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"Pharmacokinetic drug evaluation of tedizolid for the treatment of skin infections."

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Abstract

Introduction: Tedizolid is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Although tedizolid shares many similar properties with linezolid, another oxazolidinone used to treat ABSSSI, the two antibiotics have several key differences.

Areas covered: This review provides a detailed summary of the overall pharmacodynamics, pharmacokinetics, clinical efficacy, and safety of tedizolid for the treatment of ABSSSI.

Expert opinion: Compared to other antibiotics used for ABSSSI, tedizolid has several advantages. Tedizolid has a long half-life, allowing for once daily dosing. Tedizolid also has broad spectrum of activity against Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus*, Coagulase-negative Staphylococci, and Enterococci – including isolates demonstrating resistance to linezolid. It is available in both oral and intravenous formulations, and, has outstanding oral bioavailability, allowing for oral-step down therapy. There is also some evidence that, tedizolid has fewer significant interactions with serotonin reuptake inhibitors or monoamine oxidase inhibitors than linezolid. Finally, thrombocytopenia may occur less often with tedizolid than linezolid. However, these benefits must be weighed against the financial cost of tedizolid and the availability of alternative antibiotic choices.

Keywords

Tedizolid; new antibiotics; linezolid; oxazolidinones; Gram-positive infections; pharmacokinetics; skin and soft tissue infections; acute bacterial skin and skin structure infections

2.5 Introduction:

Skin and soft tissue infections (SSTI) are among the most common reasons to seek medical care the United States. These infections account for approximately 6.3 million outpatient visits annually in the United States [1]. Unfortunately, the incidence of these infections is rising. The number of hospital admissions for SSTI increased by 30% between 2000 and 2004, while admissions for pneumonia remained unchanged, which, may be related to the rise in community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections [2]. The continued increase in incidence of multidrug resistant organisms (MDRO), such as MRSA, is considered a significant health threat by the Centers for Disease Control and Prevention (CDC), and contributes to 2 million infections, 23,000 deaths, and up to $20

billion dollars in excess healthcare costs annually in the United States [3]. SSTIs are predominately caused by Gram-positive pathogens, including MRSA. In fact, the Infectious Diseases Society of America (IDSA) guidelines strongly endorse empiric MRSA coverage for patients with severe and/or purulent SSTI [4]. In the medical profession, SSTIs are used as a clinical practice designation unlike the term acute bacterial skin and skin structure infections (ABSSSI) which is a U.S. Food and Drug Administration designation used for clinical trials.

2.6 Body of Review

2.6.1 Overview of the Market:

Many drugs are currently available to treat SSTIs. Drugs with activity against MRSA that are used in the treatment of SSTIs include ceftaroline, clindamycin, dalbavancin, daptomycin, doxycycline, linezolid, oritavancin, tedizolid, telavancin, trimethoprim-sulfamethoxazole, and vancomycin [4–11].

Older drugs used to treat known or suspected MRSA SSTIs, such as vancomycin, daptomycin, trimethoprim-sulfamethoxazole, doxycycline, and clindamycin, have various drawbacks. Vancomycin, generally considered the first-line agent for hospitalized patients with severe SSTI, requires frequent blood draws to monitor for toxicity and therapeutic levels, is associated with a significant number of side effects, generally requires twice daily dosing for patients, and is limited to IV administration for systemic infections. Daptomycin, a cyclic lipopeptide, can be utilized as an alternative agent to vancomycin for hospitalized patients with severe SSTI; however, is only available in an IV formulation, has been associated with myopathy and rhabdomyolysis, and requires at least weekly monitoring of blood creatinine phosphokinase levels. Older highly bioavailable oral drugs, such as trimethoprim-sulfamethoxazole, doxycycline, and clindamycin may not be adequate therapy to initially treat more severe infections. [4]. Furthermore, trimethoprim-sulfamethoxazole and doxycycline have questionable activity against *Streptococcus pyogenes*, another common cause of SSTIs [12,13]. There is also increasing evidence of resistance to some of these agents, for example, epidemiologic studies suggest that MRSA isolates are exhibiting increasing resistance to clindamycin [14,15]. A number of new antibiotics have been recently approved by the FDA that address some of the limitations of vancomycin, daptomycin, trimethoprim-sulfamethoxazole, clindamycin, and doxycycline.

