SUPPLEMENT ARTICLE

Tedizolid Phosphate for the Management of Acute Bacterial Skin and Skin Structure Infections: Safety Summary

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The novel oxazolidinone tedizolid phosphate is in late-stage clinical development. In an effort to improve efficacy and safety, the adverse event profile and safety aspects of tedizolid phosphate have been evaluated in several preclinical animal models and through ongoing clinical trials. Early dose-ranging studies demonstrated a favorable overall adverse event profile and low thrombocytopenia rates, which have been consistently confirmed in phase 2 and 3 clinical trials. Pharmacokinetic modeling suggests a lower potential for monoamine oxidase interaction, and animal and human subject testing has confirmed these predictions. Studies in special patient populations showed a consistent and predictable pharmacokinetic profile across age groups and comorbid conditions, without evidence of increased incidence of adverse effects over matched controls. The favorable safety profile makes tedizolid phosphate an important new option for the management of serious Gram-positive infections, including those caused by methicillin-resistant *Staphylococcus aureus*.

Keywords. tedizolid phosphate; ABSSSI; safety; clinical trials; treatment-emergent adverse events.

Acute bacterial skin and skin structure infections (ABSSSIs) are often caused by aerobic Gram-positive cocci, including *Staphylococcus aureus*, beta-hemolytic streptococci, and certain coagulase-negative staphylococci [1]. Antibiotic-resistant strains, including methicillin-resistant *S. aureus* (MRSA), have become challenging pathogens in both healthcare and community settings across the globe [2]. Recent estimates suggest that >90% of MRSA infections involve ABSSSIs [3]. Today, treatment for MRSA skin infections can begin in a hospital, emergency department, or community setting [4–6]. The latter setting presents unique challenges involving poor patient compliance with complicated dosing schedules and monitoring of potential adverse effects (AEs) during therapy.

Linezolid has become an important antibiotic option for the treatment of ABSSSIs across inpatient and outpatient settings, given its overall efficacy against Gram-positive pathogens, general safety profile, and option for equal-dose intravenous or oral therapy [7, 8]. Although generally safe when used at the recommended dose and duration of therapy, linezolid has been associated with gastrointestinal AEs (including nausea and vomiting), mild reversible inhibition of monoamine oxidase (MAO) activity, reversible myelosuppression (anemia, thrombocytopenia leukopenia, or pancytopenia), and peripheral and central neuropathies [8]. Both myelosuppression and neuropathies have been associated with oxazolidinone-induced impairment of mitochondrial proteins synthesis [9]. AE risk increases with prolonged drug exposure and dosing [8, 10].

Through improved understandings of the structure–function attributes of oxazolidinones [8, 11–13], novel molecule development has been directed to improving the efficacy, safety, and tolerability of agents such as tedizolid. Tedizolid phosphate, a novel oxazolidinone prodrug in late-stage development for ABSSSIs, offers greater

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potency (lower minimum inhibitory concentration) against clinically important pathogens such as MRSA, including those that have developed resistance to linezolid [14] and achieves these goals with a significantly lower daily drug dose than linezolid [7, 8]. Tedizolid, the microbiologically active moiety, also shows a larger intraphagocytic accumulation and improved activity against the intracellular forms of *S. aureus* and *Legionella pneumophila* compared with linezolid [15], an attribute that may contribute to clinical efficacy at lower doses.

EARLY DOSE ESCALATION STUDIES

Although it is anticipated that the duration of tedizolid phosphate treatment for ABSSSIs will be <21 days, a phase 1 dose-ranging study with 21 days of drug exposure was undertaken to fully evaluate the impact of tedizolid phosphate on subject safety [16–18]. This double-blind, placebo-controlled, oral dose escalation trial evaluated the safety, tolerability, and pharmacokinetic profile in healthy adult subjects, compared with a placebo arm and a linezolid arm. The study enrolled 40 male and female subjects who were assigned in treatment cohorts of 10 subjects (2 subjects each were assigned to the 200-, 300-, and 400-mg tedizolid phosphate once-daily drug treatment groups, 2 subjects were assigned to the 600-mg linezolid BID group, and 2 subjects were assigned to the placebo arm). The maximum plasma concentration (C_{max}) and area under the concentration–time curve (AUC) for tedizolid increased in proportion to the administered dose [16]. The elimination half-life (8–11 hours) and volume of distribution for tedizolid were nearly double the values for linezolid, with no evidence for net tedizolid accumulation over time.

