Formulary Drug Reviews

Tedizolid Phosphate

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Generic Name:	Tedizolid phosphate
Proprietary Name:	Sivextro (Trius Therapeutics)
Approval Rating:	1P
Therapeutic Class:	Oxazolidinones
Similar Drugs:	Linezolid
Sound- or Look-Alike Names:	Linezolid

INDICATIONS

Tedizolid phosphate is indicated for the treatment of acute bacterial skin and skin structure infections (SSSIs) caused by susceptible isolates of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible [MSSA] and methicillin-resistant [MRSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* (including *Streptococcus intermedius* and *Streptococcus constellatus*), and *Enterococcus faecalis*.¹

To reduce the development of drug-resistant bacteria, tedizolid should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.¹

CLINICAL PHARMACOLOGY

Tedizolid phosphate is a novel, next-generation oxazolidinone prodrug. Tedizolid phosphate is rapidly converted in vivo to tedizolid (previously referred to as torezolid).^{1,4} Tedizolid inhibits the synthesis of bacterial proteins by interacting with the 50S subunit of bacterial ribosome, resulting in inhibition of protein synthesis.¹ Tedizolid has been shown to have activity against clinically relevant gram-positive aerobic and anaerobic bacteria, such as *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, and *Haemophilus influenzae*; it has also shown activity against isolates resistant to vancomycin, daptomycin, and linezolid.^{1,2,4-12} Cross-resistance is unlikely, because tedizolid inhibits bacterial protein synthesis by a different mechanism of action from other non-oxazolidinone antibacterial drugs.¹ Additionally, tedizolid was

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shown to have activity against linezolid-resistant *S. aureus* with the chloramphenicol-florfenicol resistance (cfr) gene.^{1,3,8,9,11,13} Organisms resistant to oxazolidinones via mutations in genes encoding 23S ribosomal RNA or ribosomal proteins (L3 and L4) are generally cross-resistant to tedizolid.¹ In comparison with linezolid, tedizolid has been shown to have 4- to 16-fold greater in vitro activity against methicillin-sensitive *S. aureus*, MRSA, *streptococci*, and *enterococci*.^{6,7,14,15} Tedizolid also has activity against some gram-negative pathogens.^{7,9} Tedizolid has nearly equivalent oral and intravenous (IV) bioavailability; therefore, it is being developed for oral and IV administration.^{16,17}

PHARMACOKINETICS

Tedizolid phosphate is a prodrug that is rapidly converted to tedizolid by hydrolysis of the phosphate group via nonspecific phosphatases.^{1,2,18} Tedizolid phosphate is best described by a 2-compartment model with zero-order dose delivery to the depot compartment and subsequent first-order absorption.^{19,20}

The peak plasma concentrations (C_{max}) of tedizolid under fasting conditions are achieved within about 3 hours of oral dosing of tedizolid phosphate. If tedizolid is given IV, they occur at the end of the 1-hour infusion.¹ Oral administration during fasted and fed (high-fat, high-calorie) conditions results in a similar total systemic exposure; therefore, it may be given with or without food.¹ Following multiple once-daily oral or IV doses of tedizolid phosphate, steady-state concentration is achieved within approximately 3 days, with an accumulation of approximately 30%.¹ In mice and humans, the area under the curve (AUC) for tedizolid in the blood is similar following IV and oral administration.^{1,2,16,21} Renal or hepatic impairment does not change the pharmacokinetics of tedizolid; therefore, it is not necessary to adjust the dose in patients with reduced renal or hepatic function.^{1,22} Fecal excretion is the predominate route of elimination, primarily as the microbiologically inactive metabolite tedizolid sulfate accompanied by the minor metabolites tedizolid and carboxy tedizolid. In the urine, the major metabolite is tedizolid sulfate accompanied by 3 minor metabolites, carboxy tedizolid, tedizolid, and desmethyl tedizolid.^{1,18}

Table 1. Comparison of pharmacokinetic parameters of tedizolid phosphate and linezolid after a single dose in adult humans^{a,1,23}