The two newest classes of antibiotics used to treat SSTIs are lipoglycopeptides (telavancin, oritavancin, and dalbavancin) and oxazolidinones (linezolid and tedizolid). The newest generation of lipoglycopeptides, which includes oritavancin and dalbavancin, possess several advantages compared to the historical drugs mentioned above. First, lipoglycopeptides have activity against both MRSA and other common Gram-positive pathogens which cause SSTIs, including *Streptococcus pyogenes* [6, 8]. Second, both drugs can be dosed as a single infusion [8, 16]. Additionally, a randomized controlled trial has suggested that dalbavancin has fewer side effects when compared to a regimen of vancomycin followed by linezolid step-down therapy [6].

However, there are several significant drawbacks to lipoglycopeptides. First, lipoglycopeptides currently only exist as IV formulations. Second, both drugs have an incredibly long half-life and cannot be removed through dialysis [17, 18], making management of an acute allergic reaction very limited. Lastly, cross-reactivity rates between vancomycin and lipoglycopeptides are unknown; due to the possibility of cross-reactivity, lipoglycopeptides should be used with caution in patients with a history of glycopeptide allergy and should be avoided in those with documented severe reactions [19].

2.6.2 Introduction to the Compound:

Tedizolid, a novel oxazolidinone, was initially synthesized at Dong-A Pharmaceuticals Co. in Seoul, South Korea [20]. However since then, it has been developed, studied, and marketed by a number of pharmaceutical companies including Trius Therapeutics, Cubist, and most recently Merck [21]. Tedizolid is currently approved by the FDA for the treatment of ABSSSIs at a dose of 200 mg orally or intravenously once daily for a total of 6 days [21]. Alternative names for tedizolid include tedizolid phosphate (prodrug) and Sivextro [21].

2.6.3 Chemistry:

The chemical name of tedizolid phosphate, the prodrug for tedizolid, is [(5R)-(3-(3-fluoro-4-[6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl]phenyl)-2-oxooxazolidin-5-yl]methyl dihydrogen phosphate [21]. The molecular formula for tedizolid phosphate is $C_{17}H_{16}FN_6O_6P$, and the molecular weight is 450.317705 g/mol. Tedizolid phosphate is converted to tedizolid through plasma phosphatases [21].

The structure of tedizolid is very similar to linezolid. Both drugs share identical A-rings, B-rings, and similar C-rings. However, two important differences should be noted. First, tedizolid phosphate has a hydroxymethyl C-5 sidechain that improves water solubility and oral bioavailability while reducing interactions with monoamine oxidase (MAO) [22, 23]. Second, tedizolid, possesses a 4^{th} para-oriented ring structure (D-ring) which increases the number of hydrogen binding sites and enhances ribosomal binding compared to linezolid [23, 24]. These small differences in chemical structure, however, provide tedizolid with several *in vitro* advantages compared to linezolid in terms of therapeutic target, pharmacodynamics, and pharmacokinetics.

2.6.4 Therapeutic Target and Mechanism of Action

As oxazolidinones, both tedizolid and linezolid have similar therapeutic targets and mechanisms of action. Specifically, both antibiotics inhibit protein synthesis by binding to the bacterial 23S ribosomal RNA of the 50S ribosomal subunit [25, 26]. This inhibition prevents the 70S ribosomal initiation complex from forming [27–29]. However, the D-ring mentioned above, provides significantly stronger ribosomal binding affinity as compared to linezolid [29, 30].

2.6.5 Pharmacodynamics and Microbiology

Tedizolid, like linezolid, has potent activity against a variety of Gram-positive organisms, including MRSA, methicillin-susceptible *S. aureus* (MSSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Enterococcus species*, and Coagulase-

negative Staphylococci [31–33]. Tedizolid and linezolid also retain activity against both vancomycin intermediate and resistant Staphylococci and Enterococci [31–33]. Off-label uses of linezolid primarily include disease processes that have a propensity of being caused by resistant Gram-positive organisms, including endocarditis, peritonitis, and infections of foreign objects such as left ventricular assist devises and prosthetic joints [34]. Linezolid has also been utilized in treating atypical Gram-positive bacterial infections and some Mycobacterial infections. Knowledge surrounding the use of tedizolid outside of its FDA indication is sparse; however it can likely be used in a similar manner as linezolid. For example, a recent case study which showed successful treatment of a prosthetic joint infection using tedizolid [35].

