INTRODUCTION

Between 2001 and 2003, acute bacterial skin and skin structure infections (ABSSSIs) accounted for more than 11 million ambulatory care visits, with a visit rate of 410.7 per 10,000 persons. As a broader term, ABSSSI encompasses the following (Table 1):2,4

1. Cellulitis/erysipelas
2. Wound infection
3. Major cutaneous abscess

This infection is characteristically identified by a measurable lesion (based on edema, redness, and induration) of at least 75 cm² with systemic signs of infection and/or lymphadenopathy.2,4 For major abscesses and wound infections, the area of erythema or induration must also extend 5 cm or more from the peripheral margin of the lesion.3,4 A common contributing pathogen in this setting is *Staphylococcus aureus*, particularly methicillin-resistant *S. aureus* (MRSA).1,4 Several pharmacological options, including oxazolidinones, are available for use (Table 2).5,6

In 2000, linezolid (Zyvox, Pfizer) became the first oxazolidinone approved by the Food and Drug Administration (FDA). Its mechanism of action entails inhibition of bacterial protein synthesis by binding 23S ribosomal RNA within the 50S subunit. Indications for use include the management of skin and skin structure infections (complicated and uncomplicated), community-acquired pneumonia, nosocomial pneumonia, and vancomycin-resistant *Enterococcus faecium* infections. Linezolid is bacteriostatic against staphylococci and enterococci, and bactericidal against streptococci strains. Convenitely dosed at 600 mg twice daily, it can be administered intravenously or orally in a 1:1 ratio. Notable warnings and precautions are serotonin syndrome, myelosuppression, and postmarketing reports of hypoglycemia with concomitant use of antihyperglycemic agents.6

Since its release, however, there have been reports of MRSA strains resistant to linezolid due to the acquisition of a natural resistance gene known as *cfr* (chloramphenicol-florfenicol resistance). As a result, Cfr methyltransferase is expressed and alters the 23S rRNA component of the ribosomal subunit in bacteria.7,8 Introducing a unique challenge for the management of multidrug-resistant gram-positive organisms, new drug developments have been explored.

In June 2014, the FDA approved tedi-zolid phosphate (Sivextro, Cubist Pharmaceuticals) as a second-generation oxazolidinone with potentially four- to 16-fold anti-MRSA potency compared with linezolid.9–11 Favorable results from clinical trials have led to its indication for the treatment of ABSSSIs in adult patients with susceptible bacteria.12 This article reviews the information available to date on this product in relation to safety and efficacy.

CLINICAL PHARMACOLOGY

Tedizolid phosphate is a prodrug that is converted by plasma phosphatases to microbiologically active tedizolid in vivo. It interacts with the bacterial 23S ribosome initiation complex and binds to the 50S subunit to prevent the formation of the 70S complex. As a result, tedizolid inhibits bacterial translation and protein synthesis.3,10

MICROBIOLOGICAL ACTIVITY

Tedizolid has activity against clinically relevant gram-positive pathogens such as MRSA, methicillin-susceptible *S. aureus* (MSSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, enterococci, and coagulase-negative staphylococci (Table 3). In addition, this drug has demonstrated activity against linezolid-resistant staphylococci (Table 4).10–12

Specific to *S. aureus* strains in vitro, tedizolid had a minimum inhibitory concentration (MIC) range of 0.125 to 0.5 mcg/mL of tedizolid phosphate and linezolid.
Further evaluation showed that 95% of MRSA isolates and 72% of MSSA isolates had a MIC of 0.25 mcg/mL or less. For penicillin-resistant *Streptococcus pneumoniae*, in vitro susceptibility results showed a MIC of 0.125 to 0.25 mcg/mL and MIC\(_{50}\) (the MIC at which 50% of the isolates were inhibited) of 0.25 mcg/mL. When considering MIC\(_{90}\) (the MIC at which 90% of the isolates were inhibited), tedizolid was four times more potent than linezolid, with values of 0.25 mcg/mL and 1 mcg/mL, respectively.14

**PHARMACODYNAMICS AND PHARMACOKINETICS**

Using a neutropenic murine *S. aureus* pneumonia model, the mean free drug area under the curve (FAUC) over 24 hours divided by the MIC, or fAUC/MIC ratio, associated with a bacteriostatic endpoint was comparable between tedizolid and linezolid: 20 versus 19, respectively. The average fAUC/MIC ratio for a bactericidal or 1-log unit kill endpoint was about two-fold higher when compared with bacteriostatic endpoints, with no difference between treatment groups (tedizolid, 36.4, and linezolid, 46.1, respectively; \(P = 0.334\)). Moreover, tedizolid has been shown to be bacteriostatic at 24 hours and bactericidal by day 3 of treatment in *S. aureus* isolates.15