Safety assessment included AE reporting; physical, neurologic, and ophthalmologic examinations; electrocardiography; and laboratory evaluations [17, 18]. Treatment-emergent AEs (TEAEs) include AEs that occurred or worsened after the first dose of study medication. The most common AEs reported were gastrointestinal (nausea, stomach discomfort) and were mild to moderate in severity. Subjects taking 200-mg tedizolid phosphate once daily experienced AE rates similar to the placebo-treated population, whereas subjects taking the 400-mg dose experienced higher rates [17]. Reported AEs were mild to moderate for placebo- and tedizolid phosphate–treated subjects, and there were no serious AEs over 21 days of tedizolid phosphate exposure, nor were there significant changes in plasma lactate levels, neurologic or ophthalmologic examinations, or QT intervals [17]. Four subjects discontinued tedizolid phosphate treatment based on protocol-prespecified clinical laboratory thresholds: 2 subjects in the 400-mg arm for low blood cell counts (reticulocytes and white blood cell count, respectively), 1 subject in the 200-mg arm for elevated alanine aminotransferase (5 times the upper limit of normal), and 1 subject in the linezolid arm for decreased reticulocyte counts [17].

When administered at 600 mg twice daily, linezolid is associated with mild and reversible myelosuppressive effects that develop over time [19–21], with increased risk for patients with underlying hematologic abnormalities or renal insufficiency [19, 22]. Whereas early studies with 600-mg twice-daily linezolid demonstrated that patient hemoglobin and neutrophil levels were similar to the control group over 25 days of therapy, platelet counts tended to decline faster than in the comparator arm by 14 days of therapy [19]. In the phase 1 tedizolid study, there were no significant hematologic changes at any dose tested (200–400 mg once daily) during the first 7 days of treatment compared with placebo [18]. Between days 8 and 21, hematologic changes correlated with the dose administered. For individuals receiving 200-mg tedizolid phosphate, hematologic variables remained similar to those in placebo-treated subjects through 21 days, but subjects receiving 300-mg tedizolid phosphate experienced detectable albeit minimal changes compared with placebo over the same time interval. At the 400-mg tedizolid phosphate dose, hematologic changes were similar to those observed for subjects treated with linezolid 600 mg twice daily [18].

EFFECTS RELATED TO MAO ACTIVITY

MAOs are enzymes involved with the metabolism of amines, including several key neurotransmitters or exogenous tyramine. MAO-A, present in nervous tissues, the gastrointestinal tract, liver, and placenta, acts preferentially on norepinephrine and serotonin. MAO-B, present in nervous tissue and platelets, is more directly involved with metabolism of dopamine [23]. The latter activity is important for the maintenance of normal neurotransmitter levels in peripheral and/or central pathways. Oxazolidinones are weak and reversible inhibitors of MAO-A activity [8, 13, 21]. To elucidate MAO-related safety concerns, animal and human testing focused on 2 major aspects of MAO activity: potential interactions with dietary tyramine or sympathomimetic agents, investigating peripheral pressor responses [24, 25]; and potential interactions with selective serotonin reuptake inhibitors (SSRIs) affecting central nervous system neurotransmitter function and leading to excess elevation of serotonin [26]. Early linezolid testing confirmed that therapeutic plasma concentrations of linezolid were associated with blood pressure elevations during a tyramine challenge [24, 25]. Although SSRI and serotonin–norepinephrine reuptake inhibitor interactions were not identified in premarketing clinical trials for linezolid [21], sporadic postmarketing case reports [27] and retrospective chart reviews [28] brought this safety concern to the attention of healthcare providers and regulators. The US Food and Drug Administration has issued warning

letters about the potential for serious reactions associated with concomitant linezolid and SSRI administration [29].