Tedizolid appears to have several pharmacodynamic advantages compared to linezolid. Due to its higher ribosomal binding affinity, tedizolid has 4-8 fold lower minimum inhibitory concentrations (MICs) against most pathogens compared to linezolid [31–32]. Tedizolid also appears to retain activity against plasmid-mediated linezolid resistance through the chloramphenicol resistance gene, *cfr* [35–36]. However, if organisms have both plasmid- and chromosomal mediated linezolid resistance, the organism has a high likelihood of also being resistant to tedizolid [37].

Tedizolid also appears to retain excellent activity against other multidrug resistant Gram-positive bacteria. For example, tedizolid retains activity against both vancomycin intermediate and resistant Staphylococci and Enterococci [31–34]. There are two proposed mechanisms for tedizolid's superior activity. First, due to its stronger ribosomal binding affinity, tedizolid binds to both the same ribosomal sites as linezolid and additional sites on the 23 rRNA, thus retaining activity against linezolid-resistant isolates [35]. Second, tedizolid accumulates in phagocytic cells, which may aid in clearing infection [38]. Such benefits may explain why tedizolid was identified as bactericidal, in an *in vivo* murine thigh infection model, unlike linezolid, which was identified as bacteriostatic [38].

Antibiotic Susceptibility—The *in vitro* MIC values of tedizolid have shown to have a 2 to 8 fold greater potency than linezolid in Gram-positive isolates [39]. This is seen regardless of whether the condition is a skin infection or a pneumonic process. Specifically, the MIC90 of tedizolid has been shown to be lower than that of linezolid (0.5 mcg/mL vs. 2 mcg/mL) for MSSA, MRSA, *Streptococcus* species, *Enterococcus faecalis,* and vancomycin resistant Enterococcus (VRE) [39–41]. The MIC90 of tedizolid and linezolid against linezolid-resistant VRE is 1 mcg/mL and 4 mcg/mL, respectively [40–41,43]. Looking at linezolid-susceptible CoNS and linezolid-resistant CoNS, MIC90 values for tedizolid and linezolid are 0.25 mcg/mL vs. 2 mcg/mL and 2 mcg/mL vs 16 mcg/mL, respectively [40–43]. When compared to vancomycin and daptomycin, tedizolid has shown either improved or equivalent potency [41].

2.6.6 Pharmacokinetics and Metabolism

Tedizolid has an oral bioavailability of over 90%, a half-life of approximately 12 hours, a volume of distribution of 67–80 L, and achieves steady state concentrations in three days [39, 41, 45–47]. It does not require any dose adjustment when transitioning between IV and

oral formulations, nor does it require dose adjustment based on renal or hepatic impairment. The drug can be taken with food or on an empty stomach [47]. Tedizolid is 70 to 90% protein bound and is metabolized into an inactive sulfate metabolite in the liver, with 82% eliminated in the feces and 18% in the urine [47–49].

Some pharmacokinetic comparisons between tedizolid and linezolid are described below. After standard dosing, tedizolid's maximum drug concentration is 2.2 mg/L (+/− 0.6) compared to 21.2 mg/L (+/− 5.78) for linezolid [50–52]. Time to maximum drug concentration is 3.5 (1.0 to 6.0) hours to tedizolid compared to 1.03 (+/− 0.64) hours for linezolid. Additional pharmacokinetic parameters comparing tedizolid and linezolid are described in further detail in Table 1. Important clinical implications, such as CYP450 interactions, drug-drug interactions, and important side effects are discussed in detail in the safety, tolerability, and toxicity section.

2.6.7 Pharmacogenetics

There have been a few studies that focused on effects of tedizolid in patients of different genders, ethnicities, and cultural backgrounds. Alejandro and colleagues compared the ESTABLISH-1 and ESTABLISH-2 trial dataset vs patients of Latino origin enrolled in those trials [54]. Groups were broken down into Latino vs non-Latino and further divided into linezolid vs tedizolid, as in the ESTABLISH model. The baseline demographics of these groups were the same [54]. Tedizolid demonstrated comparable efficacy to linezolid at 48-72 hours in the intention-to-treat population. Tedizolid and linezolid treated Latino patients sustained analogous clinical success rates at the end of therapy, 86.8% for tedizolid and 88.9% for linezolid [54]. Tedizolid was well tolerated with lower rates of abnormal platelets and gastrointestinal side-effects. Overall, there were no major differences between groups (Latino vs non-Latino) regarding the tolerability and efficacy of tedizolid [54]. A few studies, including the ESTABLISH-1 and ESTABLISH-2 trials, have found no statistically significant differences between male and female subjects [41, 54–57].

