Tedizolid (Sivextro)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Tedizolid phosphate is an oxazolidinone antibiotic prodrug, which inhibits bacterial protein synthesis in its active form by binding to the 50S subunit of the bacterial ribosome. It has shown in vitro activity against *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (including *Streptococcus anginosus, Streptococcus intermedius and Streptococcus constellatus*), and *Enterococcus faecalis*.[1]
Indications under Review in this document (may include off label)	Tedizolid phosphate is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by select Gram-positive susceptible isolates.
Dosage Form(s) Under Review	Intravenous Powder for Solution, 200mg Oral Tablet, 200mg
REMS	☐ REMS ☒ No REMS
Pregnancy Rating	Category C

Executive Summary

Efficacy	• The FDA approval of tedizolid phosphate was based on two multinational phase 3 non-inferiority trials evaluating tedizolid phosphate 200mg once daily for 6 days vs linezolid 600mg twice daily for 10 days for the treatment of ABSSSI.[2,3] • The primary efficacy endpoint for these pivotal trials was early clinical response at 48 – 72 hours. The definition of early clinical response was no increase in lesion surface area from baseline and oral temperature of ≤ 37.6°C in one trial and ≥20% reduction in lesion surface area compared to baseline in the other. • Results from both studies demonstrated tedizolid phosphate was non-inferior to linezolid in treating ABSSSI.[2,3]
Safety	• The most common adverse reactions (≥2%) are nausea, headache, diarrhea, vomiting, and dizziness. • The warnings and precaution state that the safety and efficacy of tedizolid phosphate in patients with an ANC < 1000 cells/mm^3 has not been adequately evaluated and alternative treatments should be considered in patients with ABSSSI and neutropenia.[1] • Tedizolid phosphate has been shown to be a reversible inhibitor of monoamine oxidase (MAO) *in vitro*, but no restrictions exist for concomitant use of drugs with adrenergic and serotonergic activity or tyramine containing foods according to the prescribing information.[1] Of note, patients taking such medications were excluded from Phase 2 and 3 trials.
Potential Impact	• Tedizolid phosphate is indicated for the treatment of ABSSSI. Tedizolid is administered once daily and available in both intravenous and oral formulations.[1]

Background

Purpose for review

The purpose of the review is to evaluate the efficacy and safety of tedizolid phosphate.

- ✔ Evidence of need
- ✔ Does tedizolid phosphate offer advantages to currently available alternatives?
- ✔ What safety issues need to be considered?

Other MRSA therapeutic options

Formulary Alternatives	Other Considerations in Adults[4,5,6,7]
Ceftaroline	• Availability: IV • Limited experience with other MRSA infections besides skin and skin structure infections

	• Pregnancy category B
Clindamycin	• Availability: IV and PO • D-zone test recommended for detection of inducible resistance • Most common adverse effect is diarrhea and *Clostridium difficile* may occur more frequently than other antibiotics • Pregnancy category B
Daptomycin	• Availability: IV • Possible cross-resistance with vancomycin • Associated with myopathies and CPK monitoring is recommended • Pregnancy category B
Linezolid	• Availability: IV and PO • Long term use limited by hematologic toxicity, peripheral and optic neuropathy and lactic acidosis. • Reversible inhibitor of monoamine oxidase with possible drug interaction with SSRIs. • Pregnancy category C
Tetracyclines	• Availability: IV and PO • CA-MRSA isolates can confer resistance to doxycycline, with no impact on minocycline. • May be associated with an increase in all-cause mortality for patients with serious infections • Pregnancy category D
TMP-SMX	• Availability: IV and PO • Not FDA-approved for treatment of *staphylococcus aureus* infections • Increased risk of hyperkalemia in elderly patients particularly if receiving concomitant inhibitors of renin-angiotensin or those with chronic renal insufficiency • Pregnancy category D
Vancomycin	• Availability: IV • Requires monitoring of levels and has been shown to kill *staphylococcus* more slowly than β-lactams • Associated with nephrotoxicity and Redman syndrome • Pregnancy category C

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to February 2014) using the search terms tedizolid phosphate and Sivextro. The search was limited to studies performed in humans and published in the English language. All randomized, Phase 3 controlled trials published in peer-reviewed journals were included.

