

# Tedizolid phosphate for the treatment of acute bacterial skin and skin-structure infections: an evidence-based review of its place in therapy

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**Introduction:** Tedizolid phosphate is an oxazolidinone approved for the treatment of acute bacterial skin and skin-structure infections (ABSSSIs) and active against methicillin-resistant *Staphylococcus aureus*.

**Aims:** The objective of this article was to review the evidence for the efficacy and safety of tedizolid phosphate for the treatment of ABSSSI.

**Evidence review:** Approval of tedizolid phosphate for the treatment of ABSSSI was based on the results of two phase III randomized controlled trials, ESTABLISH-1 (NCT01170221) and ESTABLISH-2 (NCT01421511), comparing 6-day once-daily tedizolid vs 10-day twice-daily linezolid. In ESTABLISH-1, noninferiority was met with early clinical response rates of 79.5% and 79.4% in tedizolid and linezolid groups, respectively (difference 0.1%, 95% CI –6.1% to 6.2%, with a 10% noninferiority margin). In ESTABLISH-2, noninferiority was met with 85% and 83% rates of early clinical response in tedizolid and linezolid groups, respectively (difference 2.6%, 95% CI –3.0% to 8.2%). Pooled data from ESTABLISH-1 and ESTABLISH-2 indicated a lower frequency of thrombocytopenia in tedizolid-treated than in linezolid-treated patients.

**Conclusion:** Tedizolid offers the option of an intravenous to oral switch, allows once-daily administration, and presents lower risk of myelotoxicity when a 6-day course is used for the treatment of ABSSSI. Greater economic cost associated with this antibiotic could be offset by its shorter treatment duration and possibility of oral administration in routine clinical practice, although either sponsored or nonsponsored postmarketing observational experience remains essential for ultimately confirming the effectiveness and tolerability of tedizolid outside clinical trials.

**Keywords:** ABSSSI, MRSA, oxazolidinone, *Staphylococcus*, efficacy, safety

## Scope, aims, and objectives

Acute bacterial skin and skin-structure infections (ABSSSIs) are defined as bacterial infections of the skin with a lesion area of at least 75 cm<sup>2</sup>.<sup>1</sup> Their clinical presentation is heterogenous, ranging from mild infections to life-threatening invasive diseases.<sup>1,2</sup> ABSSSIs affect both outpatients and inpatients, and an important increase in ambulatory visits and hospital admissions for ABSSSIs has been observed over the last two decades.<sup>3,4</sup> This reflects increases in incidence and severity of ABSSSI, relying at least in part on population aging and the related expansion of comorbid conditions, which predispose to either development or worsening of ABSSSI.<sup>1,2</sup>

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**Table 1** Core evidence clinical impact summary for tedizolid phosphate for the treatment of ABSSSI

Outcome measure	Evidence	Implications
<b>Disease-oriented evidence</b> Early clinical response	Randomized, double-blind, noninferiority clinical trial	6-day once-daily oral tedizolid noninferior to 10-day twice-daily oral linezolid for ABSSSI; similar results observed when tedizolid and linezolid administered intravenously, with optional oral stepdown
<b>Patient-oriented evidence</b> Safety	Randomized, double-blind, noninferiority clinical trial	Most frequent adverse events in randomised clinical trials nausea and headache; serious adverse events rare; pooled data from ESTABLISH-1 and ESTABLISH-2 indicated lower frequency of thrombocytopenia in tedizolid-treated than linezolid-treated patients
<b>Economic evidence</b> Net benefit	High-level evidence still unavailable, although potential saving over linezolid for the treatment of ABSSSI has been suggested in a simulated cohort	Economic analyses warranted to optimize the use of tedizolid and maximize its advantages for treatment of ABSSSI (eg, short duration of treatment, activity against some linezolid-resistant MRSA isolates, reduced toxicity)

**Abbreviations:** ABSSI, acute bacterial skin and skin-structure infection; MRSA, methicillin-resistant *Staphylococcus aureus*.

