An acute bacterial skin and skin-structure infection (ABSSSI) is a bacterial infection of the skin with a lesion size of ≥75 cm², which is measured by the area of redness, edema, or induration. The types of infections that comprise ABSSSIs include cellulitis or erysipelas, major cutaneous abscesses, and wound infections; these infections can be life-threatening and may require hospitalization and surgery.

Streptococcus pyogenes and Staphylococcus aureus, including methicillin-resistant S aureus (MRSA), are the most common bacterial pathogens responsible for ABSSSIs. The less common ABSSSI-causing pathogens include other Streptococcus species, Enterococcus faecalis, and gram-negative bacteria. In the United States, more than 2 million individuals are infected with antibiotic-resistant bacteria annually, and at least 23,000 die annually as a direct result of these infections.

Cellulitis, a skin infection that is primarily attributed to streptococci, is most often caused by Streptococcus and Staphylococcus; however, the incidence of MRSA as the cause of cellulitis is increasing. The prevalence rate of leg erysipelas or cellulitis, which can occur anywhere on the body but usually affects the lower leg, is estimated to be more than 1 per 1000 persons annually.

S aureus, particularly MRSA, is associated with major health complications and mortality. Furthermore, S aureus infections are particularly challenging to treat because of their potential for resistance to antimicrobial drugs. In addition, S aureus imposes a substantial economic burden on patients and on hospitals. In intensive care units, an estimated 59.5% to 64.4% of S aureus strains are methicillin-resistant. A study sponsored by the Centers for Disease Control and Prevention (CDC) showed that S aureus–related hospitalizations increased 62% between 1999 and 2005, and MRSA-related hospitalizations more than doubled during this period. Furthermore, S aureus–related deaths averaged 10,800 and MRSA-related deaths averaged 5500 annually.

Most MRSA infections involve ABSSSI. MRSA continues to be a major public health concern in the United States. According to the CDC, an estimated 75,309 individuals in the United States are infected with invasive MRSA infections annually. Despite its high incidence, life-threatening, hospital-acquired MRSA infections declined 54% between 2005 and 2011, with 9000 fewer MRSA-associated deaths among hospitalized patients in 2011 than in 2005.

Recent evidence indicates that community-acquired MRSA strains are spreading into healthcare institutions. Consequently, there is an urgent need to reduce the inappropriate use of antimicrobial agents and to increase awareness about MRSA in the community setting, including in daycare centers, schools, and environments with at-risk individuals (eg, the elderly, immunodeficient persons).

More expensive to treat than susceptible infections, antimicrobial drug-resistant infections are associated with a 30% to 100% increase in mortality, illness, and direct costs. In a study that assessed 1,472,965 hospitalization episodes, of which 23,026 had skin and skin-structure infections as a secondary diagnosis, patients with skin and skin-structure infections had significantly (5 days) longer hospital stays, a higher mortality rate (5.4% vs 3.5%, respectively), and higher (excess of >$21,000) hospital costs compared with matched controls.

The management of ABSSSIs presents several challenges. For example, aside from its link to drug-resistant gram-positive pathogens, an ABSSSI often requires antimicrobial or antibiotic therapy. Antibiotic resistance and adverse effects may limit the use of some antibiotic agents—factors that underscore the need for novel therapies to help combat drug-resistant pathogens.

Tedizolid Phosphate: A New Treatment Option for ABSSSIs

On June 20, 2014, the US Food and Drug Administration (FDA) approved tedizolid phosphate (Sivextro; Cubist Pharmaceuticals) for the treatment of adults with an ABSSSI that is caused by designated susceptible bacteria. To reduce the development of drug-resistant bacteria
Based on its designation as a qualified infectious disease drug for the treatment of serious or life-threatening infections, tedizolid phosphate was also granted an additional 5-year exclusivity period in addition to its currently specified exclusivity period.

“We still have a great deal more work to do to combat antibiotic resistance and ensure we have the tools necessary to help the patients who need it the most.”

