toxicity). Therefore, the use of other medications that also contain a cyclodextrin at the same time as VIBATIV is not recommended
- You are pregnant, think you may be pregnant, or are trying to become pregnant. VIBATIV should not be given to pregnant women unless it is absolutely necessary. Women of childbearing potential should either abstain from sexual activity or use double-barrier means of contraception while on VIBATIV. It is not known if VIBATIV passes into

breast milk in humans. Breastfeeding should be discontinued during VIBATIV treatment

VIBATIV should not to be used in children or adolescents less than 18 years old.

VIBATIV may interfere with some laboratory tests that measure how well your blood is clotting. The test results can suggest poor blood clotting when, in fact, there is no problem. Tell your doctor that you are receiving VIBATIV.

VIBATIV may interfere with some laboratory tests that measure proteins in the urine. Tell your doctor that you are receiving VIBATIV.

What to do if certain conditions develop while taking the medication
Contact your doctor if the following occur while taking VIBATIV:

- You develop skin reactions to the product. Your doctor may decide to adjust the dosing of the infusion.
- You develop diarrhea during or shortly after your treatment. Tell your doctor immediately if this happens.
- You develop heart palpitations or fainting spells.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

The combination of VIBATIV with medicines that leave the body mainly via the urine should be used with caution. These may affect the excretion of telavancin via the urine. Your doctor will tell you if this is the case.

PROPER USE OF THIS MEDICATION

Usual adult (over 18 years) dose:
Your doctor will decide how much medicine you will take and for how long. The dose you will be given will depend on how much you weigh. The dose for adults is 10 milligrams (mg) for every kilogram (kg) of body weight, given once daily. This dose is given as an infusion directly into your blood stream (into a vein) over a period of about 60 minutes.

If your kidneys do not work well, the dose may be reduced.

The course of treatment usually lasts for 7 to 14 days for skin infections or 7 to 21 days for pneumonia.

Overdose:

If you think you have taken too much VIBATIV, contact your attending healthcare professional, hospital emergency department or regional Poison Control Centre, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Any medicine may have unintended or undesirable effects, so-called side effects.

The most commonly (≥1%) reported adverse drug reactions in patients taking VIBATIV for skin infections were dysgeusia (disturbed or metallic taste), nausea, vomiting, urine abnormality (foamy urine), headache, pruritus (skin itch), diarrhoea, infusion-site reaction, constipation, insomnia, dizziness, rash, rigors (shivering), fatigue, decreased appetite, fungal infection, dyspepsia (upset stomach), dry mouth and blood creatinine increased. These reactions were generally mild to moderate in severity.

The most commonly (≥1%) reported adverse drug reactions in patients taking VIBATIV for pneumonia were diarrhea, nausea, vomiting, alanine aminotransferase increased, blood creatinine increased, kidney failure acute, rash, aspartate aminotransferase increased and electrocardiogram QT corrected interval prolonged.

Hearing loss has also been reported with the use of telavancin.

If these side effects become bothersome, consult your doctor.

If you experience symptoms such as severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness, you may have Clostridium difficile colitis (bowel inflammation). If this occurs, stop taking VIBATIV and contact your healthcare professional immediately.

Other side effects may also occur rarely and as with any prescription medication, some side effects may be serious. Ask your doctor or pharmacist for more information. Tell your doctor promptly about these or any other unusual symptoms.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Common			
Kidney problems and symptoms such as foamy urine	✓		
Uncommon			

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and**
Serious allergic reaction and symptoms such as severe rash, itching, swelling of hands and feet, trouble breathing, vaginal itching, chest discomfort; skin flushing of upper body; feeling abnormal.			✓
Septic shock (blood pressure drop due to complication of infections and body wide inflammation)			✓

This is not a complete list of side effects. For any unexpected effects while taking VIBATIV, contact your doctor or pharmacist.

HOW TO STORE IT

VIBATIV in its original package should be stored at refrigerated temperatures of 2°C to 8°C.

Keep out of reach and sight of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting PENDOPHARM, Division of Pharmascience Inc. at: 1-888-550-6060 or through its website http://www.pendopharm.com

This leaflet was prepared by PENDOPHARM, Division of Pharmascience, Inc., Montreal, QC, H4P 2T4

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