Review of Efficacy

The FDA indication for tedizolid phosphate is based upon two randomized, double-blind, multinational phase 3 non-inferiority trials evaluating tedizolid phosphate versus linezolid for the treatment of ABSSSIs defined as cellulitis/erysipelas, wound infection, or major cutaneous abscess with a minimal lesion surface area of 75cm^2.[2,3,8] The first trial (ESTABLISH-1) compared 6 days of oral tedizolid phosphate 200 mg daily versus 10 days of oral linezolid 600 mg twice daily for the treatment of ABSSSI and the second trial (ESTABLISH-2) compared 6 days of IV tedizolid phosphate 200 mg daily versus 10 days of IV linezolid 600 mg twice daily for the treatment of ABSSSI with optional oral conversion for completion of therapy. The study designs for the ESTABLISH-1 and ESTABLISH-2 trials were similar (Refer to Table 1). Of note, a difference existed in measurement of lesion surface area. The ESTABLISH-1 trial utilized erythema alone in measurement of the lesion whereas ESTABLISH-2 lesion surface area could be based on erythema, edema, or induration.

Table 1: Study Designs of ESTABLISH-1 and -2 Trials[2,3]

Stratification	Key Inclusion Criteria	Key Exclusion Criteria
• Geographic region • Type of ABSSSI • Presence/absence of baseline fever (ESTABLISH-1 only)	• Lesion surface area ≥75 cm^2 • Systemic sign of infection: ○ Lymphadenopathy ○ Fever ≥38°C ○ Leukocytosis (>10x10^9/L) ○ Leukopenia (<4x10^9/L) ○ >10% immature neutrophils • Gram-positive pathogen suspected or documented	• Receiving systemic or topical antibiotics with gram-positive activity within 96 hours before first dose of study drug • Previous treatment failure • Chronic Infection • MAO inhibitors and of drugs with adrenergic and serotonergic activity

The primary efficacy endpoint for ESTABLISH-1 and ESTABLISH-2 trials was early clinical response at 48 to 72 hour after initiation of treatment. The definition of early clinical response for the ESTABLISH-1 trial was defined as no increase in lesion surface area from baseline and oral temperature of ≤ 37.6°C (confirmed by a second temperature measurement within 24 hours) compared to the ESTABLISH-2 trial which defined early clinical response at the 48 to 72 hour assessment as ≥20% reduction in lesion surface area compared to baseline. This difference in primary efficacy outcome was due to a release in June 2012 from Biomarkers Consortium of the Foundation for the National Institutes of Health, which recommended defining early clinical response in clinical trials for ABSSSI as a decrease from baseline of ≥20% in lesion area. The US Food and Drug Administration incorporated the definition from Biomarkers Consortium in their Guidance for industry on ABSSSIs and the investigators performed a sensitivity analysis on the original data from the ESTABLISH-1 trial utilizing the new definition of early response.[8]

Secondary efficacy analyses were performed on the intent to treat (ITT) as well as a clinically evaluable (CE) population. CE was defined as all ITT patients who complied with the protocol without major violations, did not receive treatments that might confound outcomes and completed specified assessments for a particular outcome. Secondary efficacy endpoints evaluated by the FDA Briefing document[9] for the ESTABLISH-1 and ESTABLISH-2 trials were sustained clinical response at end of treatment (EOT) on day 11 relative to first dose of study drug given on day 1 in the ITT, sustained clinical response at EOT in the CE, and investigator assessment of clinical success at post-therapy evaluation (PTE) 7 to 14 days after EOT in both the ITT and CE population. Non-responder clinical outcomes for early clinical response at 48 to 72 hours were not carried over for secondary efficacy analysis.