	Tedizolid phosphate 200 mg ^b		Linezolid 600 mg	
	Tablet	IV	Tablet	IV
Prodrug	Yes		No	
C_{max}	2 mcg/mL	2.3 mcg/mL	12.7 mcg/mL	12.9 mcg/mL
T_{max}	2.5 hours	1.1 hours	1.28 hours	0.5 hour
Half-life	12 hours		4.26 hours	4.4 hours
AUC	23.8 mcg•h/mL	26.6 mcg•h/mL	91.4 mcg•h/mL	80.2 mcg•h/mL
Volume of distribution	–	67 to 80 L ^c	–	40 to 50 L ^c
Absolute bioavailability	91%		100%	
Protein binding	70% to 90%		31%	
Clearance	115 mL/min	107 mL/min	127 mL/min	138 mL/min
Metabolism	N-demethylation and oxidation		Oxidation	
Elimination	Feces: 82%; primarily as sulfate conjugate Urine: 18% primarily as sulfate conjugate Less than 3% in the feces and urine as unchanged tedizolid		Feces: 6% hydroxyethyl glycine metabolite; 3% aminoethoxyacetic acid metabolite Urine: 30% unchanged linezolid; 40% hydroxyethyl glycine metabolite; 10% aminoethoxyacetic acid metabolite	

^a T_{max} = time to maximum concentration.

^bPharmacokinetic parameters are of tedizolid due to negligible systemic exposure of tedizolid phosphate following oral and intravenous (IV) administration.

^cSteady state.

Pharmacokinetics for tedizolid phosphate and linezolid when administered orally and IV are summarized in Table 1.

COMPARATIVE EFFICACY

Indication: Acute Bacterial Skin and Skin Structure Infections

Guidelines

Guideline: Infectious Disease Society of America practice guidelines for the diagnosis and management of skin and soft-tissue infections

Reference: Stevens DL, et al, 2005²⁴

Comments: Guideline recommends empiric treatment of minor skin and soft-tissue infections with semi-synthetic penicillin, first- or second-generation oral cephalosporins, macrolides, or clindamycin. For the outpatient treatment of community-acquired MRSA, trimethoprim-sulfamethoxazole, tetracycline, doxycycline, or minocycline are recommended, with an evaluation 48 to 72 hours after initial dose to verify a clinical response. For patients with an infection severe enough to require hospitalization or with an infection that is progressing despite empirical antibiotic therapy, treatment strategy should be based upon results of appropriate gram stain, culture, and drug susceptibility analysis. When treating *S. aureus*, it is appropriate to assume that the organism is methicillin-resistant because of the high prevalence of community-associated MRSA strains; the guideline recommends treatment with agents effective against MRSA, such as vancomycin, linezolid, or daptomycin. The role of tedizolid in the treatment of these types of infections is not addressed in this document.

Studies

Drug: Tedizolid Phosphate vs Linezolid

Reference: Moran GJ, et al, 2013 (ESTABLISH-2)^{1,25,26}

Study Design: Phase 3, randomized, double-blind, double-dummy, parallel-group, multicenter, international, noninferiority study

Study Funding: Cubist Pharmaceuticals

Patients: 666 patients with acute bacterial SSSI caused by a documented or suspected gram-positive pathogen. Median age was 46 years and 66% were male; 47% of patients were in North America, 33% were in Europe, and 14% were in South Africa. Patients were required to have a lesion surface

area of at least 75 cm² and at least 1 systemic or regional sign of infection (eg, lymphadenopathy, raised body temperature, white blood cell count of at least 10,000/mcL or less than 4,000/mcL, greater than 10% immature neutrophils). Median lesion area was 231.3 cm² in the tedizolid phosphate group and 238.6 cm² in the linezolid group, and median abscess area was 155.1 cm² in the tedizolid phosphate group and 178.8 cm² in the linezolid group. Infection types were similar between the groups, with cellulitis/erysipelas at 50% in each group and major cutaneous abscess at 20% in each group. Infected wounds occurred in 30% and 29% for tedizolid phosphate and linezolid, respectively. At least 1 gram-positive pathogen was isolated in 60% of patients; MSSA was identified in 53% and 55% of these patients and MRSA was identified in 27% and 28% of patients in the tedizolid phosphate and linezolid groups, respectively. At baseline, 42% of patients were already admitted to or already located in the hospital.