Tedizolid phosphate was approved by the FDA under its expedited review process. Based on its designation as a qualified infectious disease drug for the treatment of serious or life-threatening infections, tedizolid phosphate was also granted an additional 5-year exclusivity period in addition to its currently specified exclusivity period.12

**Dosing and Administration**

Tedizolid phosphate is available in 2 dosage forms—as a 200-mg, sterile, lyophilized powder in a single-use vial for reconstitution for intravenous (IV) infusion, and as a 200-mg tablet.13

The oral tablet of tedizolid phosphate is administered once daily for 6 days, and the IV infusion is administered once daily for 1 hour for a duration of 6 days.13

**Mechanism of Action**

Tedizolid phosphate is the prodrug of tedizolid, which is a member of the oxazolidinone class of antibacterial agents.13 Tedizolid’s antibacterial activity is mediated by binding to the 50S subunit of the bacterial ribosome, resulting in the inhibition of protein synthesis. Tedizolid inhibits bacterial protein synthesis through a mechanism of action different from that of other nonoxazolidinone classes of antibacterial drugs; therefore, cross-resistance between tedizolid and other classes of antibacterial drugs is unlikely. The results of in vitro time-kill studies show that tedizolid is bacteriostatic against enterococci, staphylococci, and streptococci.13

**Key Clinical Studies**

The safety and efficacy of tedizolid phosphate were evaluated in 2 multicenter, multinational, double-blind, non-inferiority clinical trials that involved 1315 adults with ABSSSIs.2,15 In both studies, tedizolid 200 mg once daily for 6 days was compared with linezolid 600 mg every 12 hours for 10 days. Patients with cellulitis or erysipelas, major cutaneous abscess, or wound infection were enrolled in the clinical trials. Patients with wound infections could have received aztreonam and/or metronidazole as an adjunctive therapy for gram-negative bacterial coverage, if needed. The intent-to-treat (ITT) patient population included all randomized patients.2,15

**The ESTABLISH-1 Clinical Trial**

The ESTABLISH-1 clinical trial (Trial 1) showed that tedizolid phosphate 200 mg once daily for 6 days was noninferior to linezolid 600 mg every 12 hours for 10 days in early clinical response (ie, 48-72 hours after initial treatment for an ABSSSI), indicating that tedizolid phosphate may be a useful alternative to linezolid for appropriate patients.2,13

In Trial 1, patients received oral tedizolid phosphate. A total of 323 patients with ABSSSI were randomized to tedizolid phosphate, and 326 patients were randomized to linezolid. The majority (91%) of the patients who received tedizolid phosphate were aged <65 years; the median age was 43 years. In these patients, the overall median surface area of infection was 190 cm².2,13

The infection types included cellulitis or erysipelas (40%), wound infection (30%), and major cutaneous abscess (30%). In addition to the local signs and symptoms of infection, patients were also required to have at least 1 regional or systemic sign of infection at baseline, defined as lymphadenopathy (87% of patients), a temperature of ≥38°C (16%), a white blood cell (WBC) count of >10,000 cells/mm³ or <4000 cells/mm³ (43%), or ≥10% band forms on a WBC differential (4%).2,13

The primary end point of the study was early clinical response, defined as no increase from the baseline lesion area at 48 to 72 hours after the first dose of tedizolid phosphate and an oral temperature of ≤37.6°C, to be confirmed by a second temperature measurement within 24 hours in the ITT population.2,13

The key findings from Trial 1 are shown in Table 1.

**The ESTABLISH-2 Clinical Trial**

In the ESTABLISH-2 clinical trial (Trial 2), tedizolid...
phosphate 200 mg for 6 days was shown to be noninferior to twice-daily linezolid 600 mg for 10 days, demonstrating that tedizolid phosphate may be a useful therapeutic option for the treatment of an ABSSSI in the hospital and the outpatient settings.\textsuperscript{13,15}

In Trial 2, patients could have received oral tedizolid phosphate therapy after a minimum of 1 day of IV tedizolid phosphate therapy. A total of 332 patients with an ABSSSI were randomized to tedizolid phosphate, and 334 patients were randomized to linezolid. The majority (87%) of the patients who received tedizolid phosphate were aged <65 years; the median age was 46 years. The patients’ overall median surface area of infection was 231 cm\textsuperscript{2}.\textsuperscript{13,15}

The infection types included cellulitis or erysipelas (50%), wound infection (30%), and major cutaneous abscess (20%). In addition to the local signs and symptoms of infection, patients were also required to have at least 1 regional or systemic sign of infection at baseline, defined as lymphadenopathy (71% of patients), temperature of ≥38°C (31%), WBC count of >10,000 cells/mm\textsuperscript{3} or <4000 cells/mm\textsuperscript{3} (53%), or ≥10% band forms on a WBC differential (16%).\textsuperscript{13,15}

The primary end point of this study was early clinical response, which was defined as a ≥20% decrease from baseline in lesion area at 48-72 hrs.\textsuperscript{13,15}

