CLINICAL INVESTIGATION

# Telavancin in the treatment of nosocomial pneumonia: review of the clinical evidence

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Nosocomial pneumonia (NP) is a frequent and severe infection arising mainly in intensive care units. Despite recent advances in supportive care and a wide range of prevention measures, it remains a significant cause of patient morbidity and mortality. A risk factor for increased mortality is the inappropriate antimicrobial therapy, often caused by antimicrobial resistance. The increased frequency of multidrug-resistant bacteria, especially methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant strains, has led to an urgent need for new antibiotics. Telavancin is a novel antibiotic-semisynthetic lipoglycopeptide, which deploys a dual mechanism of action that involves the inhibition of cell-wall synthesis and disruption of bacterial cell-membrane barrier functions and is rapidly bactericidal against methicillin-resistant *S. aureus* and Gram-positive bacteria resistant to vancomycin. It has been approved for the treatment of severe NP. This article reviews telavancin's pharmacological characteristics resulting from clinical trials, giving a detailed picture of recent available data in NP management.

**Keywords:** hospital pneumonia • linezolid • lipoglycopeptides • methicillin-resistant *Staphylococcus aureus* • telavancin • treatment • vancomycin

Nosocomial pneumonia (NP) is the second most common nosocomial infection – accounting for up to 25% of all intensive care unit infections and for more than 50% of antibacterial agent prescriptions – with mortality rates as high as 76% reported under some circumstances in ventilated patients [1–3], or when lung infection is caused by high-risk pathogens. Factors commonly related to this increased mortality are inappropriateness of empiric antibiotic treatment, the existence of bacteremia and the virulence of the microorganism. The most commonly encountered causative pathogens of NP reported are higher-level antibiotic-resistant Gram-negative bacteria, such as *Pseudomonas aeruginosa*, *Acinetobacter spp.*, or methicillin-resistant *Staphylococcus aureus* (MRSA) [1,4]. In an interesting study by Kollef *et al.* demonstrated that patients infected with MRSA were more likely to receive inappropriate antimicrobial therapy [5]. Moreover, rates of MRSA are over 50% in the USA, accounting for over 125,000 hospitalizations annually, and are still increasing [6].

For decades, vancomycin has been the mainstay of therapy in the treatment of this pathogen. During the 1990s, strains of *S. aureus* with reduced susceptibility to glycopeptides (vancomycin intermediate *S. aureus* [VISA] or glycopeptide-intermediate *S. aureus*, heteroresistant VISA strains [hVISA] and extremely uncommon strains of *S. aureus* fully resistant to vancomycin [VRSA]) have emerged in the clinical arena [7]. At the same time, it has long been recognized that vancomycin exerts a slow bactericidal effect with numerous reports of frank treatment failures on *S. aureus* infections [8,9]. Overall there has been an increase in the minimum inhibitory concentrations (MICs) of vancomycin against MRSA,

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associated with poorer outcomes, which has prompted the Clinical and Laboratory Standards Institute to lower vancomycin's breakpoint from ≤4 μg/ml to ≤2 g/ml for susceptible strains, from 8–16 μg/ml to 4–8 μg/ml for intermediately susceptible strains, and from ≥32 μg/ml to ≥16 μg/ml for resistant strains [101].

In addition to concerns regarding staphylococci, enterococci may also demonstrate resistance to vancomycin. Vancomycin-resistant enterococci (VRE) are the fourth most common cause of nosocomial bloodstream infections in North America [10].

As antimicrobial resistance continues to increase worldwide, more active as well as less toxic antibacterial agents are still needed, especially for the above mentioned problematic pathogens like MRSA and VRE.

## Telavancin

Among several potential new antibiotics, telavancin (Vibatin, Astellas Pharma Europe, Ltd and Theravance, Inc.) is a lipoglycopeptide analogue of vancomycin, which in September 2011 received approval from the EC for the treatment of adults with hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) known or suspected by MRSA [102,103].

### Chemistry

Telavancin is a semisynthetic derivative of vancomycin bearing both lipophilic and hydrophilic groups. The chemical structure of telavancin is depicted in Figure 1. It results from the alkylation of the vancosamine nitrogen with a hydrophobic (decylaminoethyl) side chain and the addition of a hydrophilic (phosphonomethylaminomethyl) group on the resorcinol-like position on the cyclic peptidic core [11,12,102]. Modification and/or addition of side chains to the glycopeptides backbone help to explain some of the distinguishing pharmacokinetic and pharmacodynamic properties of telavancin.