Intervention: Patients were randomized 1:1 to receive IV tedizolid phosphate 200 mg (*n* = 332) once daily for 6 days or IV linezolid 600 mg (*n* = 334) twice daily for 10 days with optional oral step-down. All patients were given a respective matching placebo to maintain blinding. Patients were eligible for oral therapy if at least 2 of the following criteria were met: no increase from baseline in primary lesion area, length, or width; temperature of less than 37.7°C; no worsening of local signs and symptoms at the primary infection site; improvement of 1 or more local signs or symptoms since the previous visit. In patients with wound infections, aztreonam, metronidazole, or both could be added for gram-negative or anaerobic coverage, as deemed appropriate by the investigator.

Results:

Primary Endpoint(s):

- Investigator-assessed clinical response (defined as a 20% or greater reduction in area of the primary lesion from baseline, systemic concomitant antibiotics with gram-positive activity were not received, and deaths from any cause did not occur within 72 hours of the first dose) in the intention-to-treat (ITT) population at 48 to 72 hours after the start of treatment was 283 of 332 (85%) in the tedizolid phosphate group and 276 of 334 (83%) in the linezolid group.

- Investigator-assessed clinical success (defined as resolution or near resolution of disease-specific signs and symptoms, absence or near resolution of baseline systemic signs of infection, and no further antibiotic treatment was required for the treatment of the primary acute bacterial SSSI lesion) in the ITT population 48 to 72 hours after the start of treatment was 304 of 332 (92%) in the tedizolid phosphate group and 302 of 334 (90%) in the linezolid group; there was a difference of 1.2% between groups (95% confidence interval [CI], -3.3% to 5.6%).

Secondary Endpoint(s):

- Investigator-assessed clinical response at day 7 after the start of treatment was 93% in the tedizolid phosphate group and 92% in the linezolid group; there was a difference of 0.9% between groups (95% CI, -3.2% to 4.9%).
- Programmatically determined clinical response (defined as decreased lesion area from baseline; absence or near resolution of fever, tenderness, or purulent drainage; no treatment discontinuation due to adverse events; and no major protocol violations) at end of treatment (day 11) in the ITT population was 87% in the tedizolid phosphate group and 88% in the linezolid group.
- Programmatically determined clinical response at end of treatment (day 11) in the clinically evaluable population was 272 of 304 (90%) in the tedizolid phosphate group and 280 of 299 (94%) in the linezolid group; there was a difference of -4.1% between groups (95% CI, -8.8% to 0.3%).
- Investigator-assessed clinical success at end of treatment (day 11) in the clinically evaluable population was 281 of 296 (95%) in the tedizolid phosphate group and 284 of 293 (97%) in the linezolid group; there was a difference of -2% between groups (95% CI, -5.7% to 1.2%).
- Investigator-assessed clinical success 7 to 14 days after the end of treatment in the ITT group was 88% in the tedizolid phosphate group and 88% in the linezolid group; there was a difference of 0.3% between groups (95% CI, -4.8% to 5.3%).
- Changes in patient-reported pain throughout the study, assessed by visual analog scale (0 to 100) and faces rating scale (0 to 10), were similar at baseline (60 and 6, respectively) and days 10 through 13 (10 and 1) for both groups.

Other Endpoint(s)

- Clinical success 18 to 25 days after end of treatment was 98% in the tedizolid phosphate group and 99% in the linezolid group; there was a difference of -1.1% between groups (95% CI, -3.8% to 1.3%).

Comments: IV to oral once-daily tedizolid phosphate 200 mg was noninferior to twice-daily linezolid 600 mg for the treatment of acute bacterial SSSI. The ITT population included all patients randomized to a treatment group. Patients with uncomplicated SSSI, infections associated with prosthetic devices or vascular catheter sites, thrombophlebitis, diabetic foot infections, infected burns, chronic skin ulcers, non-clean surgery, known bacteremia at screening, septic shock or severe sepsis, a history of opportunistic infections, receiving long-term systemic immunosuppressive treatment or antipyretic drugs (other than aspirin 200 mg/day or less), severe renal disease, or severe hepatic disease were excluded.