A prospective, open-label, multiple-dose study evaluated the pharmacokinetics of tedizolid phosphate 200 mg by mouth (PO) once daily for three days. A total of 20 healthy adult patients completed the study, with an average age of 28 ± 9 years and weight of 82.4 ± 12.5 kg. There was no difference in drug concentrations obtained immediately prior to the third dose and at 24 hours (\(P = 0.947\)), indicating steady-state concentrations. Plasma pharmacokinetic data obtained from bronchoalveolar samples on day 3 revealed a maximum drug concentration (C\(_{max}\)) of 2.4 ± 0.4 mcg/mL, time to C\(_{max}\) (T\(_{max}\)) of two hours (range: 0.5 to 4 hours), terminal half-life (t\(_{1/2}\)) of 8.1 ± 2 hours, and protein binding of 87.3 ± 1.3%. It was also found that tedizolid freely distributes into adipose and muscle tissue following the single dose, with similar levels detected in free plasma concentrations.18

Active tedizolid had a mean total clearance (CL) of 8.28 L/hr and distribution clearance (CLD) of 2.95 L/hr. A central compartment volume (V1) of 71.4 L and peripheral compartment volume (V2) of 27.9 L were reported.10

In summary, according to the prescribing information, peak plasma concentrations are attained within approximately three hours after oral tedizolid therapy and one hour following a tedizolid infusion. The absolute bioavailability is approximately 91% for both formulations, with a reported 70% to 90% plasma protein binding capacity. The volume of distribution at steady state for a single intravenous (IV) dose is on average 67 to 80 L. Tedizolid seems to be an unlikely substrate of the CYP450 enzymes. However, a majority of the compound is hepatically eliminated.11 Table 5 compares the pharmacokinetic parameters of tedizolid phosphate and linezolid.

**PIVOTAL CLINICAL TRIALS**

**Phase 2 Trial**

Prokocimer et al. conducted a randomized, double-blind, dose-ranging study involving tedizolid phosphate at 12 U.S. sites. Eligible patients had to be 18 to 75 years old with complicated skin and skin structure infection (cSSSI) and a suspected or confirmed gram-positive pathogen. Types of infections included were deep extensive cellulitis, abscesses, and surgical or post-traumatic wounds.10

<table>
<thead>
<tr>
<th>Table 4 Comparison of Tedizolid vs. Linezolid-Resistant <em>Staphylococcus</em> coagulase-negative or <em>S. aureus</em></th>
<th>MIC Range (mg/L)</th>
<th>Resistant Strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative <em>staphylococci</em></td>
<td>Tedizolid: 0.06 to 16</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Linezolid: 8 to &gt; 128</td>
<td>100</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Tedizolid: 0.5</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Linezolid: 8 to 16</td>
<td>100</td>
</tr>
</tbody>
</table>
The main difference between cSSSI and ABSSSI is a distinguishing factor of lesion size present with the latter.

Patients were randomized in a 1:1:1 ratio to receive 200, 300, or 400 mg of oral tedizolid phosphate daily for five to seven days. The primary objective was clinical response rates in each group at the test-of-cure visit in the clinically evaluable (CE) and clinical modified-intent-to-treat (cMITT) populations. A total of 188 patients were included in the modified intent-to-treat (MITT) and cMITT analysis (200-mg group, n = 63; 300-mg group, n = 63; 400-mg group, n = 62). The most common pathogen isolated was S. aureus (90.3%), with a majority identified as MRSA strains (80.6%). Patients were treated for an average of 6.4 days. The clinical response rates were similar in all dosing arms: MITT, 87.8%; CE, 95.7%; microbiologically evaluable, 96.2%. Data trends were also similar irrespective of lesion type or size and infection severity.10