### Table 1  Early Clinical Response in the ITT Patient Population: Tedizolid Phosphate versus Linezolid (Trials 1 and 2)

<table>
<thead>
<tr>
<th>Patients/responders</th>
<th>Tedizolid phosphate 200 mg</th>
<th>Linezolid 1200 mg</th>
<th>Treatment difference (2-sided 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1, N</td>
<td>323</td>
<td>326</td>
<td></td>
</tr>
<tr>
<td>• Responders, N (%)</td>
<td>256 (79.3)</td>
<td>258 (79.1)</td>
<td>0.1 (–6.2 to 6.3)</td>
</tr>
<tr>
<td>Trial 2, N</td>
<td>332</td>
<td>334</td>
<td></td>
</tr>
<tr>
<td>• Responders, N (%)</td>
<td>286 (86.1)</td>
<td>281 (84.1)</td>
<td>2.0 (–3.5 to 7.3)</td>
</tr>
</tbody>
</table>

≥20% decrease from baseline in lesion area at 48-72 hrs\textsuperscript{a}\textsuperscript{b}

<table>
<thead>
<tr>
<th>Patients/responders</th>
<th>Tedizolid phosphate 200 mg</th>
<th>Linezolid 1200 mg</th>
<th>Treatment difference (2-sided 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1, N</td>
<td>323</td>
<td>326</td>
<td></td>
</tr>
<tr>
<td>• Responders, N (%)</td>
<td>252 (78.0)</td>
<td>246 (75.5)</td>
<td>2.6 (–4.0 to 9.1)</td>
</tr>
<tr>
<td>Trial 2, N</td>
<td>332</td>
<td>334</td>
<td></td>
</tr>
<tr>
<td>• Responders, N (%)</td>
<td>283 (85.2)</td>
<td>276 (82.6)</td>
<td>2.6 (–3.0 to 8.2)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Primary end point for Trial 1; sensitivity analysis for Trial 2.
\textsuperscript{b}Primary end point for Trial 2; sensitivity analysis for Trial 1.

CI indicates confidence interval; ITT, intent-to-treat.

Source: Sivextro (tedizolid phosphate) prescribing information; June 2014.

### Table 2  Clinical Response at Posttherapy Evaluation: Tedizolid Phosphate versus Linezolid (Trials 1 and 2)

<table>
<thead>
<tr>
<th>Patient population, by trial</th>
<th>Tedizolid phosphate 200 mg, n/N (%)</th>
<th>Linezolid 1200 mg, n/N (%)</th>
<th>Treatment difference (2-sided 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent-to-treat</td>
<td>277/323 (85.8)</td>
<td>279/326 (85.6)</td>
<td>0.2 (–5.3 to 5.6)</td>
</tr>
<tr>
<td>Clinically evaluable</td>
<td>257/270 (95.2)</td>
<td>260/273 (95.2)</td>
<td>–0.0 (–3.9 to 3.7)</td>
</tr>
<tr>
<td>Trial 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent-to-treat</td>
<td>292/332 (88.0)</td>
<td>293/334 (87.7)</td>
<td>0.3 (–0.8 to 3.3)</td>
</tr>
<tr>
<td>Clinically evaluable</td>
<td>268/290 (92.4)</td>
<td>269/280 (96.1)</td>
<td>–3.7 (–7.7 to 0.2)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

Source: Sivextro (tedizolid phosphate) prescribing information; June 2014.
after the end of therapy) in the ITT population and in the clinically evaluable population. Clinical success was defined as the resolution or near resolution of most disease-specific signs and symptoms; the absence or near resolution of systemic signs of infection if present at baseline (eg, lymphadenopathy, fever, >10% immature neutrophils, abnormal neutrophils, abnormal WBC count); and no new signs, symptoms, or complications attributable to an ABSSSI that would require further treatment of the primary lesion (Table 2).2,13,15

Clinical Success, by Baseline Pathogens

Early clinical response by baseline pathogens from the primary infection site or blood cultures for the microbiologic ITT patient population in Trials 1 and 2 are shown in Table 3.2,13,15

Adverse Events

The most common (≥2%) adverse reactions associated with tedizolid phosphate are nausea, headache, diarrhea, vomiting, and dizziness.13 Tedizolid phosphate has no contraindications.