Demographics and baseline characteristics for the ITT populations did not demonstrate a notable imbalance between the groups in either trial (Table 2). *Staphylococcus aureus* was the most common pathogen isolated in each study, accounting for ~80% of pathogens isolated. Additionally, MRSA accounted for ~40% and ~27% of pathogens identified in the ESTABLISH-1 and ESTABLISH-2, respectively

Table 2: Demographic Characteristics in the ITT Population[2,3]

	ESTABLISH-1		ESTABLISH-2	
	Tedizolid phosphate (N=332)	**Linezolid (N=335)**	**Tedizolid phosphate (N=332)**	**Linezolid (N=334)**
Sex, n (%)				
Female	128 (38.6)	137 (40.9)	107 (32.2)	120 (35.9)
Male	204 (61.4)	198 (59.1)	225 (67.8)	214 (64.1)
Age (years)				
Mean (Std)	43.6 (14.96)	43.1 (15.06)	45.6 (15.79)	45.6 (15.57)
PMH, n (%)				
DMII	26 (3.9)	26 (3.9)	32 (9.6)	41 (12.3)

IV Drug use	117 (35.2)	132 (39.4)	66 (19.9)	74 (22.2)
Previous ABSSSI	75 (22.5)	81 (24.2)	71 (21.4)	63 (18.8)
Infection, n (%)				
Cellulitis/erysipelas	135 (40.7)	139 (41.5)	166 (50.0)	168 (50.3)
Major Cutaneous Abscess	100 (30.1)	98 (29.3)	68 (20.5)	68 (20.4)
Lesion size, cm^2 Median	188	190	231	239
	(n=209)	**(n=209)**	**(n=197)**	**(n=202)**
MRSA*	88, 42.1%	90, 43.1%	53, 26.9%	56, 27.7%
Procedures, n (%)				
Incision & Drainage	153 (46.1)	160 (47.8)	182 (54.8)	183 (54.8)

*Percentage of common pathogenic organisms obtained from baseline primary ABSSSI site or blood culture

In the package insert, the primary efficacy endpoint for the ESTABLISH-1 (i.e., early clinical response defined as no increase in lesion surface area from baseline and oral temperature of ≤ 37.6°C) demonstrated no difference in treatment groups [79.3% (256/323) in the tedizolid phosphate group and 79.1% (258/326) in the linezolid group; 0.1 (95% CI -6.2, 6.3)].[1] Three sites (18 patients) from the ESTABLISH-1 trial were excluded from the package insert and FDA Briefing document's analysis and alter the denominator for efficacy calculations in Table 3 from those presenting in primary literature.[9] Additionally, for consistency in presentation of trial results the FDA Briefing document eliminated an oral temperature ≤ 37.6°C from the primary endpoint of the ESTABLISH-1 trial.[9] Overall, results from both ESTABLISH-1 and ESTABLISH-2 presented in the FDA briefing document (Table 3) and primary literature demonstrated tedizolid phosphate was non-inferior to linezolid in treating ABSSSIs in terms of Early Clinical Response at 48-72 hours, Sustained Clinical Response at EOT, and Investigator Assessment of Clinical Response at PTE. The sensitivity analysis performed in the ESTABLISH-1 trial on early clinical response showed no difference in treatment groups with a response rate of 78% (259/332) in the tedizolid phosphate group and 76% (255/335) in the linezolid group.[1]

The ESTABLISH-1 trial evaluated patients with Gram-positive infections at PTE in the ITT and showed response rates for MSSA isolates of 88.0% (73/83) vs 94.3% (82/87) and response rates for MRSA isolates of 85.2% (75/88) vs 85.6% (77/90) for tedizolid phosphate and linezolid, respectively.[2] The ESTABLISH-2 trial evaluated patients with Gram-positive infections for early clinical response with outcomes consistent with the overall results and response rates for MSSA isolates of 92% (97/105) vs 85% (94/111) and response rates for MRSA isolates of 83% (44/53) vs 79% (44/56) for tedizolid phosphate and linezolid, respectively.[3]