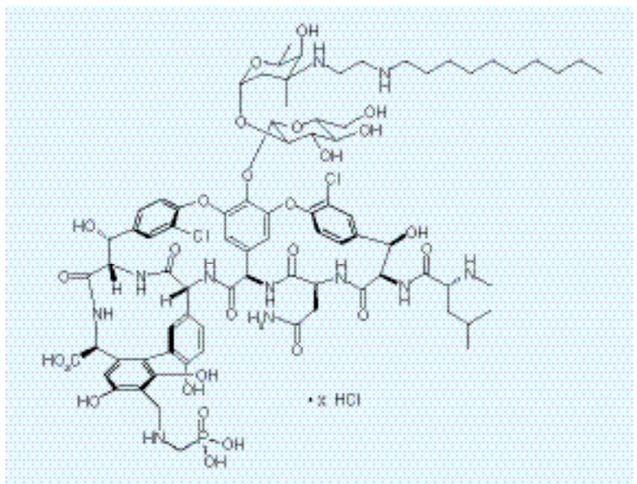

**Figure 1. Chemical structure of telavancin.**

### Mechanism of action

Telavancin is a lipoglycopeptide antibiotic with bactericidal activity against clinically important Gram-positive bacteria, such as staphylococci (including MRSA, hVISA and VISA strains) and streptococci (including penicillin-resistant *Streptococcus pneumoniae*) as well as Gram-positive anaerobic and fastidious aerobic bacteria [13]. *In vitro*, it has a rapid (within 10 min), concentration-dependent bactericidal effect, which is thought to be due to its dual mechanism of action, disrupting bacterial cell wall synthesis and membrane integrity.

It is postulated that the hydrophobic side chain of telavancin amplifies the interaction with the bacterial cell wall, increasing the binding for the terminal D-alanyl-D-alanine; which potentially improves activity of telavancin against MRSA and enterococci with the VanA gene, and would explain the tenfold greater peptidoglycan synthesis inhibition of telavancin when compared with vancomycin [14].

It has been demonstrated that telavancin exerts a concentration-dependent increase in bacterial membrane permeability, leading to depolarization of the cell membrane.

This lipophilic moiety enhances the affinity of telavancin for lipid II, a component of the bacterial cell membrane [15]. In *S. aureus*, it has been reported using flow cytometry assay, that binding to lipid II is necessary for telavancin to induce membrane depolarization, increasing in permeability and leakage of cellular ATP and $K^+$, although this may not be the decisive step in membrane disruption. This second mechanism of action may promote or be the lone reason for its rapid bactericidal activity. These multiple mechanisms of action may be responsible for the low frequency of spontaneous resistance to telavancin.

Noteworthy, telavancin was found to have the potential to kill nongrowing bacteria [16] and possesses bactericidal activity against intraphagocytic *S. aureus*, irrespective of resistance phenotypes (MRSA, VISA, VRSA) enabling killing of intracellular bacteria [17].

### Pharmacokinetics & pharmacodynamics

Telavancin, like other members of the glycopeptides class, is a large compound with poor oral bioavailability, and thus is administered in a dose of 10 mg/kg over 60 min by an intravenous infusion [18]. In a sequential ascending-dose study, 54 healthy adult male subjects (mean [SD] age: 25.3 [4.7] years; mean [SD] weight: 80.5 [10.0] kg) were administered telavancin 0.25–15 mg/kg intravenously (iv.) once-daily for up to 7 days [19] (Table 1). Telavancin was reported to have linear and predictable pharmacokinetics supportive of a once-daily regimen. In a single dose of telavancin at the US FDA-approved adult dose (10 mg/kg), the mean $C_{max}$ was 87.5 μg/ml, $AUC_{0-24}$ was 762 (±81) μg h/ml, half-life was 7.5 (±2.28) h, clearance was 11.8 (±1.4) ml/h/kg and the volume of distribution was 115 (±6) ml/kg [102,104].