The severity of ABSSSI also depends on the causative agent, with methicillin-resistant *Staphylococcus aureus* (MRSA) being among the most feared pathogens, not only for its well-known association with the development of invasive infection but also because of the production of Pantone–Valentine leucocidin by community-acquired MRSA strains.<sup>5,6</sup> Notably, the prevalence of MRSA among *S. aureus* isolates from ABSSSI may exceed 25% in some endemic countries.<sup>7</sup> Consequently, anti-MRSA agents are frequently an essential component of the therapeutic approach to ABSSSI.

Tedizolid phosphate (previously known as R701, DA7218), a prodrug of tedizolid (previously TR700, DA7157), is a novel oxazolidinone approved for the treatment of ABSSSI and active against MRSA.<sup>8,9</sup> In this review, we discuss its antimicrobial and pharmacological properties, as well as the available efficacy and safety data (Table 1).

## Methods

A Medline/PubMed search was conducted using various combinations of keywords and MeSH terms: “tedizolid”, “TR-701”, “DA-7218”, “DA-7158”, and “bacterial skin infection”. Then, pertinent full texts, as well as abstracts and posters presented at the most recent international congresses, were evaluated and discussed, and ultimately summarized in a narrative presentation of the topic based on the highest-available level of evidence, divided into sections: mechanism of action, drug formulation and dosing, in vitro antimicrobial activity, pharmacokinetics and

pharmacodynamics, efficacy in clinical studies, safety in clinical studies, potential place in therapy of tedizolid phosphate for the treatment of ABSSSI, and conclusion.

## Mechanism of action

Tedizolid exerts its bacteriostatic activity by inhibiting bacteria protein synthesis through binding of the 23S ribosomal RNA of the 50S subunit.<sup>10</sup> The chemical structure of tedizolid is similar to linezolid. Both are synthetic molecules containing an oxazolidinone ring (ring A) and a lateral chain at C5, which potentiates their activity against some Gram-positive bacteria and mycobacteria.<sup>11</sup>

The major chemical difference between the two compounds lies in the fact that tedizolid has a hydroxymethyl group in the lateral chain that is responsible for its activity against some bacterial strains with the *cfr* gene.<sup>12</sup> Moreover, tedizolid has a *para*-oriented ring structure (D-ring), which increases the number of binding sites with the peptidyl transferase center, thus enhancing its potency with respect to linezolid.

## Drug formulation and dosing

Tedizolid has a double formulation for both oral and intravenous routes, which are nearly equivalent. Due to a prolonged half-life of more than 10 hours, tedizolid only needs to be administered once daily, and the recommended adult dose of tedizolid for its approved indication is 200 mg (regardless of the route of administration) for 6 days. No dose adjustments are required in patients with hepatic

and/or renal impairment or in those undergoing hemodialysis.<sup>11</sup>

## In vitro antimicrobial activity

Tedizolid exerts potent in vitro activity against a wide spectrum of Gram-positive bacteria, including MRSA, methicillin-resistant *S. epidermidis*, and vancomycin-resistant enterococci<sup>13,14</sup>. In a recently published study by Karlowsky et al, tedizolid displayed four fold more potent in vitro activity against *S. aureus* (both methicillin-susceptible and methicillin-resistant strains) than linezolid.<sup>15</sup> Similarly, tedizolid and linezolid minimum inhibitory concentrations (MICs) of MRSA isolates from ABSSTIs were 0.125–0.5 mg and 0.25–4 mg/L, respectively.<sup>16</sup> In another study involving 150 MRSA isolates, tedizolid MICs were two- to five fold lower than those of linezolid.<sup>17</sup> Similar results were observed against enterococci,<sup>18</sup> as also testified by another study in which the in vitro activity of tedizolid was higher than that of linezolid against 302 MRSA isolates and 220 vancomycin-resistant enterococci.<sup>19</sup>