For the primary endpoint, the noninferiority margin was set at -10% of the lower bound 95% CI for treatment difference between groups. Treatment-emergent adverse events leading to discontinuation of study drug were reported by 1 (less than 1%) patient in the tedizolid group and 4 (1%) patients in the linezolid group. Patients with missing data for any component of the primary endpoint were considered nonresponders; these were 2% of patients for tedizolid phosphate and 4% of patients for linezolid. A tipping point analysis was conducted to assess the influence of missing data on noninferiority findings. The analysis assumed that if all patients with missing data in the linezolid group were considered to be responders and all those in the tedizolid group with missing data were considered nonresponders, noninferiority was preserved (95% CI, -6.9 to 3.7). The mean duration of IV treatment was 1.7 and 1.8 days for tedizolid phosphate and linezolid, respectively. Mean duration of IV treatment for patients in the United States was 2.2 and 2 days for tedizolid phosphate and linezolid, respectively, and for patients outside of the United States, it was 4.6 and 4.7 days, respectively. The most commonly reported adverse events were nausea (8% and 11%), headache (6% and 7%), abscess (4% and 3%), diarrhea (3% and 5%), and vomiting (3% and 5%) for tedizolid phosphate and linezolid, respectively.

Limitations: Enrolled patients had a lower incidence of comorbidities than patients have had historically in clinical practice.

Reference: Prokocimer P, et al, 2013 (ESTABLISH-1)^{1,26,27}

Study Design: Phase 3, randomized, double-blind, multicenter, international, noninferiority study

Study Funding: Trius Therapeutics

Patients: 667 patients with acute bacterial SSSI with a median age of 43 years, approximately 60% were male, and approximately 80% were from North America. Patients were required to have a lesion surface area of at least 75 cm², at least 1 local and 1 regional lymphadenopathy, or 1 systemic sign of infection (oral temperature of at least 38°C, white blood cell count of at least 10,000/mcL or less than 4,000/mcL, or 10% of immature neutrophils). Additionally, a gram-positive pathogen was documented or suspected. The median infection area was 188 cm² and 190 cm² for the tedizolid phosphate and linezolid groups, respectively. Infection types were similar between the groups for cellulitis/erysipelas (40.7% vs 41.5%), major cutaneous abscess (30.1% vs 29.3%), and infected wound (29.2% vs 29.3%) for tedizolid phosphate and linezolid, respectively. MRSA was identified in 42.1% and 43.1% of infections in the tedizolid phosphate and linezolid groups, respectively.

Intervention: Patients were randomized 1:1 to receive tedizolid phosphate 200 mg (*n* = 332) orally once daily for 6 days or linezolid 600 mg (*n* = 335) orally twice daily for 10 days.

Results

Primary Endpoint(s)

- Clinical response (defined as an afebrile temperature of 37.6°C or less and cessation of lesion spread) at the 48- to 72-hour assessment period: 79.5% (95% CI, 74.8% to 83.7%) in the tedizolid phosphate group and 79.4% (95% CI, 74.7% to 83.6%) in the linezolid group. There was a difference of 0.1% between groups (95% CI, -6.1% to +6.2%).

Secondary Endpoint(s)

- Sustained clinical treatment response rates at day 11 were 69.3% and 71.9% in the ITT tedizolid phosphate and linezolid groups, respectively. Response rates in the clinically evaluable end-of-treatment analysis set were 80.2% (*n* = 273) and 81.1% (*n* = 286) for tedizolid phosphate and linezolid, respectively.

- Investigator-assessed posttreatment evaluation (7 to 14 days after the end of treatment) clinical response rates were 85.5% and 86% in the ITT tedizolid phosphate and linezolid groups, respectively. In the clinically evaluable post-treatment evaluation analysis, set response rates were 94.6% and 95.4% for tedizolid phosphate and linezolid, respectively.

Comments: The noninferiority margin was set at -10% of the lower bound 95% CI for between-group treatment differences. Missing temperature data or measurements outside the prespecified time window occurred in 11.1% and 9.6% of patients in the tedizolid phosphate and linezolid groups, respectively. A total of 8.1% and 10.4% of patients in the tedizolid phosphate and linezolid groups, respectively, were true non-responders. Most commonly reported adverse events were nausea (8.5% and 13.4%), headache (6.3% and 5.1%), diarrhea (4.5% and 5.4%), and vomiting (2.7% and 6%) for tedizolid phosphate and linezolid, respectively. In the tedizolid phosphate and linezolid groups, 2.3% and 4.9% of patients, respectively, had substantially abnormal platelet counts of less than 75% the lower limit of normal, but these abnormalities resolved without intervention.

Limitations: Concern that a late posttherapy clinical response could reflect the natural history of the disease rather than the effect of antibacterial treatment. Hepatitis C infection was present in 30.7% of the tedizolid phosphate group and 35.5% of the linezolid group.