Wong *et al.* observed no sex-related differences in the pharmacokinetic disposition of telavancin [20]. Telavancin demonstrates a higher degree of plasma protein binding than vancomycin (93 vs 50%) [21]. In an *in vitro* model, the presence of human albumin and human serum had a modest effect on the antibacterial activity of telavancin against methicillin-susceptible *S. aureus* (MSSA) and MRSA as demonstrated by time-kill curves [16,22].

Penetration of telavancin into possible sites of infection has been examined in healthy subjects. Gotfried *et al.* reported that telavancin penetrated well into epithelial lining fluid (ELF; mean [±SD] concentrations of 3.73 [±1.28] μg/ml at 8 h and 0.89 [±1.03] μg/ml at 24 h) and extensively into alveolar macrophages (mean [±SD] concentrations of 19.0 [±16.8] μg/ml at 8 h, 45.0 [±22.4] μg/ml at 12 h, and 42.0 [±31.4] μg/ml at 24 h) in 20 healthy volunteers [23]. Based on plasma and ELF pharmacokinetic data obtained from 20 healthy subjects, Lodise *et al.* used population pharmacokinetic modeling and Monte Carlo simulation techniques, and found the mean AUC ELF:free AUC plasma penetration ratio to be 1.01 (±0.96), suggesting that telavancin penetrates well into ELF [24]. Unlike daptomycin, the antibacterial activity of telavancin activity is not affected by pulmonary surfactant [23]. Telavancin achieves good penetration into skin blister fluid, with the AUC in blister fluid approximately 40% of that in plasma following three daily doses of telavancin 7.5 mg/kg [18].

Published data in humans is lacking to characterize the penetration of telavancin into the CNS. However, in an experimental rabbit meningitis model, the penetration of telavancin into inflamed meninges was approximately 2%, while penetration into noninflamed meninges was less than 1% [22].

Preliminary results from an *in vitro* MRSA model suggest that free drug AUC:MIC ratios of 50–100 are associated with a 1- to 2-log decrease in bacterial counts and minimal resistance emergence [25]. An AUC:MIC ratio of 50, corresponding to a human dosage of 10 mg/kg once-daily and a minimum concentration in plasma of 5 mg/l, was the lowest concentration that resulted in no bacterial growth at 24 h, while maximal activity was observed at total AUC:MIC of 404 [26].

The post-antibiotic effect (PAE) of telavancin against most Gram-positive organisms has been reported to range from 4–6 h, which is at least four times longer than the PAE observed with vancomycin. In one study, the PAE of telavancin against MSSA, MRSA and VISA strains were ≥4 h [16,27].

The pharmacokinetic properties of telavancin in pediatrics (<18 years of age) and pregnant females have not been studied.

The primary mode of elimination of telavancin from the body is via the renal route, with up to 70% of the dose excreted in the urine as unchanged drug. When it was administered at doses between 7.5 and 15 mg/kg iv. over 1 h, the mean elimination half-life ranged from 6.0 (±0.6) to 7.5 (±1.3) h [11,13]. The dose of telavancin for patients with Creatinine clearance ranging from 30–50 ml/min should be 75% of the dose administered to healthy adults, whereas

**Table 1. Pharmacokinetic properties of telavancin in healthy subjects.**

| | 10 mg/kg/d single dose over 2 h (n = 5) | 7.5 mg/kg/d for 3 days over 1 h (n = 39) | 15 mg/kg/d for 3 days over 1 h (n = 34) | 7.5 mg/kg/d for 7 days over 0.5 h (n = 6) | 15 mg/kg/d for 7 days over 0.5 h (n = 6) |
|---|---|---|---|---|---|
| $C_{max}$ (μg/ml) | 87.5 ± 6 | 87.5 ± 12.8 | 186 ± 27 | 96.7 ± 19.8 | 151 ± 17 |
| $AUC_0$ | 858 ± 109 | NR | NR | 700 ± 114 | 1.03 ± 91 |
| $AUC_{0-24}$ (μg/h/ml) | NR | 599 ± 96 | 1282 ± 201 | NR | NR |
| Vd (ml/kg) | 115 ± 6 | 111 ± 32 | 119 ± 14 | 105 ± 20 | 119 ± 18 |
| CL (ml/h/kg) | 11.8 ± 1.4 | 13 ± 3.6 | 12 ± 9 | 10.9 ± 1.6 | 12.2 ± 1.1 |
| $t_{1/2}$ (h) | 7.5 ± 0.6 | 6 ± 0.6 | 7.5 ± 1.3 | 8.83 ± 1.71 | 9.11 ± 2.33 |

Values listed are mean ± SD.
CL: Clearance; $C_{max}$: Maximum concentration; NR: Not reported; $t_{1/2}$: Elimination half-life; Vd: Volume of distribution.
Data taken from [19,20].

patients with Creatinine clearance ranging from 10–30Ml/min should be administered the full dose (10 mg/kg) every 48 h [25]. Hepatic impairment does not appear to influence telavancin CL [28].