Pressor Response

As weak inhibitors of MAO activity, oxazolidinones can potentiate reversible increases in blood pressure in the presence of adrenergic agents, such as excess dietary tyramine or exogenously administered sympathomimetic agents, or in certain clinical conditions, such as hypertensive diseases, pheochromocytoma, or carcinoid syndrome. Provocative testing in animal models and humans can uncover these potential interactions [22, 30]. To assess the effects of tedizolid phosphate and tedizolid on MAO activity, MAO-A and -B enzyme activity was assessed in vitro, and the blood pressure response to tyramine was evaluated in tedizolid phosphate–pretreated Sprague-Dawley rats [31, 32]. In vitro testing of MAO enzymatic activity revealed that tedizolid and linezolid are both weak and reversible MAO inhibitors with similar potency (on a molar basis), whereas the pro-drug tedizolid phosphate did not inhibit enzyme activity [31, 32]. Absence of an MAO effect of tedizolid phosphate is related to the "masking" effect of the phosphate group against the tedizolid C5 hydroxymethyl group [8].

Although gut MAO-A plays the major role in metabolism of dietary amines, it was anticipated that the absence of MAO activity for tedizolid phosphate would result in no impact on pressor responses caused by dietary or orally administered monoamines. When tested in an animal model, linezolid (50 mg/kg) pretreatment increased blood pressure after tyramine administration, whereas tedizolid phosphate (at doses up to 150 mg/kg) had no effect [31]. Tedizolid phosphate was recently evaluated in humans for MAO interaction in 2 randomized, double-blind, placebo-controlled crossover phase 1 studies [32, 33]. Tedizolid phosphate did not potentiate the rise in blood pressure associated with pseudoephedrine or tyramine, in contrast with the published effects of linezolid in similar studies [24, 25].

Serotonin Toxicity

Serotonin toxicity is a rare event associated with excess levels of serotonin in the central nervous system that can produce a spectrum of clinical symptoms, with severity ranging from mild to life-threatening [26]. In a single-center chart review, Taylor and colleagues retrospectively reviewed the records for patients treated with linezolid plus an SSRI and found that two patients (3%) had symptoms consistent with serotonin toxicity [28]. In animal models, excess serotonin levels are associated with higher-than-normal head-twitch behavior, which can be used to identify potential interactions. In a preclinical study reported by Flanagan and colleagues [32], head twitches were counted in mice administered intraperitoneal linezolid (1× human exposure) or tedizolid phosphate (1×, 3×, 10×, and 30× human exposure) and compared with placebo and positive control (MAO inhibitor [moclobemide] and SSRI [fluoxetine]) groups. Tedizolid phosphate, at exposures up to 30 times the human equivalent therapeutic exposure, did not cause an increased serotonergic response in mice, whereas linezolid, at approximately the human equivalent therapeutic exposure, caused an approximately 4.5 times increase in head-twitch activity over the placebo, an effect similar to that observed in animals treated with an SSRI (fluoxetine).

ADDITIONAL PRECLINICAL STUDIES

As mentioned, tedizolid shows a larger intracellular accumulation than linezolid in phagocytic cells. This may be considered as an advantage when dealing with intracellular infections [10] and has also been proposed as the basis of the increased cidality of tedizolid when tested in the presence of neutrophils [34]. However, it was also feared that this increased accumulation could result from an increased binding to mitochondria, which is the basis for several of the linezolid-induced mid- and long-term toxicities analyzed in this review. Thus, cell fractionation studies were undertaken to assess the subcellular distribution of tedizolid using murine macrophages exposed to both therapeutic and supratherapeutic concentrations and relying on mass-spectrometry methods to detect and quantify tedizolid in the fractions [35]. No stable association with mitochondria was detected, with all measurable cell-associated tedizolid appearing freely soluble, in accordance with what had been described concerning its activity against intracellular bacteria [15]. Preclinical screening studies have revealed no significant P450 interactions for tedizolid (Cubist Pharmaceuticals, unpublished data).

PHASE 2 STUDIES

A randomized, double-blind, phase 2 dose-ranging study evaluated oral tedizolid phosphate in adult outpatients diagnosed with complicated skin and skin structure infections involving a suspected or confirmed Gram-positive pathogen [36]. Eligible infection types included abscess, surgical or posttraumatic wound, and deep extensive cellulitis with clinical signs and symptoms associated with serious infections. The study was conducted at 12 US sites, and patients were randomized to receive 200, 300, or 400 mg of oral tedizolid once daily for at least 5 days but not more than 7 days. Patients who received at least 1 dose of study medication (188 patients) were evaluated for tedizolid safety at screening (day 1); days 2, 3, and 5; at end of therapy; and at a test-of-cure visit 7–14 days after treatment. A late follow-up visit (by phone or in person) occurred between 21 and 28 days after treatment. Safety assessments included vital signs, physical exam, electrocardiography findings (read by a blinded cardiologist), and AEs.