Table 3: Primary and select secondary efficacy endpoints of tedizolid phosphate vs linezolid for ABSSSI per FDA Briefing Document[a,9]

		Primary efficacy	**Secondary efficacy**			
		Early clinical response – ITT[b] (95% CI)[c]	**Sustained clinical response – EOT-ITT (95% CI)[c]**	**Sustained clinical response – CE-EOT (95% CI)[c]**	**Investigators assessment of clinical success – PTE-ITT (95% CI)[c]**	**Investigators assessment of clinical success – CE-PTE (95% CI)[c]**
ESTABLISH-1 (≥ 18 years old with ABSSSI)	Tedizolid phosphate	**(n=323)** 280, 86.7%	**(n=323)** 262, 81.1%	**(n=265)** 234, 88.3%	**(n=323)** 277, 85.8%	**(n=270)** 257, 95.2%
	Linezolid	**(n=326)** 277, 85%	**(n=326)** 265, 81.2%	**(n=280)** 246, 87.9%	**(n=326)** 279, 85.6%	**(n=273)** 260, 95.2%
	Absolute Treatment Difference	**1.7 (-3.7 – 7.1)**	**-0.2 (-6.2 – 5.9)**	**-1.0 (-7.6 – 5.5)**	**0.2 (-5.3 – 5.6)**	**-0.0 (-3.9 – 3.7)**
ESTABLISH-2 (≥ 12 years old with ABSSSI)	Tedizolid phosphate	**(n=332)** 283, 85.2%%	**(n=332)** 289, 87.0%	**(n=304)** 272, 89.5%	**(n=332)** 292, 88.0%	**(n=290)** 268, 92.4%
	Linezolid	**(n=334)** 276, 82.6%	**(n=334)** 294, 88.0%	**(n=299)** 280, 93.6%	**(n=334)** 293, 87.7%	**(n=280)** 269, 96.1%
	Absolute Treatment Difference	**2.6 (-3.0 – 8.2)**	**-1.0 (-6.1 – 4.1)**	**-4.1 (-8.8 – 0.3)**	**0.3 (-4.8 – 5.3)**	**-3.7 (-7.7 – 0.2)**

Overall quality of evidence: High (Refer to Appendix A); please note that all trials were funded by Cubist Pharmaceuticals.
a - Adapted from Tables 5-5, 5-8, and 5-11 from FDA Briefing Document[9]
b - No fever component included in analysis for ESTABLISH-1 trial which differs from package insert
c - 95% CI lower limit set at -10% for non-inferiority

Efficacy Summary

- The FDA approval of tedizolid phosphate was based on two multinational phase 3 non-inferiority trials evaluating tedizolid phosphate vs linezolid for the treatment of ABSSSI. Results from both ESTABLISH-1 and ESTABLISH-2 demonstrated tedizolid phosphate was non-inferior to linezolid in treating ABSSSIs in terms of Early Clinical Response at 48-72 hours, Sustained Clinical Response at EOT, and Investigator Assessment of Clinical Response at PTE.

Potential Off-Label Use

- FDA labeled indications for linezolid that may lead to use of tedizolid phosphate other than ABSSSIs include community-acquired pneumonia, nosocomial pneumonia, and vancomycin-resistant enterococcus faecium infection.
- IDSA MRSA Guidelines recommend linezolid for the following conditions that may lead to use of tedizolid phosphate:
  - Bacteremia & infective endocarditis, pneumonia, bone and joint infections, and infections of the CNS.[5]
- A Phase 3 trial sponsored by Cubist comparing tedizolid phosphate to linezolid for nosocomial pneumonia is currently recruiting participants.[10]