2.6.8 Clinical Efficacy

Clinical efficacy for tedizolid was primarily tested via the ESTABLISH-1 and ESTABLISH-2 trials [11, 56]. Both were phase 3 multicenter randomized double-blind non-inferiority trials comparing the efficacy of tedizolid against that of linezolid in the treatment of ABSSSI suspected of being caused by Gram-positive bacteria. This class of infection includes such diagnoses as cellulitis, erysipelas, skin abscesses, and wound infections.

The ESTABLISH-1 trial randomized 667 patients diagnosed with ABSSSI to treatment with oral tedizolid at 200mg once daily for 6 days, against treatment with oral linezolid 600mg every 12 hours for 10 days [56]. The primary study endpoint was considered to be clinical response to therapy at 48-72 hours after start of therapy, however the investigators also evaluated patients at the end of therapy as well as 1-2 weeks after therapy. Clinical response was considered to be lack of fever, with no growth of the lesion size and no death or use of other antibiotics. Ultimately 332 patients ended up in the tedizolid group, compared to 335 in the linezolid group, sufficiently powered to detect a 10% non-inferiority margin of efficacy. Intention-to-treat analysis showed no statistically significant difference between the

two arms of the trial at the primary outcome, end-of-therapy, or 1-2 week follow-up time points. At 48 hours approximately 80% of patients had responded to either drug, dropping to around 70% at the end of therapy.

The ESTABLISH-2 trial was very similar to ESTABLISH-1, however in place of only comparing oral formulations of tedizolid and linezolid, this study evaluated IV therapy with optional oral step down after 2 doses of IV medication [11]. They also used a modified criterion for clinical response in that patients needed to have a ≥20% decrease in lesion size instead of just lesion stabilization, and fever was no longer part of the criterion. In this study, 666 patients were randomized to a regimen of either tedizolid 200mg IV daily for 6 days, or linezolid 600mg IV every 12 hours for 10 days [11]. As in ESTABLISH-1, no statistically significant difference in clinical response were seen between the two arms at any of the assessment points after treatment, with high degrees (>80%) of clinical success in both treatment arms.

2.6.9 Safety, Tolerability, Toxicity, and potential off-target effects related to safety liabilities

Tedizolid has been well tolerated with the most common adverse-effects being mild bradycardia, headache, and nausea (Table 2) [46, 56, 58]. In the ESTABLISH trials the most common adverse-effects were gastrointestinal dysfunction (nausea, vomiting, and diarrhea), and these were less common in tedizolid than in linezolid in a subsequent pooled analysis (tedizolid, 8.2% vs. linezolid, 12.2%; P=0.02) [46, 52, 55, 56]. Elevated liver enzymes have been seen with both tedizolid and linezolid, however patients who were continued on either medication had no sign of liver dysfunction.

Serotonin syndrome is a well-established adverse effect of linezolid's interaction with serotonergic agents including (MAO) inhibitors, serotonin reuptake inhibitors, serotonin noradrenalin reuptake inhibitors, tricyclic antidepressants, opioids, amphetamines, cocaine, and St. John's Wort [59]. It is defined as a central nervous system disease with clinical manifestations that include altered mental status, ataxia, restlessness, lower extremity hyper-reflexia and diaphoresis which can progress to severe symptoms such as delirium, seizure, shock, coma, and death. Linezolid and tedizolid exhibit non-selective inhibitory action against MAO. While linezolid has shown clinical association with serotonin syndrome, tedizolid has failed to reveal significant serotonergic symptoms in mouse models [22].