Reduced susceptibility to tedizolid is rare, with MICs >1 mg/L having been observed in only nine cases among a collection of 1,231 Gram-positive isolates.<sup>20</sup> This possibly relies on the fact that in contrast to linezolid, tedizolid largely retains in vitro activity against Gram-positive bacteria harboring the *cfr* gene–encoded methylase enzyme.<sup>21,22</sup> On the other hand, chromosomal mutations in domain V of rRNA or ribosomal L3 or L4 proteins have been reported to confer resistance to both linezolid and tedizolid.<sup>11,23</sup> An additional resistance mechanism has been found in enterococci, owing to the presence of an ABC transporter codified by the *optrA* gene carried by plasmids, which confers resistance to phenicols and oxazolidinones.<sup>24</sup>

Of note, tedizolid also displays in vitro activity against *Clostridium difficile* and *Bacteroides fragilis*.<sup>25,26</sup> In addition, tedizolid shows more potent in vitro activity than linezolid against the most common species of *Nocardia* and some species of nontuberculous mycobacteria, including *Mycobacterium avium* complex, *M. abscessus*, *M. fortuitum*, *M. marinum*, *M. chelonae*, and *M. kansasii*.<sup>27,28</sup>

## Pharmacokinetics and pharmacodynamics

Oral tedizolid phosphate is converted into its active moiety, tedizolid, though apical alkaline phosphatases, which allows intestinal absorption.<sup>29</sup> Tedizolid exhibits excellent bioavailability (about 92%), although lower values of 83%–86% have been reported in Chinese and Japanese patients.<sup>11</sup> Pharmacokinetics of tedizolid after intravenous

administration are similar to those following oral administration, and thus no dose adjustments are needed when switching routes.<sup>30</sup>

Tedizolid shows a high volume of distribution (67–80 L following a single dose, double to triple that of linezolid), and its binding to plasma proteins is 70%–90%.<sup>31,32</sup> Tedizolid has a long half-life of 12 hours, and steady-state concentrations are achieved in 3 days.<sup>33,34</sup> Metabolism of tedizolid occurs mostly in the liver, and the major, largely inactive metabolite isolated from feces and urine (82% and 18%, respectively) is tedizolid sulfate.<sup>35</sup> Pharmacokinetic parameters of tedizolid are summarized in Table 2.

With regard to special patient populations, no particular differences are observed in pharmacokinetic parameters between adults and adolescent individuals (12–17 years), while no data are available for tedizolid phosphate in subjects younger than 12 years.<sup>36</sup> Pharmacokinetic parameters of tedizolid are also similar between nonobese and both obese (body-mass index  $\geq 30$  kg/m<sup>2</sup>) and severely obese patients (body-mass index  $\geq 35$  kg/m<sup>2</sup>), and thus no dosage adjustments are needed in such populations.<sup>37</sup>

Based on available murine infection–model data, tedizolid activity correlates best with AUC:MIC ratios and may be reduced in the setting of granulocytopenia.<sup>38</sup> In a Monte Carlo simulation based on pharmacokinetic parameters in humans, the probability of reaching an AUC<sub>0–24</sub>:MIC ratio of 3 was nearly zero for MICs  $\geq 2$  mg/L and >98% for MICs  $\leq 0.5$   $\mu$ g/mL.<sup>11</sup>

**Table 2** Mean (SD) tedizolid pharmacokinetic parameters

<b>Dose</b>	200 mg OD IV/PO
<b>C<sub>max</sub> (mg/L) IV</b>	3±0.7
<b>C<sub>max</sub> (mg/L) PO</b>	2.2±0.7
<b>t<sub>1/2</sub>, hours</b>	12
<b>AUC (mg*h/L) IV</b>	29.2±6.2
<b>AUC (mg*h/L) PO</b>	25.6±8.5
<b>Protein binding</b>	70%–90%
<b>Excretion</b>	Inactive metabolite 80% in feces 20% in urine
<b>Need for renal adjustment</b>	No
<b>Need for hepatic adjustment</b>	No

**Abbreviations:** C<sub>max</sub>, maximum serum concentration at steady state; OD, once daily; PO, per os (orally); t<sub>1/2</sub>, half-life; AUC, area under the curve at steady state.