Safety

Boxed Warning	• None
Contraindications	• None
Warnings/Precautions	• Patients with Neutropenia: Safety and efficacy in patients with neutrophil counts <1000 cells/mm^3 have not been adequately evaluated. In animal models antibacterial activity of tedizolid phosphate was reduced in absence of granulocytes • *Clostridium difficile*-Associated Diarrhea: Treatment with antibacterial agents can alter the normal flora of the colon and my permit overgrowth of *C. difficile* • Development of Drug-Resistant Bacteria: Prescribing tedizolid phosphate without a proven or strongly suspected indication is unlikely to provide benefit and increases the risk of development of drug-resistant bacteria

Safety Considerations

The safety of tedizolid phosphate was evaluated in nineteen clinical studies and included 438 subjects in phase 1, 388 subjects in phase 2, and 662 subjects in phase 3 clinical trials.[9]

Hematologic Parameters

- According to tedizolid phosphate prescribing information, a dose and duration effect on hematologic parameters may have been observed in a Phase 1 trial with treatment beyond 6 days in healthy adults exposed to 21 days of tedizolid phosphate.[1] In phase 3 trials, the occurrences of clinically significant changes in hematologic parameters (hemoglobin, platelet count, and absolute neutrophil count) were similar between linezolid and tedizolid phosphate.[1]

Peripheral and Optic Neuropathy

- In phase 3 trials, adverse effects associated with neurologic and optic nerve disorders did not differ between treatment groups.[2,3,9] However; patients were treated with 6 days of tedizolid phosphate and 10 days of linezolid.
  - Eight (1.2%) of patients in the tedizolid phosphate arm and 5 (0.8%) in the linezolid arm experienced at least one neurologic treatment emergent adverse event including hypoesthesia, cranial nerve VII paralysis, paresthesia, and sensory loss.[9]
  - Two (0.3%) of patients in the tedizolid phosphate arm and one (0.2%) in the linezolid arm experienced at least one optic nerve disorder.[9]

Adverse Reactions[1,2,3]

Common adverse reactions	• **Incidence ≥5%:** headache, nausea • **Incidence 2 – 5%:** diarrhea, vomiting, dizziness

	• **Incidence <2%:** hypoesthesia, paresthesias, VIIth nerve paralysis, anemia, palpitations, sinus tachycardia, flushing, hypertension, asthenopia, blurred vision, visual impairment, hypersensitivity, pruritus, urticaria, elevated hepatic enzymes, insomnia, peripheral neuropathy
Death/Serious adverse reactions	• Serious AE occurred 1.8% (n=12) with tedizolid phosphate vs 2.0% (n=13) for the comparator in phase 3 trials; none of these SAEs were considered related to tedizolid. • 3 deaths occurred in phase 3 trials: 0.3% (n=2) tedizolid phosphate vs. 0.2% (n=1) linezolid comparator arm; all deaths unrelated to study drug or comparator
Discontinuations due to adverse reactions	• Discontinuation due to AE occurred 0.5% (n=3) with tedizolid phosphate vs. 0.9% (n=6) in the comparator arm phase 3 trials. Discontinuation due to AE considered related to the study drug occurred 0.3% (n=2) with tedizolid phosphate vs. 0.8% (n=5) in the comparator arm phase 3 trials
Laboratory abnormalities	• Reduction in Hemoglobin <10.1 g/dL in males and <9 g/dL in females occurred 3.1% with tedizolid phosphate vs 3.7% for the comparator arm in phase 3 trials • Reduction in Platelet count <112 x 10^3/mm^3 occurred 2.3% with tedizolid phosphate vs 4.9% for the comparator arm in phase 3 trials • Reduction in Absolute neutrophil count <0.8 x 10^3/mm^3 occurred 0.5% with tedizolid phosphate vs 0.6% for the comparator arm in phase 3 trials