Phase 3 Trials

**ESTABLISH-1**

The efficacy and safety of tedizolid phosphate versus linezolid in ABSSSI were evaluated in a multicenter, randomized, double-blind, double-dummy, noninferiority, phase 3 trial. Patients had to be 18 years of age or older with cellulitis/erysipelas, major cutaneous abscess, or wound infection. Along with erythema and a total lesion area of at least 75 cm², patients also had to have at least one local, regional, or systemic sign of infection and a documented or suspected gram-positive bacterium. Patients were excluded if they had an uncomplicated ABSSSI, a vascular catheter site–associated ABSSSI, thrombophlebitis, or surgery other than clean surgery; if they received any other topical or systemic antibiotics with similar spectrum of activity within 96 hours of the first dose of study drug; or if they previously failed therapy at the same infection site. Eligible patients were randomized on a 1:1 basis to receive either tedizolid phosphate 200 mg PO once daily for six days or linezolid 600 mg PO twice daily for 10 days. The primary endpoint was an early clinical response irrespective of lesion type or size and infection severity.11

A total of 667 patients were randomized to tedizolid phosphate (n = 332) or linezolid (n = 335). The median age was 43 years (range: 18 to 100 years). A majority of patients had cellulitis/erysipelas (41.1%) versus major cutaneous abscess (29.7%) or wound infections (29.2%). S. aureus was the most common pathogen detected, with MRSA isolated in both tedizolid phosphate (42.1%) and linezolid (43.1%) groups. Treatment response rates were similar at the 48- to 72-hour assessment in those taking tedizolid phosphate (79.5%; 95% confidence interval [CI], 74.8 to 83.7%) and linezolid (79.4%; 95% CI, 74.7 to 83.6%). Noninferiority was achieved with an absolute treatment difference of 0.1% (95% CI, –6.1 to 6.2%). Sustained clinical success rates at the end of treatment using the ITT data were comparable between the tedizolid phosphate (69.3%; 95% CI, 64 to 74.2%) and linezolid (79.1%; 95% CI, 66.6 to 80.2%) groups (absolute treatment difference, –2.6%; 95% CI, –9.6 to 4.2%). Similar trends were noted in clinical responses assessed by investigators.12

**ESTABLISH-2**

A subsequent randomized, double-blind, parallel-group, noninferiority phase 3 trial evaluated the use of IV tedizolid phosphate or linezolid with an option to switch to oral therapy. Patients had to be 12 years of age or older with a minimum lesion area of 75 cm², a documented or suspected gram-positive infection, and at least one regional or systemic sign of infection. The margin of abscess or wound, if present, had to extend 5 cm or more from the abscess and wound, induration, erythema, or edema. Exclusion criteria were analogous to the ESTABLISH-1 trial. Eligible patients received randomly, in a 1:1 ratio, IV tedizolid phosphate 200 mg once daily for six days or IV linezolid 600 mg twice daily for 10 days. Patients who received at least two doses of therapy were eligible to switch to oral therapy if they met at least two of the following criteria: no increase in lesion size compared with baseline, temperature of 37.7°C or less, or absence of worsening signs and symptoms of the affected area. Additional therapy to broaden coverage for gram-negative or anaerobic bacteria was permitted for wound infections at the discretion of the investigator. The primary outcome was early clinical response 48 to 72 hours following the initiation of treatment. Treatment responders were defined as patients who had a 20% or more reduction in the primary lesion from baseline, did not receive any other systemic antibiotic therapy with overlapping gram-positive activity, and did not die from any cause within 72 hours of receiving the first dose of study drug.13

A total of 666 patients received either tedizolid phosphate (n = 332) or linezolid (n = 334). There was no difference in baseline characteristics between the groups. The median age of patients receiving tedizolid phosphate was 46 years (range: 17 to 86). Cellulitis or erysipelas accounted for a majority of the ABSSSIs (tedizolid phosphate, n = 166, 50%; linezolid, n = 168, 50%). Other reported infections included major cutaneous abscess (tedizolid phosphate, n = 68, 20%; linezolid, n = 68, 20%) and infected wounds (tedizolid phosphate, n = 98, 30%; and linezolid, n = 98, 29%). Approximately 59.5% of the study population had at least one gram-positive organism identified at baseline (tedizolid phosphate, n = 197, 59%; linezolid, n = 202, 60%). At 81.5%, S. aureus was the most common organism identified (tedizolid phosphate, n = 158, 80%; linezolid, n = 167, 83%), with 27.5% being MRSA isolates and 54% MSSA isolates. Other gram-positive bacteria identified were beta-hemolytic streptococci, Group A streptococcus, and Enterococcus species (7.1%), including 13% of MRSA strains.