## Efficacy in clinical studies

The efficacy of tedizolid phosphate for the treatment of complicated SSSIs was initially evaluated in a phase II, double-blind, randomized trial in which the drug was administered for 5–7 days at once-daily dosages of 200, 300, and 400 mg.<sup>39</sup> The registered clinical cure rates on the test of cure in the clinically evaluable population (n=164) were 98.2%, 94.4%, and 94.4% in patients treated with daily dosages of 200, 300, and 400 mg, respectively. In patients with isolation of *S. aureus* at baseline, clinical cure rates were 96.6% overall and 96.8% when only patients with MRSA infection were considered.<sup>39,40</sup> The approval of tedizolid phosphate for the treatment of ABSSSI by the US Food and Drug Administration in 2014 and the European Medicines Agency through the Committee for Medicinal Products for Human Use in 2015 was based on the results of two phase III randomized controlled trials: ESTABLISH-1 (NCT01170221) and ESTABLISH-2 (NCT01421511).<sup>8,9</sup>

ESTABLISH-1 was a phase III, randomized, double-blind, noninferiority trial comparing 6-day once-daily oral tedizolid vs 10-day twice-daily oral linezolid for ABSSSI, with early clinical response at 48–72 hours as the primary outcome measure. In the intent-to-treat (ITT) population, 332 patients were randomized to receive tedizolid and 336 to receive linezolid. Noninferiority was met by with clinical response rates of 79.5% and 79.4% in the tedizolid and linezolid groups, respectively (difference 0.1%, 95% CI –6.1% to 6.2%, with a 10% noninferiority margin). Of note, response rates at 7–14 days after the end of treatment were similar between tedizolid-treated and linezolid-treated patients with MRSA infection (85.2% vs 85.6%, respectively).<sup>9</sup>

ESTABLISH-2 was another phase III, randomized, double-blind, noninferiority trial comparing 6-day once-daily tedizolid vs 10-day twice-daily linezolid for ABSSI, again with early clinical response at 48–72 hours as the primary outcome measure and a 10% noninferiority margin. However, in this study tedizolid and linezolid were administered intravenously, with optional oral stepdown. In the ITT population, 332 patients received tedizolid and 334 linezolid, with 85% and 83% rates of early clinical response, respectively (difference 2.6%, 95% CI –3.0% to 8.2%). Rates of early clinical response in patients with MRSA infection were 83% (44 of 53) and 44 of 56 (79%) in the tedizolid and linezolid groups, respectively (difference 4.4%, 95% CI –10.8% to 19.5%).<sup>8</sup>

Some post hoc subgroup analyses have also been performed. In intravenous drug users from ESTABLISH-1 and ESTABLISH-2 (pooled ITT population), early clinical response rates were similar in the tedizolid and linezolid groups: 82.5% (151 of 183) and 79.6% (164 of 206), respectively (difference 2.9%, 95% CI –4.9% to 10.7%). Similar rates of early clinical response were also observed in the tedizolid (391 of 481, 81.3%) and linezolid (367 of 463, 79.3%) groups in non-intravenous drug users.<sup>41</sup> Another post hoc analysis found similar efficacy of tedizolid and linezolid in outpatients from the pooled US ITT population of ESTABLISH-1 and ESTABLISH-2. Early clinical response was 84.2% and 79.0% in 403 tedizolid-treated and 410 linezolid-treated outpatients, respectively (difference 3.4%, 95% CI –2.1% to 8.8%).<sup>42</sup>

A post hoc analysis was performed in the subgroups of patients of Latino and non-Latino origin from the pooled ITT population. In patients of Latino origin, rates of early clinical response were 80.2% (146 of 182) and 81.9% (140 of 171) for tedizolid and linezolid, respectively (difference –1.65%, 95% CI –9.88% to 6.65%). Rates of clinical response were also similar in patients of non-Latino origin: 82.2% (396 of 482) for tedizolid and 78.5% (391 of 498) for linezolid (difference 3.64%, 95% CI –1.37% to 8.55%).<sup>43</sup> Finally, similar rates of early clinical response between tedizolid-treated and linezolid-treated patients were observed in different subgroups according to various severity measures, as well as in the subgroups of patients with and without lower-extremity infections.<sup>44,45</sup>