In order to elucidate any potential synergy, antagonism or indifference resulting from combinations of telavancin with other antimicrobial agents, a checkerboard methodology was employed to yield a fractional inhibitory concentration index. The results of the study demonstrated the absence of antagonism with any of the studied combinations and synergy with telavancin combined with cefepime or piperacillin/tazobactam against VISA and VRSA isolates [29]. Another study was conducted to examine the synergistic activity of telavancin in combination with the antibiotics rifampin, gentamicin, cefepime, ceftriaxone, oxacillin, meropenem and ciprofloxacin against 40 strains of *S. aureus*: community-acquired MRSA (15), hospital-acquired MRSA (12), VISA (8), VRSA (3) and hVISA (2). Telavancin was reported to have synergy when combined with all the examined antibiotics, but the highest synergy rates were observed at 24 h when subinhibitory concentrations of telavancin were combined with clinically relevant, subinhibitory concentrations of gentamicin, ceftriaxone, meropenem and rifampin [30].

## Antimicrobial activity

Telavancin is active *in vitro* against a broad spectrum of Gram-positive organisms (Table 2). The spectrum of its antimicrobial activity closely mirrors that of glycopeptides, except that telavancin maintains its activity against relevant organisms with decreased susceptibility to glycopeptides. $MIC_{90}$s are generally two- to eight-fold lower than vancomycin against *S. pneumoniae, S. aureus, Staphylococcus epidermidis, Enterococcus faecalis and Enterococcus faecium* [18,22,31–34]. The $MIC_{90}$ of telavancin of the *S. aureus* and coagulase-negative staphylococci strains is ≤1 μg/ml, regardless of the methicillin resistance. Mendes *et al.* studied the *in vitro* activity of telavancin against 1017 clinical isolates of MRSA and 950 clinical isolates of coagulase-negative staphylococci strains collected from 28 hospitals in 13 European countries in 2007–2008 [32]. All isolates were inhibited at a concentration of ≤0.5 μg/ml with a $MIC_{90}$ of 0.25 μg/ml. Results from a European surveillance study showed that telavancin MICs range between 0.06 and 0.5 μg/ml for both MSSA and MRSA, which was two- to four-fold lower than that for vancomycin, four- to 80-fold lower than that for linezolid and

**Table 2. Clinical cure rates, evaluated at a visit scheduled 7–14 days after the last dose of medication, in the evaluable population of all the patients of the ATTAIN study.**

| Infection type | Telavancin (% of patients [n]) | Vancomycin† (% of patients [n]) | Treatment difference (% of patients [95% CI]) |
|---|---|---|---|
| All *Staphylococcus aureus*‡ | 78.1 (171/219) | 75.2 (161/214) | 3 (-5–11) |
| All MRSA§ | 74.8 (104/139) | 74.7 (115/154) | 0.4 (-9.5–10.4) |
| Monomicrobial *S. aureus* | 84.2 (123/146) | 74.3 (113/152) | 9.9 (0.7–19.1) |
| Vancomycin MIC ≤0.5 μg/ml¶ | 89.2 (33/37) | 78.6 (22/28) | 10.1 (-9–28.8) |
| Vancomycin MIC ≥1 μg/ml# | 87.1 (74/85) | 74.3 (78/105) | 12.5 (0.5–23) |
| MRSA | 81.8 (72/88) | 74.1 (86/116) | 7.9 (-3.5–19.3) |
| MSSA | 87.9 (51/58) | 75.0 (27/36) | 12.2 (-4.2–28.8) |
| *Streptococcus pneumoniae* | 90.0 (18/20) | 85.7 (18/21) | 5.9 (-19.1–29.7) |
| Mixed infections†† | 66.2 (45/68) | 79.4 (50/63) | -12.6 (-26.9–3.2) |
| Mixed infections with adequate Gram-negative therapy‡‡ | 63.2 (12/19) | 66.7 (14/21) | -0.8 (-28.9–25.7) |