Myelosuppression has been another major adverse-effect surrounding oxazolidinones as a class. Under therapeutic conditions, linezolid-associated hematological toxicity is typically mild, reversible, and duration dependent (greater than 14 days) [59]. Individually, no significant differences in leukopenia or thrombocytopenia were seen between tedizolid and linezolid in either of the ESTABLISH trials. However, thrombocytopenia was significantly lower for tedizolid than linezolid in two pooled analyses (4.9% compared to 10.5% respectively) [52, 61]. More studies need to be completed to fully understand the implications of tedizolid on myelosuppression as the literature surrounding it being used for more than 6 days is limited.

The ESTABLISH trials also noted a lower association of neurotoxicity, both peripheral and optic neuropathy, with the use of tedizolid compared to linezolid [62]. Regarding peripheral neuropathy, incidence in the linezolid arm was 1.2% vs 0.6% for the tedizolid arm. The incidence of optic neuropathy for linezolid was 0.3% vs 0.2% for tedizolid, although these complications are very rare [63].

Tedizolid has very little association with hepatic CYP enzymes and thus a majority of pharmacokinetic drug-drug interactions are considered unlikely. However, there have been reported cases of interactions between linezolid and rifampin, clarithromycin, levothyroxine, and warfarin [64]. It is postulated that powerful inducers with high increase in CYP3A expression levels can result in a small increase in linezolid and probably tedizolid metabolism [64, 65].

Tedizolid has one very important safety liability. As the drug concentrates in granulocytes, the antibacterial activity of tedizolid was reduced in a neutropenic animal model [38]. Thus, tedizolid should be avoided in patients who have an absolute neutrophil count of less than 1000 cells per microliter.

2.6.11 Dosing Routes

Tedizolid is available in both IV and oral formulations. Due to its excellent bioavailability, tedizolid is considered an excellent choice for clinician or pharmacy directed IV to oral step-down therapy [66]. Such antimicrobial stewardship interventions may be associated with a cost savings and decreased length of stay.

2.6.12 Regulatory Affairs

Tedizolid has been well received by the global market. Tedizolid has been approved for the treatment of ABSSSI by the FDA since 2014 and by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) since 2015. There are a number of planned and ongoing clinical trials investigating tedizolid. Tedizolid is currently being studied for the treatment of nosocomial pneumonia (NCT02019420) and bone and joint infections (NCT03009045) [67]. Pediatric (NCT02750761) and adolescent (NCT02276482) trials are also currently ongoing. [67]

2.7 Conclusion

SSTIs are common and frequently involve MRSA. Although there are many drugs available to treat ABSSSI that are suspected to be caused by MRSA, oxazolidinones such as linezolid and tedizolid, offer many advantage compared to competitor compounds.

In 2 phase 3 clinical trials, tedizolid has been shown to be non-inferior to linezolid in the treatment of ABSSSI. Tedizolid appears to offer several advantages compared to linezolid in terms of tolerability, safety, dosing frequency, and treatment duration. Furthermore, tedizolid appears to have both lower MICs against common Gram-positive pathogens and retained activity against vancomycin and linezolid resistant organisms. However, these benefits must be weighed against the financial cost of tedizolid and the availability of alternative choices.

2.8 Expert Opinion

What, if any, improvement does the drug hold over other therapies?

Tedizolid and linezolid are the only two antibiotics that have oral formulations for the treatment of SSTIs and ABSSSIs, thus both drugs are well positioned as potential IV to oral step down agents to improve hospital length of stay. These properties give both medications an advantage over vancomycin, daptomycin, and the long acting lipoglycopeptides. Compared to linezolid, tedizolid has a more favorable dosing frequency, improved tolerability, broader activity against MDROs, and fewer drug interactions with serotonergic agents.

What, if any, impact is this drug likely to have on current treatment strategies?

It is difficult to know. Tedizolid has entered the ABSSSI market during a tumultuous time. Linezolid, a competitor drug is in the process of coming off patent – dramatically decreasing prices. Furthermore, oritavancin and dalbavancin, long acting lipoglycopeptides, are being marketed to emergency departments to bypass hospital admissions altogether. If these drugs are successful at reducing hospital admissions for ABSSSI, and clinicians choose to utilize linezolid due to more favorable pricing, then tedizolid will be used infrequently.

How likely are physicians to prescribe the drug?

At this point in time, we believe that physicians are unlikely to prescribe tedizolid for ABSSSI. The market is currently crowded with alternative agents, and linezolid, its closest competitor and a non-inferior antibiotic to treat ABSSSIs based on phase 3 studies, is likely to be significantly less expensive than tedizolid for the foreseeable future. Furthermore, many clinicians are likely waiting to see if the *in vitro* and early *in vivo* advantages of tedizolid over linezolid translate to improved patient outcomes or better tolerability.