A phase III, randomized, controlled, open-label trial comparing tedizolid and linezolid for the treatment of ABSSSI was also conducted in Japanese patients.<sup>46</sup> Clinical response as an exploratory end point was assessed at 7–4 days after the end of treatment. In the ITT population, clinical response rates were 77.8% (56 of 72) and 80.0% (28 of 35) in tedizolid-treated and linezolid-treated patients, respectively (difference –2.2%, 95% CI –17.4% to 15.8%).<sup>46</sup>

## Safety in clinical studies

The most frequent adverse events in ESTABLISH-1 and ESTABLISH-2 were nausea (8.5% vs 13.4% in tedizolid and linezolid groups, respectively, in ESTABLISH-1; 8% vs 11% in tedizolid and linezolid groups, respectively, in ESTABLISH-2) and headache (6.3% vs 5.1% in tedizolid and linezolid groups, respectively, in ESTABLISH-1; 6% vs 11% in tedizolid and linezolid groups, respectively, in ESTABLISH-2).<sup>8,9</sup> Serious adverse events were rare in



both studies (1.5% vs 1.2% in tedizolid and linezolid groups, respectively, in ESTABLISH-1; 2% vs 3% in tedizolid and linezolid groups, respectively, in ESTABLISH-2).<sup>8,9</sup>

Pooled data from ESTABLISH-1 and ESTABLISH-2 indicated a lower frequency of thrombocytopenia in tedizolid-treated than in linezolid-treated patients, possibly because of the shorter treatment.<sup>47</sup> At the posttherapy evaluation (7–14 days after the end of treatment) the platelet count was  $<150,000$  cells/mm<sup>3</sup> in 4.2% and 7.7% of patients treated with tedizolid and linezolid, respectively (relative risk 0.55, 95% CI 0.33–0.90). Similar results were observed when patients with a baseline platelet count  $<150,000$  were excluded from the analysis (3.0% and 4.5% in tedizolid and linezolid groups, respectively; relative risk 0.66, 95% CI 0.34–1.29)<sup>47</sup>

Marketed oxazolidinones are weak, reversible inhibitors of monoamine oxidase (MAO) *in vitro*.<sup>48</sup> In this regard, the available data suggest a low incidence of serotonergic syndrome in patients treated with tedizolid, although the fact that patients treated with serotonergic agents were excluded from ESTABLISH-1 and ESTABLISH-2 does not allow to completely exclude possible interactions.<sup>48,49</sup> No increase in blood pressure were observed in subjects who concomitantly received tyramine or pseudoephedrine.<sup>48,50,51</sup>

Of note, the reduced inhibitory effect on central nervous system (CNS) monoamine oxidase could be due to the lower CNS penetration of tedizolid compared to linezolid, as observed in rats.<sup>52</sup> Whether or not this could also impair the efficacy of tedizolid in some possible off-label indications (eg, CNS infections) deserves further investigation. Finally, no clinically meaningful ophthalmological or neurological alterations were observed in phase I volunteers receiving tedizolid at supratherapeutic doses for 21 days.<sup>53</sup>