Drug: Tedizolid phosphate

Reference: Prokocimer P, et al, 2011²⁸

Study Design: Phase 2, randomized, double-blind, noncontrolled, dose-ranging study

Study Funding: Trius Therapeutics

Patients: 192 patients (mean age was 36.4 years, 64.9% were male, 74.5% were White, and 23.9% were Black). Patients were required to have a complicated SSSI caused by either a suspected or confirmed gram-positive pathogen. Patients were required to have at least 2 signs and symptoms of infection (purulent or seropurulent drainage, erythema, fluctuance, heat or warmth, pain or tenderness, swelling or induration, or requirement for surgical drainage) and at least 1 systemic sign of infection (oral temperature of at least 38°C,

white blood cell count at least 10,000/mcL or less than 4,000/mcL, or 10% of immature neutrophils). Mean lesion size at baseline was 13.8 cm². Of the infections, 76.6% were abscesses and 17.6% were cellulitis. Of the patients with a confirmed pathogen ($n = 154$), *S. aureus* was isolated in 90.3%, and 80.6% of these strains were MRSA.

Intervention: Patients were randomized 1:1:1 to receive 200 mg ($n = 63$), 300 mg ($n = 63$), or 400 mg ($n = 62$) of oral tedizolid phosphate once daily for 5 to 7 days.

Results

Primary Endpoint(s)

- Clinical cure (resolution of the infection or improvement of signs and symptoms of the complicated SSSI such that no further treatment was required) rate in the modified ITT group (all patients who received at least 1 dose) and clinically evaluable group (patients who received at least 5 days of therapy) at the test of cure (7 to 14 days posttreatment):
- Modified ITT:
 - 200 mg: (56 of 63) 88.9%.
 - 300 mg: (56 of 63) 88.9%.
 - 400 mg: (53 of 62) 85.5%.
- Clinically evaluable:
 - 200 mg: (55 of 56) 98.2%.
 - 300 mg: (51 of 54) 94.4%.
 - 400 mg: (51 of 54) 94.4%.

Secondary Endpoint(s)

- Cure rates at the end-of-therapy visit were consistent with the test-of-cure visit overall cure rate of 96.6% in the clinically evaluable population.
- Microbiological response rates:
 - In an analysis of specimens from these 133 patients, tedizolid phosphate minimal inhibitory concentrations were up to 0.12 mcg/mL for 5.1%, 0.25 mcg/mL for 89%, and 0.5 mcg/mL for 5.9% of specimens.
 - 97.7% overall eradication rate, 92.6% to 100% eradication rate for MRSA, and 88.9% to 100% for methicillin-sensitive *S. aureus* in the 3 dosing groups.

Comments: No hospitalized patients were enrolled in this study. No patients discontinued treatment because of adverse events. Reasons for discontinuing the study drug were loss to follow-up (2.7%), withdrawal of consent (0.5%), *S. aureus* bacteremia (0.5%), gram-negative infection requiring

antibiotic treatment (0.5%), gram-negative infection requiring IV antibiotic treatment (0.5%), and insufficient therapeutic effect (0.5%). Safety was evaluated in the modified ITT population. The most common adverse events were nausea (18.6%), secondary abscess (11.7%), headache (11.2%), and vomiting (10.1%). Nausea, diarrhea, vomiting, and headache were the most common adverse events determined to be drug related.

Limitations: Dose-ranging study with no comparator group.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

None.¹A history of severe hypersensitivity reaction to the drug or any of the product ingredients should be considered a possible contraindication to tedizolid therapy. The tablets contain microcrystalline cellulose, mannitol, crospovidone, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, talc, and yellow iron oxide. The injection contains sodium hydroxide and hydrochloric acid.¹

Contraindications for tedizolid and linezolid are summarized in **Table 2**.

