

TELAVANCIN

In September, 2009, the United States Food and Drug Administration (US FDA) approved telavancin Vibativ® for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive bacteria, including *Staphylococcus aureus*, both methicillin-resistant (MRSA) and methicillin-susceptible (MSSA) strains, as well as *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius* and *S. constellatus*) and *Enterococcus faecalis* (vancomycin susceptible isolates only). Telavancin was licensed in Canada in 2009 but has not been marketed to date.

Telavancin exhibits potent activity against MSSA, MRSA, methicillin-susceptible *S. epidermidis* (MSSE) and methicillin-resistant *S. epidermidis* (MRSE). Telavancin is active against vancomycin-intermediate *S. aureus* (VISA) but is not very active versus vancomycin-resistant *S. aureus* (VRSA). Telavancin is active against streptococci including *S. pneumoniae*, with no variability in MIC between penicillin-susceptible, intermediate, and resistant phenotypes. Telavancin maintains activity against enterococci with activity against VanB vancomycin-resistant enterococci (VRE), but not against VanA VRE. Telavancin is active against *Clostridium spp.*

Telavancin is administered by intravenous infusion and displays linear pharmacokinetics. The half-life of telavancin in serum ranges from 7-9 hours which allows for once-daily dosing. The volume of distribution of telavancin in healthy adults following a single 10 mg/kg dose is 0.115 L/kg. Protein binding is ~93%. The activity of telavancin *in vitro* is not affected by the presence of pulmonary surfactant. The primary mode of elimination of the drug from the body is via the renal route, with up to 70% of the dose excreted

in the urine as unchanged drug. The half-life of telavancin in patients with renal dysfunction is extended compared to that reported in healthy individuals, and increases with increasing renal dysfunction, thus making dosage adjustments necessary. The dose of telavancin for patients with a Cl_{cr} ranging from 30 to 50ml/min should be 75% of the dose administered to healthy adults, whereas patients with end stage renal disease (ESRD) should be administered the full dose (10mg/kg) every 48 hours, rather than every 24 hours as in healthy volunteers. Telavancin is not an inhibitor, inducer, nor a substrate for cytochrome P450 isoenzymes.

The telavancin Phase III clinical program consisted of two large, multinational, double-blind, randomized Phase III clinical studies, ATLAS I and ATLAS II, designed to compare the efficacy and safety of telavancin (10 mg/kg IV once daily) versus vancomycin (1 gm IV q 12hr) in adult patients with cSSSI caused by Gram-positive bacteria. A total of 1,867 patients were enrolled and treated, 719 of whom had infections with MRSA. In both of these studies, telavancin achieved its primary endpoint of non-inferiority relative to the standard of care, vancomycin. Telavancin has not been studied in children.

The most common adverse reactions (≥10% of patients treated with telavancin) observed in the Phase III cSSSI clinical trials were taste disturbance, nausea, vomiting, and foamy urine. In the Phase III cSSSI clinical trials, serious adverse events were reported in 7% of patients treated with telavancin and most commonly included renal, respiratory, or cardiac events. Serious adverse events were reported in 5% of vancomycin-treated patients, and most commonly included cardiac, respiratory, or infectious events.



Women of childbearing potential should have a serum pregnancy test prior to administration of telavancin. Avoid use of telavancin during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. Adverse developmental outcomes observed in three animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans. New onset or worsening renal impairment occurred in patients who received telavancin. Renal adverse events were more likely to occur in patients with baseline co-morbidities known to predispose patients to kidney dysfunction and in patients who received concomitant medications known to affect kidney function. Renal function should be monitored in all patients receiving Vibativ prior to initiation of treatment, during treatment, and at the end of therapy. Clinical cure rates in telavancin-treated patients were lower in patients with baseline CrCl ≤ 50 mL/min compared to those with CrCl > 50 mL/min. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this age group.

Telavancin should be administered over a period of 60 minutes to reduce the risk of infusion related reactions. Rapid intravenous infusions of the glycopeptide class of antimicrobial agents can cause "Red man Syndrome" like reactions including: flushing of the upper body, urticaria, pruritus, or rash. Caution is warranted when prescribing telavancin to patients taking drugs known to prolong the QT interval. In a study involving healthy volunteers, telavancin prolonged the QTc interval. Use of telavancin should be avoided in patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy. Telavancin does not interfere with coagulation, but does interfere with certain tests used to monitor coagulation such as prothrombin time, international normalized ratio, activated partial thromboplastin time, activated clotting

time, and coagulation based factor Xa tests. Blood samples for these coagulation tests should be collected as close as possible prior to a patient's next dose of telavancin.