What data is still needed?

Larger studies analyzing the safety profile of tedizolid would be helpful. Clinicians are still wary about using tedizolid in the setting of concomitant serotonergic agents or for longer durations (when used in an off-label setting). Better characterizations of peripheral neuropathy, optic neuropathy, and thrombocytopenia from larger cohorts would be helpful in allaying clinician’s fears and obtaining a competitive edge compared to linezolid.

Where is drug likely to be in 5 years’ time?

The highest utilization of tedizolid likely lies outside of ABSSSI. As additional studies are performed and the safety profile is better established, we see tedizolid as a promising antibiotic for conditions like ventilator-associated bacterial pneumonia. As a bactericidal agent, tedizolid may have more favorable outcomes than linezolid for the treatment of catheter-related bloodstream infections (linezolid was inferior to vancomycin in a phase 3 study) or to provide superior toxin inhibition than linezolid or clindamycin for life threatening conditions such as necrotizing fasciitis. We also see promise for off-label use of tedizolid in situations where long-term use of linezolid would be otherwise untenable due to

side effects. These conditions may include endocarditis, bone and joint infections, and MDR mycobacteria, such as *M. chelonae*, *M. abscessus*, and *M. tuberculosis*.

Abbreviations and units

3.3

SSTI	skin and soft tissue infections
ABSSSI	acute bacterial skin and skin structure infections
MRSA	methicillin-resistant *Staphylococcus aureus*
MDRO	multidrug resistant organisms
CDC	Centers for Disease Control and Prevention
IDSA	Infectious Diseases Society of America
FDA	U.S. Food and Drug Administration
MAO	monoamine oxidase
MSSA	methicillin-susceptible *S. aureus*
MICs	minimum inhibitory concentrations
MDR	multidrug resistant
CHMP	the Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
C_{max} (mg/L)	Peak serum concentration in milligrams per liter
T_{max} (hours)	Time in hours at which Cmax is observed
$T_{½}$ (hours)	Half-life in hours
Clearance (L/hr)	measurement of the voume of plasma from which as substrate is completely removed in liters per hour
AUC (mcg*hr/mL)	Area under the curve in microgram hours per milliliter

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Box 1. Tedizolid summary

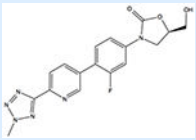
Drug name (generic)	Prodrug: tedizolid phosphate Active moiety: tedizolid
Phase	IV
Indication	Acute bacterial skin and skin structure infections (ABSSSI)
Pharmacology description/ mechanism of action	Inhibition of protein synthesis through binding to bacterial 23S ribosomal RNA of the 50S ribosomal subunit, preventing formation of a functional 70S ribosomal initiation complex
Route of administration	Oral and intravenous
Chemical structure	
Pivotal trials	ESTABLISH-1 [45] and ESTABLISH-2 [11]

Table 1.

Pharmacokinetic parameters of linezolid and tedizolid [43–46].

Side-effect Reported	**Percent of pts with adverse-effects (%)**	
	Tedizolid Group	**Linezolid Group**
	Tedizolid Phosphate (200 mg PO once daily)	**Linezolid (600 mg PO twice daily)**
C_{max} (mg/L)	2.2 ± 0.6	21.2 ± 5.78
T_{max} (hours)	3.5 (1.0 to 6.0 – median range)	1.03 ± 0.62
$T_{½}$ (hours)	12	5.4 ± 2.06
Clearance (L/hr)	8.4 ± 2.1	4.8 ± 1.74
AUC (mcg*hr/mL)	25.6 ± 8.4	138 ± 42.1

Table 2.

Common side effects of tedizolid and linezolid based on phase 3 clinical trials [11, 49].

Headache	6.2%	5.9%
Nausea	8.2%	12.2%
Vomiting	2.9%	5.6%
Dyspepsia	0.6%	1.2%
Constipation	1.4%	0.9%
Diarrhea	3.9%	5.3%
Dizziness	1.8%	2.1%
Pruritus	0.5%	1.4%
Fatigue	1.4%	1.8%
Insomnia	1.5%	0.8%