Warnings and Precautions

In patients with neutropenia (neutrophil counts less than 1,000 cells/mm³), safety and efficacy of tedizolid have not been adequately evaluated. The antibacterial activity of tedizolid was reduced in the absence of granulocytes in animal models.¹

Systemic antibacterial drugs, including tedizolid, are associated with *Clostridium difficile*-associated diarrhea (CDAD), with severity ranging from mild diarrhea to fatal colitis. CDAD has been reported in patients using tedizolid. Treatment with antibacterial agents can alter the normal flora of the colon and may permit overgrowth of *C. difficile*. CDAD must be considered in patients who present with diarrhea

Table 2. Comparison of contraindications of tedizolid and linezolid^{a,1,23}

	Tedizolid	Linezolid
Hypersensitivity		X
Monoamine oxidase inhibitors		X

following antibacterial use. CDAD has been reported to occur more than 2 months after the use of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* should be discontinued, if possible.¹

Use of tedizolid in a patient without a proven or strongly suspected bacterial infection is unlikely to provide any benefit and increases the risk of the development of drug-resistant bacteria.¹

Tedizolid is Pregnancy Category C. There are no adequate and well-controlled studies of tedizolid in pregnant women. Tedizolid should only be used during pregnancy if the benefit justifies the potential risk to the fetus. Tedizolid is known to produce fetal developmental toxicities in animal models. In pregnant mice receiving tedizolid 25 mg/kg/day (4-fold the estimated human exposure level based on AUCs), reduced fetal weights and increased incidences of costal cartilage anomalies were observed. In pregnant rats receiving tedizolid 15 mg/kg/day (6-fold the estimated human exposure based on AUCs), decreased fetal weights and increased skeletal variations, including reduced ossification of the sternabrae, vertebrae, and skull, were observed. In rabbits, reduced fetal weights but no malformations or variations were observed at doses associated with maternal toxicity.¹ There were no observed adverse effects for fetal toxicity in mice receiving tedizolid phosphate 5 mg/kg/day, maternal and fetal toxicity in rats receiving tedizolid 2.5 mg/kg/day, and rabbits receiving tedizolid 1 mg/kg/day. The aforementioned doses resulted in tedizolid AUC values approximately equivalent to (mice and rats) or 0.04-fold (rabbit) the tedizolid AUC value associated with the oral human therapeutic dose. In a pre- and postnatal study of female rats given tedizolid 3.75 mg/kg/day (approximately equivalent to the human plasma AUC exposure at the clinical dose of 200 mg/day), there were no adverse effects in the mothers or offspring.¹

It is not known whether tedizolid is excreted in human milk. Tedizolid is excreted in the milk of lactating rats; therefore, caution should be exercised when tedizolid is administered to a breast-feeding woman.¹

Safety and efficacy of tedizolid in patients younger than 18 years have not been established.¹ Tedizolid 200 mg once daily administered either IV or orally was given to healthy adolescents 12 to 17 years of age. Oral bioavailability of tedizolid 200 mg was 89%, and mean AUC values were within 10% of values previously observed for adults.²⁹

No dosage adjustment of tedizolid is required in elderly patients. There were no clinically meaningful differences in tedizolid C_{max} and $AUC_{0-\infty}$ between elderly patients (65 years and older) and younger patients.¹

No dosage adjustment of tedizolid is required in patients with renal impairment and/or patients receiving hemodialysis. Tedizolid elimination is mostly unchanged in patients with renal impairment compared with healthy patients. Following administration of a single dose of tedizolid 200 mg IV to patients with severe renal impairment (estimated glomerular filtration rate, less than 30 mL/min/1.73 m²), there was no meaningful change in C_{max} and $AUC_{0-\infty}$ was decreased by less than 10% compared with matched healthy patients. Hemodialysis does not result in meaningful removal of tedizolid from systemic circulation, as assessed in subjects with end-stage renal disease (estimated glomerular filtration rate, less than 15 mL/min/1.73 m²).¹

No dosage adjustment is required in patients with hepatic impairment. Tedizolid elimination is unchanged in patients with hepatic impairment compared with healthy patients. Following administration of a single oral dose of tedizolid 200 mg in patients with moderate (Child-Pugh class B) or severe hepatic impairment (Child-Pugh class C), no clinically meaningful changes in mean tedizolid C_{max} and $AUC_{0-\infty}$ were observed compared with healthy patients.¹

Warnings and precautions for tedizolid and linezolid are summarized in Table 3.

ADVERSE REACTIONS

The most common treatment-emergent adverse reactions in patients with acute bacterial SSSI who were treated with tedizolid were nausea (8%), headache (6%), diarrhea (4%), vomiting (3%), and dizziness (2%).¹

Adverse events occurring in at least 2% of patients with acute bacterial SSSI treated with tedizolid from pooled phase 3 clinical trials are outlined in Table 4.