Drug Interactions

- According to prescribing information, tedizolid phosphate neither inhibits nor induces the metabolism of selected CYP enzyme substrates *in vitro*.[1] No inhibition of drug uptake or efflux transporters was identified *in vitro*.[1]
- Monoamine oxidase interactions have been associated with linezolid use and *in vitro* both tedizolid phosphate and linezolid are reversible inhibitors of human MAO-A and MAO-B.[1,6] Interactions with serotonergic agents (selective serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-hydroxytryptamine receptor agonists, meperidine, or buspirone) and monoamine oxidase interactions have not been evaluated in Phase 2 or 3 trials as subjects taking such medications were excluded. However, unlike linezolid, the prescribing information for tedizolid phosphate does not list concurrent use of MAO inhibitors as a contradiction to use and according to FDA Briefing documents on tedizolid phosphate "no restrictions are necessary on concomitant use of drugs with adrenergic and serotonergic activity or food containing tyramine".[1,6,9]
- Adrenergic agent interactions were evaluated in 2 randomized, double-blind, placebo controlled crossover studies which assessed tedizolid phosphate 200mg daily's ability to increase healthy individual's presser response to oral tyramine and pseudoephedrine.[1,11]
    - In the tyramine pressor sensitivity study 30 patients were evaluated to determine the dose of tyramine required to elicit an increase in systolic blood pressure ≥ 30mmHg (TYR_{30}). Tyramine sensitivity factors are calculated as a ratio of placebo TYR_{30} to tedizolid phosphate TYR_{30}. The mean ratio of placebo to tedizolid phosphate was 1.33 with a tyramine sensitivity factor of ≥2 being considered a clinically relevant increase in tyramine sensitivity.[11] The reported tyramine sensitivity factor for linezolid is 3.48.[11]
    - In the pseudoephedrine challenge maximum increases in blood pressure and heart rate were not significantly different between tedizolid phosphate and placebo and no treatment emergent adverse event led to study drug discontinuation.[1,11]
- Serotonergic agent interactions were evaluated in an animal study evaluating serotonergic activity in murine model.[1,11]
    - Escalating doses of tedizolid phosphate were compared to linezolid, fluoxetine, and moclobemide. Head twitch response was evaluated by technicians, blinded to treatment assignment, as a surrogate marker of *in vivo* serotonin receptor 2A activation. Head twitches were statistically significantly elevated in the linezolid, fluoxetine, and moclobemide groups in contrast with tedizolid phosphate which showed no increase at any dose examined. The C_{max} of the linezolid dose administered was similar to the C_{max} observed in humans administered 600mg twice daily and the highest tedizolid phosphate doses administered were ~25 fold higher than the C_{max} observed in humans administered 200mg daily.[1,11]

Risk Evaluation

Sentinel event advisories	• None

Look-alike/sound-alike error potentials	• Sources: Based on clinical judgment and an evaluation of LASA information

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Tedizolid phosphate 200mg tab, IV soln	None	None	None	Linezolid Teduglutide
Sivextro	None	None	None	Salvax

Other Considerations

Table 4: Pharmacokinetic Profiles

Drug Name	Absorption	Distribution	Metabolism	Excretion
Tedizolid phosphate	Oral AUC: 91%	Protein binding: 70 – 90% Volume of distribution: 67 – 80L	Prodrug Not CYP mediated	Renal: 3% unchanged $T_{1/2}$: ~12 hrs
Linezolid	Oral AUC: 100%	Protein binding: 31% Volume of distribution: 40 – 50L	Not completely understood – minimal liver metabolism	Renal: 30% unchanged $T_{1/2}$: 4.69 – 5.4 hrs

Of note: tedizolid phosphate is only excreted 3% unchanged in the urine and has not been evaluated for UTI.

Microbiology

Surveillance data in the United States and Europe have evaluated the MIC_{50} and MIC_{90} of tedizolid phosphate and linezolid against MRSA, MSSA, VRE, and VSE (Refer to Table 6).[12] Data were collected from 9 US census regions and 6 countries in Europe with a total of 6884 nonduplicate, non-consecutive clinically significant Gram-positive bacteria isolates.