Tedizolid phosphate was well tolerated at all doses studied, and the percentage of patients reporting at least 1 treatment-

Table 1. Most Common Treatment-Emergent Adverse Events (phase 2, modified intent-to-treat population)

Adverse Events	No. of Positive Patients (%) by Tedizolid Phosphate Treatment Group			
	200 mg (n = 63)	300 mg (n = 63)	400 mg (n = 62)	All (n = 188)
Any TEAE	42 (66.7)	44 (69.8)	44 (71.0)	130 (69.1)
GI disorders	19 (30.2)	24 (38.1)	28 (45.2)	71 (37.8)
Common drug-related TEAEs[a]				
Nausea	9 (14.3)	12 (19)	10 (16.1)	31 (16.5)
Diarrhea	7 (11.1)	3 (4.8)	6 (9.7)	16 (8.5)
Vomiting	4 (6.3)	4 (6.3)	5 (8.1)	13 (6.9)
Headache	3 (4.8)	6 (9.5)	3 (4.8)	12 (6.4)

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Abbreviations: AE, adverse event; GI, gastrointestinal; TEAE, treatment-emergent adverse event.

[a] Most common investigator-identified drug-related TEAEs occurring in >5% of patients.

Table 2. Number of Patients[a] Experiencing Treatment-Emergent Adverse Events (phase 3 study population)

Preferred Term	Tedizolid Phosphate 200 mg Once Daily (n = 331) No. (%)	Linezolid 600 mg Twice Daily (n = 335) No. (%)
Patients with at least one TEAE	135 (40.8)	145 (43.3)
Patients with at least one serious TEAE	5 (1.5)	4 (1.2)
Discontinuation for TEAE	2 (0.6)	2 (0.6)

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Abbreviation: TEAE, treatment-emergent adverse event.

[a] Patients reporting a particular adverse event more than once are counted only once.

related AE was similar across all study doses. No patients discontinued treatment because of an AE, and there were no apparent dose-related toxicities. TEAE rates were 69.1% for the overall study population; most TEAEs were reported as mild (72.3%) or moderate (24.6%) in severity [36]. Five patients (2.7%) experienced a serious AE, none of which was considered possibly treatment related. The most common investigator-identified, drug-related AEs were nausea (16.5%), diarrhea (8.5%), vomiting (6.9%), and headache (6.4%), and they occurred with similar frequency across all study doses of tedizolid phosphate (Table 1). Hematologic parameters were unaltered by tedizolid phosphate in this phase 2 trial, consistent with earlier studies in healthy adults demonstrating no changes after 5–7 days of once-daily oral dosing [18].

PHASE 3 STUDIES

Based on a combined evaluation of (1) the in vitro potency of tedizolid against target organisms and pharmacokinetic/pharmacodynamic considerations, (2) the safety data gathered in phase 1 and phase 2 trials, and (3) the clinical efficacy data observed in phase 2, the 200-mg once-daily dose of tedizolid phosphate was selected for further evaluation in 2 phase 3 trials [37]. A recently completed phase 3 trial in adults with ABSSSIs compared the safety profiles of oral tedizolid phosphate and linezolid in adults [38, 39]. The study was designed to determine the early clinical response (noninferiority assessment) for patients receiving either 6 days of 200-mg oral tedizolid phosphate once daily (plus 4 days of placebo) or 10 days of 600-mg oral linezolid twice daily [39]. Patients (n = 666 who were enrolled and received study medication) with a clinical diagnosis of ABSSSI (cellulitis, abscess, or wound) were recruited and randomized 1:1 to the 2 treatment arms. Safety was evaluated for all patients who received ≥1 doses of either tedizolid phosphate or linezolid. Similar to the results from phase 2 studies [36], tedizolid phosphate was well tolerated in the larger phase 3 trial population, with similar percentages of patients in the tedizolid phosphate and linezolid arms experiencing at least 1 TEAE (40.8% and 43.3%, respectively) (Table 2). Most TEAEs were mild to moderate in the tedizolid arm. Commonly reported TEAEs in the tedizolid phosphate and linezolid arms included nausea (8.5% vs 13.4%, respectively), headache (6.3% vs 5.1%, respectively), and diarrhea (4.5% vs 5.4%, respectively). When compared by system organ class, gastrointestinal-related TEAEs were significantly lower in the tedizolid phosphate treated group [39]. No other significant differences were observed in the remaining system organ classes evaluated. The overall incidence of serious AEs was low in both the tedizolid phosphate (1.5%) and linezolid (1.2%) arms. Expanding on the observations from earlier phase 1 [18] and phase 2 trials [36], fewer patients in the tedizolid phosphate treatment group experienced a reduction of platelets below the lower limit of normal, including the subset of patients who began therapy with abnormally low platelet levels [40]. Treatment-emergent elevation of alanine aminotransferase levels (≥2× the upper limit of normal and ≥2× the baseline value) was observed in 4.1% of tedizolid phosphate–treated patients and 3.5% of linezolid-treated patients. Approximately 34% of the study population was positive for the hepatitis C virus. No subjects in either treatment arm had evidence of drug-induced liver toxicity by criteria for Hy's law (3 criteria for identifying drug-induced hepatotoxicity during clinical development [41]), and no patient discontinued the study based on changes in liver enzymes [39].