Additional adverse reactions reported in patients with acute bacterial SSSI treated with tedizolid at a rate of less than 2% include anemia, palpitations, tachycardia, asthenopia, vision blurred, visual impairment, vitreous floaters, infusion-related reactions, drug hypersensitivity, *C. difficile*-associated colitis, oral candidiasis, vulvovaginal mycotic infection, increased hepatic transaminases, decreased white blood cell count, hypesthesia, paresthesia,

Table 3. Comparison of warnings and precautions and special populations of tedizolid and linezolid^{1,23}

	Tedizolid	Linezolid
<i>Warnings and precautions</i>		
CDAD	X	X
Development of drug-resistant bacteria	X	X
Neutropenic patients	X	
Hypertension		X
Hypoglycemia		X
Lactic acidosis		X
Mortality, increased ^a		X
Myelosuppression		X
Neuropathy, peripheral and optic		X
Seizures		X
Serotonin syndrome		X
<i>Special populations</i>		
Renal impairment	No unique precautions	Use caution; metabolite accumulation. Dose after hemodialysis
Hepatic impairment	No unique precautions	No unique precautions
Pediatric patients	Safety and efficacy not established	Birth through 12 years and older
Elderly patients	Caution	Caution; not adequately studied
Pregnancy Category	C	C
Breast-feeding	Caution	Caution

Note: CDAD = *Clostridium difficile*-associated diarrhea.

^aAn increase in mortality was seen in patients treated with linezolid relative to vancomycin/dicloxacillin/oxacillin in an open-label study in seriously ill patients with intravascular catheter-related infections.

Table 4. Adverse reactions occurring in patients with acute bacterial SSSI receiving tedizolid ($\geq 2\%$)¹

Adverse reaction	Tedizolid 200 mg oral/IV once daily for 6 days (<i>n</i> = 662)	Linezolid 600 mg oral IV twice daily for 10 days (<i>n</i> = 662)
Nausea	8%	12%
Headache	6%	6%
Diarrhea	4%	5%
Vomiting	3%	6%
Dizziness	2%	2%
<i>Laboratory abnormalities</i>	(<i>n</i> = 618)	(<i>n</i> = 617)
Hemoglobin (< 10.1 g/dL [male] or < 9 g/dL [female])	3.1%	3.7%
Platelet count (< $112 \times 10^3/\text{mm}^3$)	2.3%	4.9%
Absolute neutrophil count (< $0.8 \times 10^3/\text{mm}^3$) ^a	0.5%	0.6%

Note: IV = intravenous; SSSI = skin and skin structure infections.

^a Less than 75% (less than 50% for absolute neutrophil count) of lower limit of normal for values were normal at baseline.

seventh nerve paralysis, insomnia, pruritus, urticaria, dermatitis, flushing, and hypertension.¹

Adverse event rates for peripheral neuropathy were 1.2% for tedizolid and 0.6% for linezolid, and adverse event rates for optic nerve disorders were 0.3% for tedizolid and 0.2% for linezolid.¹

DRUG INTERACTIONS

Tedizolid phosphate or tedizolid is not appreciably metabolized by hepatic oxidation, and they do not detectably inhibit or induce the metabolism of substrates of cytochrome P450 enzymes. Additionally, tedizolid phosphate or tedizolid was not shown to significantly inhibit drug uptake transporters (OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2) or efflux transporters (P-glycoprotein and ABCG2 [also known as BCRP]) at circulating plasma concentrations up to the C_{max} .¹

Tedizolid does not inhibit the monoamine oxidase (MAO) system in vivo in animal models; however, tedizolid is a reversible inhibitor of MAO in vitro.^{1,30,31} Two randomized, double-blind, placebo-controlled crossover, phase 1 studies have been completed evaluating the potential for tedizolid phosphate to inhibit MAO. Tedizolid phosphate was comparable with placebo vehicle in its potential to induce head twitches in murine models, and linezolid induced a head-twitch response comparable with fluoxetine.^{29,30,31} In a mouse model that predicts serotonergic activity, it was found that with doses of tedizolid phosphate up to 30-fold above the human equivalent dose, the rate of serotonergic effects did not differ from vehicle control, whereas linezolid, at approximately the human equivalent therapeutic exposure, caused an approximately 4.5 times increase in head-twitch activity over the vehicle control.^{1,29,31} The interaction with monoamine oxidase inhibitors (MAOIs) could not be evaluated in phase 2 and 3 trials because patients taking such medications were excluded.¹