†Includes five microbiologically evaluable patients who received antistaphylococcal penicillins instead of vancomycin.
‡S. aureus with and without concomitant pathogens; includes four patients in the telavancin group and one patient in the vancomycin group with pathogens isolated exclusively from blood cultures.
§MRSA with and without concomitant pathogens.
¶All vancomycin MIC values were 5 0.5 lg/ml, except for one patient in the telavancin group with MIC <0.25 lg/ml.
#All vancomycin MIC values were 5 1.0 lg/ml, except for two patients in the telavancin group with MIC 5 2.0 lg/ml.
††Mixed Gram-positive and Gram-negative infections.
‡‡Inadequate Gram-negative coverage was defined as not having received an antibiotic to which the recovered Gram-negative pathogen was susceptible until study day 3 or later, or not receiving such an antibiotic at all during study treatment.
MIC: Minimum inhibitory concentration; MRSA: Methicillin-resistant Staphylococcus aureus; MSSA: Methicillin-susceptible Staphylococcus aureus.
Data taken from [42].





twofold lower than that for daptomycin [31]. Telavancin was found to be highly active against heterogeneous hVISA, maintaining bactericidal activity both at low and high inocula, and at peak and trough concentrations [35]. This activity was superior to vancomycin and linezolid at both inocula.

Telavancin also has activity against Panton–Valentine leukocidin (PVL)-producing and nonproducing community-acquired MRSA strains with a $MIC_{90}$ of 0.5 μg/ml, which is the same for vancomycin [36].

Telavancin exhibited a consistently low $MIC_{90}$ (≤0.06 μg/ml) for *S. pneumoniae,* with no variability for penicillin-susceptible, penicillin-intermediate and penicillin-resistant phenotypes [13,33].

The development of resistance to telavancin *in vitro* has been assessed using two different methods including strains of *S. aureus, S. epidermidis, E. faecium, Streptococcus pyogenes*, *Streptococcus agalactiae* and *S. pneumoniae*. No spontaneous resistant mutants were detected when breakthrough growth was evaluated following the exposure of high bacteria inocula to suprainhibitory concentrations of telavancin [37]. In another study of Kosowska-Shick *et al.* comparing the activity of telavancin with other antistaphylococcic agents against MRSA strains, they noticed that single-step mutation frequencies for telavancin ($<4.0 \times 10^{-11}$ to $<2.9 \times 10^{-10}$ at 2× MIC) were lower than the spontaneous mutation frequencies obtained with the comparators [38]. In agreement with these observations, no resistant mutants have been detected for any strain isolated in telavancin clinical trials to date [13]. Evaluation of telavancin against biofilm-producing *S. aureus, S. epidermidis* and *E. faecalis* revealed that MICs for telavancin were eight- to 16-times lower than vancomycin, and telavancin concentrations lower than respective MICs of the isolates inhibited the development of biofilm [39]. These results might be explained by the secondary mechanism of action unique to this drug.

Telavancin has been reported to demonstrate potent *in vitro* activity against vancomycin susceptible enterococci; for susceptible *E. faecalis*, the $MIC_{90}$ is 0.5–1 μg/ml (compared with 2 μg/ml for vancomycin). However, it was much less active against vanA-positive VRE ($MIC_{90}$; 8–16 μg/ml) and had modest activity against vanB-positive VRE ($MIC_{90}$; 2 μg/ml) [33,39]. *In vitro* data suggests more potent activity (~four to 32-times) against *VanB* VRE strains compared with VanA strains [22,33]. For *E. faecium*, the $MIC_{90}$ is 0.25–0.5 μg/ml. A slightly lower $MIC_{90}$ (one dilution step) was observed for telavancin against *E. faecium* compared with *E. faecalis*.

In a study of Finegold *et al.*, the antimicrobial activities of telavancin and six comparators were evaluated against 460 isolates of anaerobic bacteria. Telavancin demonstrated excellent activity against Gram-positive anaerobes ($MIC_{90}$: 2 g/ml) and was the most potent agent tested against *Clostridium difficile* ($MIC_{90}$: 0.25 g/ml) [40]. Telavancin's activity against Gram-positive anaerobes and *Corynebacterium species* was assessed in an *in vitro* model, where it inhibited 90% of the anaerobic isolates and 100% of the *Corynebacterium* isolates at concentrations of 1 μg/ml or less [36]. The $MIC_{90}$ of telavancin for all strains tested was ≤2 mg/ml [41].