Warnings and Precautions

Patients with neutropenia. The safety and efficacy of tedizolid phosphate in patients with neutropenia (ie, neutrophil counts of <1000 cells/mm3) have not been adequately evaluated. In an animal model of infection, the antibacterial activity of tedizolid was reduced in the absence of granulocytes. An alternative therapy should be considered in patients with neutropenia.13

Clostridium difficile-associated diarrhea. Treatment with antibacterial agents can alter the normal flora of the colon and may permit overgrowth of C difficile, which contributes to the development of C difficile-associated diarrhea (CDAD). Patients who present with diarrhea after taking antibiotics should be evaluated for CDAD. If CDAD is suspected or confirmed, antibacterial medications not directed against C difficile should be discontinued, if possible. Appropriate measures should be instituted as clinically indicated.13

Use in Specific Populations

Pregnancy. No adequate and well-controlled studies were conducted with tedizolid phosphate in pregnant women. Tedizolid phosphate should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.13

Nursing mothers. It is not known whether tedizolid phosphate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tedizolid phosphate is administered to a

<table>
<thead>
<tr>
<th>Baseline pathogen</th>
<th>Tedizolid phosphate 200 mg, n/N (%)</th>
<th>Linezolid 1200 mg, n/N (%)</th>
<th>Tedizolid phosphate 200 mg, n/N (%)</th>
<th>Linezolid 1200 mg, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>274/327 (83.8)</td>
<td>276/339 (81.4)</td>
<td>279/327 (85.3)</td>
<td>273/339 (80.5)</td>
</tr>
<tr>
<td>• MRSA</td>
<td>111/140 (79.3)</td>
<td>112/144 (77.8)</td>
<td>114/140 (81.4)</td>
<td>109/144 (75.7)</td>
</tr>
<tr>
<td>• Methicillin-susceptible S aureus</td>
<td>163/187 (87.2)</td>
<td>166/197 (84.3)</td>
<td>165/187 (88.2)</td>
<td>166/197 (84.3)</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>27/33 (81.8)</td>
<td>18/20 (90.0)</td>
<td>25/33 (75.8)</td>
<td>16/20 (80.0)</td>
</tr>
<tr>
<td>Streptococcus anginosis</td>
<td>22/30 (73.3)</td>
<td>26/28 (92.9)</td>
<td>22/30 (73.3)</td>
<td>25/28 (89.3)</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>6/9 (66.7)</td>
<td>8/10 (80.0)</td>
<td>6/9 (66.7)</td>
<td>7/10 (70.0)</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>7/10 (70.0)</td>
<td>3/4 (75.0)</td>
<td>6/10 (60.0)</td>
<td>1/4 (24.0)</td>
</tr>
</tbody>
</table>

NOTE: Pooled analysis: n = number of patients in the specific category; N = number of patients with the specific pathogen isolated from the ABSSSI population.

a Primary end point of Trial 1.

b Primary end point of Trial 2.

· Baseline bacteremia in the tedizolid arm with relevant pathogens included 2 patients with MRSA, 4 patients with methicillin-sensitive S aureus, 2 patients with S pyogenes, and 1 patient with Streptococcus constellatus; all of these patients were responders at 48 to 72 hours.

ABSSSI indicates acute bacterial skin and skin-structure infection; MITT, microbiologic intent-to-treat; MRSA, methicillin-resistant S aureus.

Source: Sivextro (tedizolid phosphate) prescribing information; June 2014.
nursing woman.13

Pediatric use. The safety and effectiveness of tedizolid phosphate in pediatric patients aged <18 years have not been established.13

Geriatric use. Clinical studies of tedizolid phosphate did not include sufficient numbers of patients aged ≥65 years to determine whether they respond different from younger patients. No overall differences in pharmacokinetics were observed between elderly patients and younger patients.13

Based on its early and sustained clinical response, tedizolid phosphate was shown to be as effective as linezolid for the treatment of an ABSSSI. Tedizolid phosphate is available as an injection for IV use and in tablet form for oral administration.

Conclusion
A new treatment option for ABSSSIs became available in June 2014 when the FDA approved tedizolid phosphate. The safety and efficacy of tedizolid phosphate were evaluated in 2 clinical trials that involved 1315 patients with an ABSSSI. Based on its early and sustained clinical response, tedizolid phosphate was shown to be as effective as linezolid for the treatment of an ABSSSI. Tedizolid phosphate is available as an injection for IV use and in tablet form for oral administration. The most common adverse reactions associated with tedizolid treatment include nausea, headache, diarrhea, vomiting, and dizziness.

References