At therapeutic doses in humans, tedizolid did not produce hypertensive or serotonergic effects in provocative testing.^{1,30} Interactions with serotonergic agents were not assessed in phase 3 clinical trials because patients taking serotonergic agents (eg, selective serotonin reuptake inhibitors, tricyclic antidepressants, and serotonin 5-hydroxytryptamine receptor agonists [triptans], meperidine, buspirone) were excluded.¹

In healthy patients receiving tedizolid 200 mg at steady state, the median dose of tyramine that caused

an increase in systolic blood pressure of at least 30 mm Hg from baseline was 325 mg with tedizolid compared with 425 mg with placebo. Additionally, palpitations were reported in 21 of 29 (72.4%) tedizolid patients and 13 of 28 (46.4%) placebo patients exposed to tyramine.^{1,30}

No meaningful changes in blood pressure or heart rate were observed when tedizolid was administered with pseudoephedrine.¹

The IV solution should not be mixed with any other drugs.¹

RECOMMENDED MONITORING

Monitor for a clinical response (eg, reduction in lesion size, and resolution of fever) 48 to 72 hours after treatment initiation. Following treatment with tedizolid, monitor for signs and symptoms of CDAD.¹

DOSING

For the treatment of acute bacterial SSSI, tedizolid 200 mg administered once daily for 6 days orally, with or without food, or as an IV infusion over 1 hour in patients 18 years and older. Tedizolid should not be administered as an IV push or bolus.¹

Tedizolid lyophilized powder for injection requires preparation prior to infusion. Each single-use vial contains lyophilized tedizolid phosphate 200 mg and must be reconstituted with 4 mL of sterile water for injection. The vial should be gently swirled after the addition of the sterile water for injection to completely dissolve the powder. The reconstituted solution is then added only to 250 mL of 0.9% sodium chloride injection; no other types of solutions should be used.¹ No dosage adjustments are necessary when switching the patient from IV to oral therapy.¹

The IV solution is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.¹

Tedizolid phosphate is incompatible with any solution containing divalent cations (eg, Ca^{2+} , Mg^{2+}), including Ringer's lactate injection and Hartmann's solution. There are limited data available on the compatibility of tedizolid phosphate with other IV substances; therefore, they should not be added to tedizolid single-use vials or infused simultaneously. The IV line should be flushed before and after infusion of tedizolid with 0.9% sodium chloride injection if it will be used for sequential infusion of different drugs.¹

PRODUCT AVAILABILITY

Tedizolid phosphate was approved for marketing in the United States on June 20, 2014.³² Tedizolid phosphate is supplied as 200 mg tablets in bottles of 30 and unit-dose blister packs containing 6 tablets. Tedizolid phosphate is supplied as a sterile, lyophilized powder for injection in single-use vials of 200 mg in packages of 10 vials. Each 200 mg vial must be reconstituted with sterile water for injection and subsequently diluted only with 0.9% sodium chloride injection.¹

Tedizolid tablets and powder for injection should be stored at 20°C to 25°C (68°F to 77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F).¹ The total time from reconstitution to administration should not exceed 24 hours at room temperature or under refrigeration at 2°C to 8°C (36°F to 46°F).¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for tedizolid.³²

CONCLUSION

Tedizolid phosphate is the second oxazolidinone approved by the US Food and Drug Administration for the treatment of acute bacterial SSSI caused by susceptible gram-positive isolates that can be used orally or IV. Tedizolid phosphate is a prodrug that is rapidly converted to tedizolid by hydrolysis of the phosphate group by phosphatases. The emergence of microorganisms resistant to current treatment options indicates a need to create additional options for therapy. Tedizolid showed favorable results in the treatment of acute bacterial SSSI in 2 phase 3 trials and was shown to be noninferior to linezolid. In vitro, tedizolid has more activity than linezolid against strains of *Staphylococcus* species, *Streptococcus* species, and *Enterococcus* species, including strains with a cfr mutation with resistance to linezolid. Tedizolid has a favorable safety profile in addition to a reduced potential for drug-drug interactions over linezolid. Linezolid is scheduled to be available as a generic as early as 2015, which will likely greatly alter the cost-benefit ratio for formulary placement of an oxazolidinone antibiotic.

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