## Clinical efficacy

Unlike the other lipoglycopeptides, the FDA approved telavancin for use in complicated skin and soft tissue infections but not for the treatment of HAP, with further studies recommended aimed at a mortality end point [105].

## Hospital-acquired pneumonia

Two methodologically identical Phase III, multinational, randomized, double-blind, active-controlled clinical trials (ATTAIN 1 and ATTAIN 2) compared the efficacy and tolerability of telavancin and vancomycin in the treatment of hospital-acquired pneumonia, including VAP.

The first data from the HAP trials (ATTAIN) were published in 2011 by Rubinstein *et al.* [42,43] Table 2 and the rest were available and have been presented as abstracts at scientific meetings.

In the ATTAIN studies, a total of 1503 patients with HAP, from 38 countries, were enrolled to receive either vancomycin 1 g every 12 h or telavancin 10 mg/kg every 24 h in combination with aztreonam or piperacillin–tazobactam if a polymicrobial infection was identified. *S. aureus* was the most common pathogen isolated from the respiratory tract with approximately 60% (464 pts) MRSA. In total, 658 (44%) patients were clinically evaluable. Clinical cure (the primary end point) was similar in both groups with significantly better cure rates obtained in telavancin treated high MIC isolates (≥1 μg/ml; treatment difference 12.5%; 95% CI 0.5–23%; p = 0.03). Lower cure rates in patients with mixed infections were observed in the telavancin group. In patients with mixed infections who received adequate Gram-negative coverage, cure rates were similar between the two groups. Moreover, telavancin demonstrated potent activity against recent Gram-positive HAP isolates; MICs for all isolates ranged from 0.008 to 1 μg/ml [44].

The secondary objective was to perform a pooled analysis of the superiority of telavancin over vancomycin in patients with a confirmed MRSA infection

(the most common Gram-positive pathogen isolated). The clinical cure rates for the 159 MRSA monomicrobial patients were 86% for telavancin vs 75% for vancomycin treated patients [45].

Corey *et al.* reported the clinical outcomes of patients infected with MSSA with vancomycin MICs ≥1 µg/ml [46]. The clinical cure rates in patients who received telavancin and vancomycin were 87.1 and 74.3%, respectively ($p < 0.05$). Based on this information, telavancin might be a treatment option in patients with pneumonia due to MSSA with vancomycin MICs ≥1 µg/ml.

In patients with *S. aureus* VAP clinical cure rates were 76.3% for telavancin and 60.0% for vancomycin (treatment difference 16.9%; 95% CI: 1.2–32.8%). For MRSA VAP, clinical cure rates were 75.0% for telavancin and 57.6% for vancomycin (difference 17.8%; 95% CI: 5.1– 37.2%). Cure rates were similar for MSSA: 79.2% for telavancin versus 64.7% for vancomycin (difference 15.7%; 95% CI: 13.8%–41.3%). The incidence of adverse events (AEs) was similar between treatment groups [47].

Upon examination of results obtained from older and severely ill patients [48], telavancin was deemed to be equally effective as vancomycin in treating NP, with cure rates in patients with APACHE II scores of >20 reaching 68% in the telavancin group and 57% in the vancomycin group (95% CI: 9.4–27.5). In patients over the age of 65 years, clinical cure rates of 81% were achieved with telavancin treatment compared with 76% when vancomycin was administered. The majority of results of the ATTAIN trials have not yet been formally published.

A recent study of Pfaller *et al.*, examined the antimicrobial activity of telavancin against 2279 clinical Gram-positive cocci obtained from patients with NP worldwide [49]. Telavancin demonstrated equal or greater potency than the comparators (vancomycin, teicoplanin, daptomycin, linezolid and quinupristin/dalfopristin) against Gram-positive pathogens implicated in NP. Telavancin inhibited all staphylococci at ≤0.5 mg/l and had $MIC_{90}$ values that were fourfold lower than those of vancomycin, teicoplanin, daptomycin, linezolid and quinupristin/dalfopristin against vancomycin-sensitive enterococci isolates, but was less potent than daptomycin and linezolid against VRE.