## Potential place in therapy of tedizolid phosphate for the treatment of ABSSSI

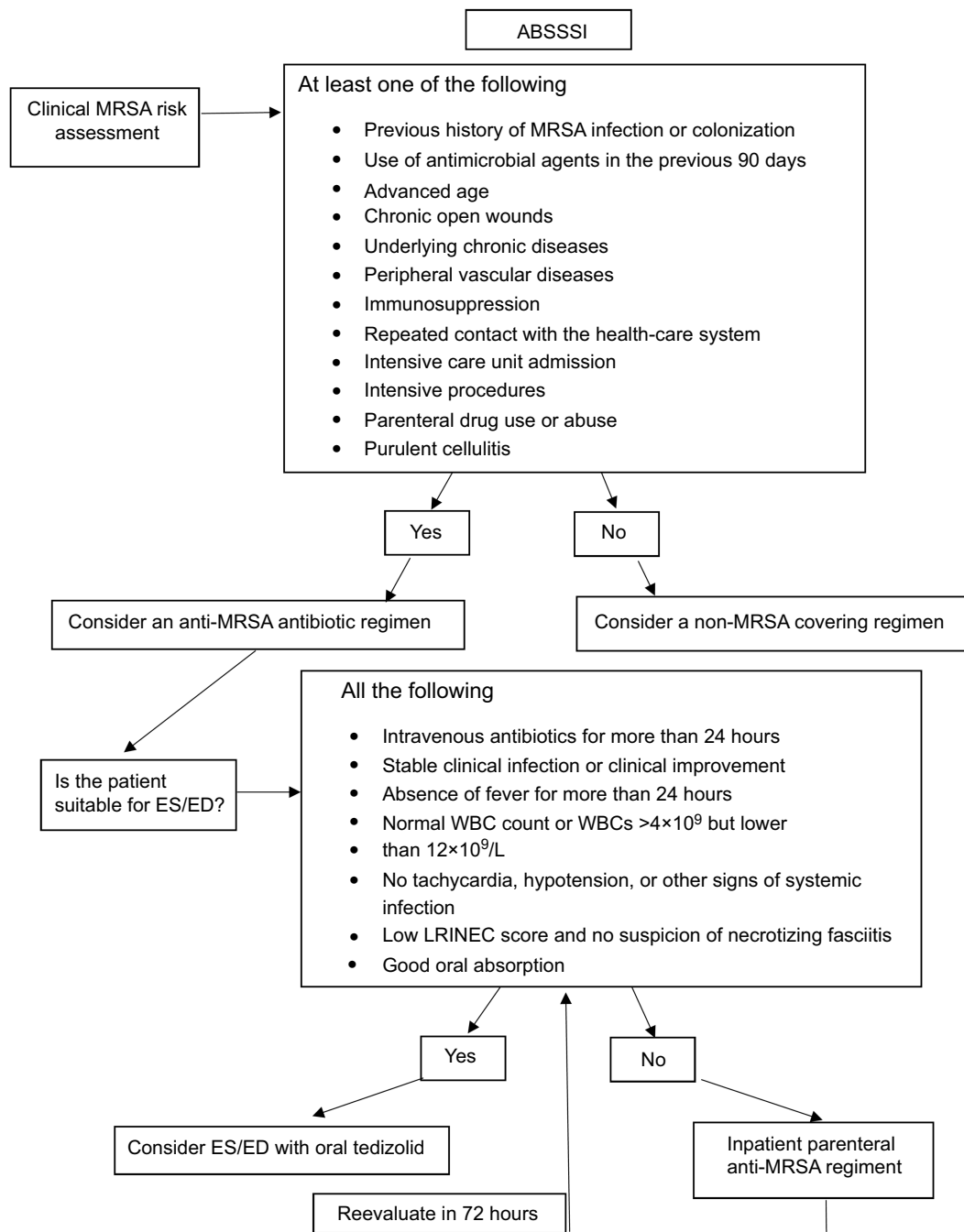
In the presence of less expansive alternatives for the treatment active against MRSA, important considerations should be made to delineate the precise place in therapy for tedizolid in the treatment of ABSSSI, ultimately aiming at maximizing its cost-effectiveness by exploiting its usefulness for early switch to oral therapy and early discharge (a possible algorithm is shown in Figure 1).<sup>54–56</sup> A first important point to be taken into account is the possibility of shorter treatment courses in comparison with other alternatives, including linezolid. In a simulated cohort of 100 inpatients, potential savings of €39,348

were projected by replacing linezolid with tedizolid for the treatment of suspected ABSSSI due to MRSA over a 1-year period.<sup>57,58</sup> Notably, projections became cost-ineffective for simulated tedizolid treatment courses  $\geq 9$  days.<sup>57</sup>