Table 5: In vitro activity of tedizolid and linezolid reported in a surveillance study[1,6,12]

Organism	Drug Name	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
MRSA* N=1770	Tedizolid Linezolid	≤0.015 – 4 0.25 – 16	0.25 2	0.5 2
MSSA* N=2729	Tedizolid Linezolid	≤0.015 – 0.5 0.25 – 16	0.25 2	0.5 2
VRE** N=163	Tedizolid Linezolid	0.12 – 2 0.5 – 16	0.25 2	0.5 2
VSE** N=705	Tedizolid Linezolid	0.03 – 0.5 ≤0.25 – 4	0.25 1	0.5 2

*Tedizolid phosphate susceptibility test interpretive criteria MIC ≤0.5; Linezolid susceptibility test interpretive criteria MIC ≤4
** Tedizolid phosphate susceptibility test interpretive criteria MIC ≤0.5; Linezolid susceptibility test interpretive criteria MIC ≤2

Dosing and Administration

- The recommended dosage of tedizolid phosphate is 200 mg administered once daily for six days either orally (with or without food) or as an intravenous (IV) infusion in patients 18 years of age or older for the treatment of ABSSSIs
- No dose adjustment is necessary when changing from intravenous to oral
- If patients miss a dose, they should take it as soon as possible anytime up to 8 hours prior to their next scheduled dose. If less than 8 hours remain before the next dose, wait until their next scheduled dose.

Special Populations (Adults)

Elderly	• Clinical studies of tedizolid phosphate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. No overall differences in pharmacokinetics were observed between elderly subjects and younger subjects
Pregnancy	• Pregnancy Category C
Lactation	• Tedizolid is excreted in the breast milk of rats. It is not known whether tedizolid is excreted in human milk. Caution should be

	exercised when tedizolid phosphate is administered to a nursing woman
Renal Impairment	• No dosage adjustment is necessary in patients with renal impairment or patients on hemodialysis
Hepatic Impairment	• No dose adjustment is necessary for patients with hepatic impairment
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy

- The CDC estimates that MRSA caused 80,461 invasive infections and 11,285 deaths in 2011.[13]
- The Infectious Diseases Society of America (IDSA) Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections and IDSA Practice Guidelines for the Management of Patients with Infections caused by MRSA are currently the only two national clinical practice guidelines that discuss MRSA ABSSSIs (tedizolid phosphate's FDA labeled indication) and both were published prior to the approval of tedizolid phosphate.[4,5]
    - The IDSA Clinical Practice Guidelines for the Management of MRSA Infections recommend clindamycin (A-II), trimethoprim-sulfamethoxazole (A-II), a tetracycline (A-II), and linezolid (A-II) for empirical coverage of community-acquired MRSA in outpatients for the management of skin and soft-tissue infections.[5] IV options for complicated skin and soft-tissue infections requiring hospitalization due to MRSA include vancomycin (A-I), oral or IV linezolid (A-I), daptomycin (A-I), telavancin (A-I), and clindamycin IV or oral (A-III).[5]
    - The IDSA Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections lists vancomycin, linezolid, clindamycin, daptomycin, ceftaroline, doxycycline/minocycline, and trimethoprim/sulfamethoxazole as antimicrobial treatment options for MRSA.[4]
    - Treatment duration discussed in available guidelines varies from 5 – 14 days depending on guideline and severity of infection.[4,5] Additional agents with FDA labeled indications for MRSA ABSSSIs not included in the guidelines include recently approved dalbavancin and oritavancin.
- Phase III clinical studies demonstrated non-inferiority of 6 days of tedizolid phosphate vs 10 days of linezolid (FDA approved duration). Long-term safety of tedizolid phosphate is currently unknown at this time.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.