### Table 5 Mean (Standard Deviation) Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tedizolid Phosphate</th>
<th>Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>2.2 ± 0.6</td>
<td>21.2 ± 5.78</td>
</tr>
<tr>
<td>Tmax (hours)</td>
<td>3.5 (1.0 to 6.0)¹</td>
<td>1.03 ± 0.62</td>
</tr>
<tr>
<td>T1/2 (hours)</td>
<td>12</td>
<td>5.4 ± 2.06</td>
</tr>
<tr>
<td>Clearance (L/hr)</td>
<td>8.4 ± 2.1</td>
<td>4.8 ± 1.74</td>
</tr>
<tr>
<td>AUC (mcg*hr/mL)</td>
<td>25.6 ± 8.4</td>
<td>138 ± 42.1</td>
</tr>
</tbody>
</table>

¹ Median (range)

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**Tedizolid Phosphate11** (200 mg PO once daily)

**Linezolid8** (600 mg PO twice daily)
**SAFETY PROFILE**

**Adverse Events**
Tedizolid phosphate was well tolerated following the oral administration of a once-daily 200-mg dose for three days. No serious adverse events (AEs) were reported; the most commonly reported AEs were mild bradycardia (n = 2), headache (n = 1), and nausea (n = 1). In the ESTABLISH-1 trial, the most common AEs associated with tedizolid phosphate were gastrointestinal in nature (nausea, vomiting, and diarrhea), although they occurred at a lesser incidence than with linezolid (15.7% for tedizolid phosphate vs. 24.8% for linezolid). Headaches were also reported (6.3% for tedizolid phosphate vs. 5.1% for linezolid). The rates of serious AEs were low in both arms. However, ala-

**Dosage and Administration**
Based on the findings of the dose-ranging study conducted by Prokocimer et al., the recommended dose for tedizolid phosphate in adult patients (18 years of age or older) is 200 mg once daily either orally or intravenously for six days. Dosage adjustments are not necessary for patients with hepatic impairment, renal impairment, or undergoing hemodialysis.

**Special Populations**
Tedizolid phosphate is classified as pregnancy category C. Animal data have shown the potential to induce toxic effects on fetal development. In rats, tedizolid was excreted in breast milk.

**Drug–Drug and Drug–Food Interactions**
Tedizolid phosphate is available as 200-mg tablets in a unit dose blister pack of six tablets or a bottle of 30 tablets. It is also available as a 200-mg single-use vial for injection. The average wholesale prices for six days of oral versus IV therapy are $2,212 and $1,692, respectively.

**P&T Committee Considerations**
Tedizolid phosphate has demonstrated good activity against clinically relevant gram-positive organisms such as MRSA. Potential advantages with the available data include enhanced potency, longer half-life, weak and reversible inhibition of MAO enzymes, and an improved safety profile when compared to linezolid. Although several agents with a similar spectrum of activity are currently available (Table 2), tedizolid phosphate may have a role in treating infections involving antimicrobial resistance. Additional efficacy and safety data are needed before P&T committees can delineate its specific role in clinical practice and make a formulary decision.

**Conclusion**
Tedizolid phosphate is a novel second-generation oxazolidinone with activity against clinically relevant gram-positive organisms. It has recently been approved

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**Drug Forecast**

Streptococcus agninus group, and Enterococcus facialis. The mean time to switch to oral therapy was similar between groups (tedizolid phosphate, 1.7 ± 1.18 days; linezolid, 1.8 ± 1.35 days, P = 0.99). There were also no statistically significant differences in the mean durations of IV treatment, which for the U.S. were 2.2 ± 2.17 days and 2.0 ± 2.03 days with tedizolid phosphate and linezolid, respectively. However, there was a disparity between patients managed outside the U.S., suggesting different clinical practices overseas. Only 18% of patients received IV study drug for the entire treatment duration. Early clinical response at 48 to 72 hours was achieved in 85% (n = 283) of patients receiving tedizolid phosphate and 83% (n = 276) of patients receiving linezolid therapy. Thus, non-inferiority was attained with an absolute difference of 2.6% (95% CI, -3.0 to 8.2).

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for the management of ABSSSIs in adults. Additional data are needed on the safety of this therapy when used in the setting of neutropenia and on coadministration with serotonergic agents. As studies continue, it will also be interesting to see the effectiveness of tedizolid phosphate in other indications such as nosocomial pneumonias (NCT02019420).  

REFERENCES