### Efficacy in animal models

The efficacy of telavancin was assessed in the treatment of pneumonia based on findings from various animal models [27,50–52]. In a neutropenic murine model of pneumonia induced by MSSA, telavancin was compared with nafcillin, vancomycin and linezolid [50]. A significantly greater reduction in the lung titer (CFU/g) of bacterial cells was found in the telavancin-treated mice compared with vancomycin- and linezolid-treated animals at both 12 and 24 h post-inoculation. Survival curves also favored telavancin over vancomycin and linezolid.

In an interesting recent report, Crandon *et al.* compared the efficacy of telavancin for the treatment of pneumonia caused by a collection of variably resistant MRSA strains in a neutropenic murine lung infection model [51]. They found that human-simulated dosing regimens of telavancin and vancomycin resulted in similar efficacies against MRSA strains with vancomycin MICs of <2 µg/ml. Against hVISA strains, similar efficacies were noted for telavancin and vancomycin after 24 h, while telavancin was more efficacious after 48 h against one of the two strains tested. Furthermore, telavancin efficacy increased from 24–48 h against all seven isolates (range: -0.6 to -2.9 log10 CFU/ml), while an additional 24 h of vancomycin treatment resulted in a decrease in efficacy (i.e., increased bacterial density) for two of the seven isolates (range: 0.3 to -2.6 log10 CFU/ml).

### Safety & tolerability

In clinical trials, telavancin was well-tolerated, with a low incidence of drug discontinuation due to adverse effects. Phase I clinical trials of telavancin in 54 healthy adults found that the most common AEs associated with its treatment were taste disturbance (75 vs 14% placebo) and headache (40 vs 29% placebo) [11,102]. Taste disturbances were mild and reversible without treatment. Headaches were reported throughout the range of doses studied (0.25–10 mg/kg). Other reported AEs included dizziness, nausea and rash in two subjects.

Another noteworthy trial evaluated the effects of telavancin on cardiac repolarization using an ECG [53]. In the study, 160 subjects received placebo, telavancin 7.5 mg/kg, or moxifloxacin (Avelox, Bayer) 15 mg/kg or 400 mg for 3 days. The mean effect on cardiac repolarization with telavancin was less than 5 ms with no dose correlation. Although these findings suggest otherwise, the drug should not be used in patients with congenital long QTc syndrome, prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy.

Telavancin should be administered over 60 min to minimize the risk of infusion-related reactions, such as flushing of the upper body, urticaria, pruritus or rash. As with most antimicrobials, the development of *Clostridium difficile*-associated diarrhea remains a growing concern [11,102]. Foamy urine is thought to be due to the excretion of cyclodextrin, a solubilizing agent incorporated into the intravenous formulation of telavancin.





Nephrotoxicity has been noted with telavancin, with increased serum creatinine levels of up to 1.5-times baseline values reported in 16% of patients in the Phase III NP studies compared with approximately 10% of vancomycin-treated patients [41]. Patients with severe renal dysfunction (CrCl <30 ml/min) have a two- to three-fold increase in telavancin exposure. The product information indicates that the telavancin administration interval should be extended to every 48 h in patients with CrCl between 10 and <30 ml/min [27,102]. Nephrotoxicity was most likely to occur in patients with baseline comorbidities that predisposed them to kidney dysfunction (e.g., pre-existing renal disease, diabetes mellitus, congestive heart failure, or hypertension). Other laboratory abnormalities reported in telavancin clinical trials have been reversible upon discontinuation of the drug and include increased transaminases (10–16%), hypokalemia (5–7%) and decreased platelet count without bleeding (0–7%; Table 3) [11,13,54,55,102].

On the assessment summary report of the European Medicines Agency outlining some of the most pertinent observations with regard to the safety of the drug [104]:

- Those entering the studies with pre-existing renal impairment and especially those already in acute renal failure were at particular risk of AEs and poor outcomes if assigned to telavancin;
- The nephrotoxic effect of telavancin is greater than that associated with vancomycin. Renal AEs occurred in telavancin-treated subjects with or without prior renal insufficiency or risk factors for developing renal injury. The risk seems to be greater in those with some predisposing factors including concomitant use of other nephrotoxic medications.