This last consideration introduces another important point worth of discussion, ie, advantages over linezolid may also be conferred by the lower toxicity observed in randomized clinical trials. However, it should be necessarily considered that this advantage, described for approved indications, such as ABSSSI (where a short 6-day course proved noninferior to 10-day linezolid), cannot be automatically extrapolated to off-label indications requiring longer tedizolid treatment courses, since long-term tolerability still has to be comprehensively assessed. Nonetheless, off-label indications certainly warrant further study, due to the undoubted theoretical advantages of less long-term toxicity than linezolid in such infections as osteomyelitis and mycobacterial diseases. In this regard, the available preliminary evidence regarding the use of tedizolid for off-label indications is briefly summarized in Table 3.<sup>59–68</sup> In addition, it is also true that there is no definite proof that a less expensive shorter course (6 days) of linezolid would be less effective than a 6-day course of tedizolid in patients with ABSSSI. Nonetheless, attention should be paid to the fact that the available high-level evidence from randomized controlled trials refers to 6-day tedizolid and 10-day courses of linezolid therapy, and thus no firm conclusion on efficacy and safety can currently be drawn about different treatment durations than those evaluated in randomized controlled trials.

Pending dedicated postmarketing data, the potential for increased risk of oxazolidinone-induced thrombocytopenia should be taken into account when treating patients with chronic liver or kidney failure.<sup>69</sup> On the other hand, the reduced risk of drug–drug interactions with linezolid might allow the use of tedizolid concomitantly with serotonergic or adrenergic agents in selected cases where an oxazolidinone could be considered the optimal choice (eg, possibility of step-down therapy and early discharge).

A recent systematic review and network meta-analysis compared the effectiveness of tedizolid and other antibacterial agents for treating ABSSSI caused by MRSA.<sup>70</sup> Eligible studies were randomized controlled trials conducted in adults with complicated SSSIs or ABSSSIS caused by suspected or documented MRSA, and 15 randomized clinical trials were ultimately selected for inclusion. In fixed-effect models, tedizolid showed superior clinical response to vancomycin at the end of treatment (OR 1.7, 95% CI 1–3), while no



**Figure 1** Potential algorithm for considering tedizolid-based early switch (ES) to oral therapy and early discharge (ED) in patients with ABSSSI.

**Note:** Potential predictors of MRSA and factors indicating suitability for ES/ED have been extrapolated from the literature; data from references 54 and 55.

**Abbreviations:** ABSSSI, acute bacterial skin and skin-structure infection; LRINEC, laboratory risk indicator for necrotizing fasciitis; MRSA, methicillin resistant *Staphylococcus aureus*; WBCs, white blood cells.

appreciable differences were observed between tedizolid and other comparators (tedizolid vs ceftaroline, OR 0.7, 95% CI 0–30.6; tedizolid vs teicoplanin, OR 2.2, 95% CI 0.6–9.0). Consistent results were generally observed in random-effect models. Overall, these results suggest that tedizolid is an important alternative option for the treatment of ABSSSI due to MRSA in adults, although with the inherent

limitations of network meta-analyses, such as quality of included studies, limited data, and publication bias,<sup>71</sup> and also those relying on the different types of SSSIs and outcome definitions in the different trials. Overall, it is likely that precise therapeutic algorithms developed toward a personalized, patient-oriented decision on the best anti-MRSA option on a case-by-case basis will be needed in the future,

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**Table 3** Potential use of tedizolid in off-label indications and related preliminary evidence