And the report of European Medicines Agency concluded that the data indicate that telavancin should not be used in those who have acute renal failure. The additional post-marketing safety experience indicated that there had been a preponderance of reports of acute renal injury despite the careful advice provided in the US labeling.

**Table 3. Safety parameters for the pooled studies safety population.**

| Safety parameter | Telavancin group (n [%]; total n = 751) | Vancomycin group (n [%]; total n = 752) |
|---|---|---|
| Death | 150 (20) | 140 (19) |
| Any TEAE | 616 (82) | 613 (82) |
| Any serious AE | 234 (31) | 197 (26) |
| Discontinued medication due to TEAE | 60 (8) | 40 (5) |
| Diarrhea | 85 (11) | 92 (12) |
| Renal impairment | 74 (10) | 57 (8) |
| Anemia | 64 (9) | 85 (11) |
| Constipation | 70 (9) | 71 (9) |
| Hypokalemia | 61 (8) | 80 (11) |
| Hypotension | 48 (6) | 52 (7) |
| Nausea | 40 (5) | 31 (4) |
| Decubitus ulcer | 39 (5) | 44 (6) |
| Insomnia | 34 (5) | 47 (6) |
| Peripheral edema | 34 (5) | 38 (5) |

AE: Adverse event; TEAE: Treatment-emergent adverse event.
Data taken from [42].

### Regulatory affairs

In June 2011, Astellas gained approval from the European Medicines Agency's Committee for Medicinal Products for Human Use for the granting of marketing authorization for VIBAT™ iv. in the treatment of NP. Subsequently, on 2 September of the same year, VIBAT iv. was granted marketing authorization for the treatment of hospital-acquired NP in adults, including VAP, known or suspected to be caused by MRSA. VIBAT iv. should be used only in situations where it is known or suspected that other alternatives are not suitable [103,104].

## Conclusion & future perspective

The development and introduction of new antibiotics has, unfortunately not kept pace with the development of bacterial resistance and the need for new agents is becoming acute. Telavancin has the potential to become a useful tool in the treatment of Gram-positive pulmonary infections, including drug-resistant organisms, particularly MRSA and it has the advantage of once daily administration. Additionally, unlike other new antibiotics against Gram-positive pathogens, telavancin is bactericidal and is not inactivated by pulmonary surfactant. The drug is generally well tolerated, with the most common adverse effects being taste disturbance and nausea. The low rate of bacterial resistance to telavancin can be related to its multiple mechanisms of action.

As data from ATTAIN clinical trials accumulates, telavancin has theoretical advantages over several antimicrobials approved to treat MRSA and VRE infections. Overall, telavancin may benefit critically ill patients with MRSA pneumonia who need a rapidly bacteriocidal agent, with better penetration into the lungs, because linezolid and tigecycline are bacteriostatic and daptomycin cannot be used for pneumonia. Based on limited data from subgroup analyses, telavancin may also be a treatment option in patients with pneumonia due to *S. aureus* with vancomycin MICs ≥1 µg/ml. More data are need to visualize the drugs

## Executive summary

- Nosocomial pneumonia is a common and fatal infection, with mortality reaching 60% in ventilator-associated pneumonia cases.
- Telavancin is a rapidly bactericidal drug with dual mechanism of action against Gram-positive cocci, including organisms with reduced susceptibility to vancomycin (e.g., vancomycin intermediate *Staphylococcus aureus* and *S. aureus* fully resistant to vancomycin). The low rate of bacterial resistance to telavancin can be related to its mechanisms of action.
- The safety profile of telavancin appears acceptable for the treatment of patients with severe infections, especially from methicillin-resistant *S. aureus*, with the most common adverse effects being taste disturbance, nausea and foamy urine. Due to the nethrotoxicity of telavancin ,the use in patients with acute renal failure or creatinine clearance <30 ml/min including patients undergoing hemodialysis is contraindicated.
- Astellas Pharma received approval from the EC in Europe (September 2011) for the treatment of adults with hospital-acquired pneumonia, including ventilator-associated pneumonia, especially those caused by methicillin-resistant *S. aureus*.
- Further studies are needed to evaluate the influence of telavancin on mortality of patients with nosocomial pneumonia and especially those with severe renal impairment.


safety profile and especially its administration in patients with severe renal impairment and critically ill patients with comorbidities, and its activity in patients with healthcare associated pneumonia.


## Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.*


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