Off-label indication	Evidence
Pneumonia	<ul style="list-style-type: none"> <li>• A noninferiority phase III, randomized, double-blind, double-dummy, controlled clinical trial (NCT02019420) comparing once-daily intravenous tedizolid (200 mg) vs twice-daily intravenous linezolid (600 mg) for 10 days for the treatment of presumed Gram-positive hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia has been recently completed, and results are awaited.</li> <li>• In neutropenic immunocompetent mice inoculated intranasally with <i>Staphylococcus aureus</i> isolates, simulation of human ELF exposure to tedizolid demonstrated greater bacterial reductions than vancomycin.<sup>62</sup></li> <li>• In a rabbit model of MRSA pneumonia, production of <math>\alpha</math>-toxin and Pantone–Valentine leukocidin was significantly inhibited when rabbits were treated with tedizolid or linezolid compared with vancomycin.<sup>63</sup></li> <li>• Tedizolid and linezolid showed antimicrobial and immunomodulatory properties in a murine model of hematogenous MRSA pulmonary infection.<sup>61</sup></li> </ul>
Osteomyelitis and prosthetic joint infections	<ul style="list-style-type: none"> <li>• A phase II, single-arm, open-label trial evaluating tolerability, safety, and efficacy of oral tedizolid for the treatment of bone and joint infections is ongoing (NCT03009045).</li> <li>• A pilot study investigating tolerance, compliance, and efficacy of tedizolid for <math>\geq 6</math> weeks as monotherapy or in combination for orthopedic device infections caused by Gram-positive cocci is currently recruiting patients (NCT03378427).</li> <li>• A case of successful treatment of VRE prosthetic joint infection has been reported.<sup>66</sup></li> <li>• Although inactive against biofilm-embedded <i>S. aureus</i> infection in the setting of bone and joint infections, tedizolid seems able to prevent biofilm formation.<sup>59</sup></li> <li>• Tedizolid alone or combined with rifampin demonstrated activity in a rat model of MRSA foreign body-associated osteomyelitis, although emergence of rifampin resistance was observed.<sup>65</sup></li> </ul>
CNS infections	<ul style="list-style-type: none"> <li>• A successful 6-month course of tedizolid therapy for CNS nocardiosis in a multiple myeloma patient has been described, without additional myelotoxicity being reported.<sup>64</sup></li> </ul>
Diabetic foot infection	<ul style="list-style-type: none"> <li>• Plasma and tissue exposure observed in hospitalized patients with diabetic foot infections after 200 mg once-daily tedizolid may support further study for this indication.<sup>67</sup></li> </ul>
Catheter-related infection	<ul style="list-style-type: none"> <li>• In a murine model of subcutaneous MRSA and MSSA catheter-related biofilm infection, a better response in terms of decreased <i>S. aureus</i> density and bioluminescent signals after treatment with tedizolid than with linezolid has been observed.<sup>60</sup></li> </ul>
Mycobacterial diseases	<ul style="list-style-type: none"> <li>• Preliminary data on long-term safety in a small sample of 24 patients have been presented in scientific congresses.<sup>68</sup></li> </ul>

**Abbreviations:** CNS, central nervous system; ELF, epithelial lining fluid; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; VRE, vancomycin-resistant enterococci.

in order to identify precisely those patients in whom the advantages of tedizolid are maximized and those in whom the advantages of other alternatives (eg, linezolid, ceftaroline, or options allowing one-dose intravenous administration like dalbavancin or oritavancin) could be preferable.

Finally, it is necessary to mention that either sponsored or unsponsored postmarketing observational experience remains essential for pragmatically confirming effectiveness and tolerability of tedizolid outside clinical trials, both for in-label and off-label indications.

## Conclusion

Optimization of management of ABSSSI should include early switch and early discharge, as well as targeting drug-resistant Gram-positive bacteria, such as MRSA. The new

oxazolidinone tedizolid offers the option of intravenous to oral switch, once-daily administration, and presents multiple advantages over linezolid, including lower risk of gastrointestinal side effects, myelotoxicity, and lower risk of drug–drug interactions with compounds with serotonergic and adrenergic activity. Greater economic cost associated with this antibiotic could be offset by its shorter treatment duration and possibility of oral administration in routine clinical practice. Efforts to expand our clinical knowledge are critical to help practicing physicians determine where this drug fits into the antibiotic armamentarium.

## Disclosure

MB reports grants and personal fees from Pfizer, MSD, and Cidara and personal fees from Astellas and Gilead

outside the submitted work. DRG reports personal fees from Stepstone Pharma GmbH and an unconditional grant from MSD Italia outside the submitted work. The other authors report no conflicts of interest in this work.

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