The second phase 3 trial included intravenous administration of tedizolid phosphate with the option to switch to oral tedizolid phosphate therapy [42], and initial results have recently confirmed a similar safety profile to the ESTABLISH 1 trial findings [43]. Before initiation of this study, the safety and venous tolerability of intravenous tedizolid phosphate infusion was assessed by Muñoz and colleagues in 10 healthy subjects in a double-blind, crossover, placebo-controlled study [44]. Over 3 days of daily 200-mg tedizolid phosphate infusion (over 60 minutes in 250 mL of saline via a 22-gauge catheter), there were no signs of pain, erythema, swelling, induration, or palpable venous cord before or after each infusion, leading to the conclusion that tedizolid phosphate venous tolerability was comparable with placebo infusion.

SPECIAL POPULATIONS

Tedizolid phosphate safety in special patient populations has also been evaluated in a series of phase 1 trials. These studies demonstrated similar pharmacokinetics observed across a wide range of intrinsic factors and indicate that no dose adjustments should be necessary on the basis of age or clearance organ function.

Elderly

Elderly patients represent a growing segment of the general and hospitalized patient population. As populations age, cumulative comorbidities and changes to drug metabolism and tolerance challenge the selection of appropriate antibiotics to treat serious infections [45]. To examine the pharmacokinetics and tolerability of tedizolid phosphate in elderly patients aged ≥65 years, a single-dose (200 mg) evaluation of pharmacokinetic parameters was performed by Dreskin and colleagues [46] and compared with a younger adult population (aged 18–45 years). Patient groups were well matched for sex and body mass index; estimated glomerular filtration rate was lower in the elderly subject group. Geometric mean ratios of C_{max} and AUC revealed slight increases of approximately 9% and 13% in elderly patients. There were no TEAEs or deaths reported. Clinical laboratory evaluations, vital signs, physical exams, and electrocardiography findings showed no clinically significant changes. Overall, tedizolid phosphate was well tolerated in older subjects, and the small pharmacokinetic changes suggest that dose adjustments should not be needed when administering tedizolid phosphate to elderly patients.

Renally Impaired

Chronic renal impairment, a common disorder in aging patients and individuals with diabetes or cardiovascular disease, complicates the management of serious infections [47]. Renal excretion is a minor pathway for the overall elimination of tedizolid (approximately 18% of radiolabeled tedizolid phosphate) [48], which differentiates this oxazolidinone from the major renal elimination route for linezolid (approximately 83% to 84% of total linezolid label; approximately 30% as linezolid) [49], and may provide an important alternative in situations where renal impairment introduces a risk for thrombocytopenia during linezolid therapy [22]. Flanagan and colleagues [50] investigated the safety of tedizolid phosphate in subjects with advanced renal impairment with and without hemodialysis (estimated glomerular filtration rate <30 mL/min). Renally impaired subjects were well matched to the control population for age, sex, and body mass index. The pharmacokinetics (C_{max}, half-life, and AUC) of tedizolid in renally impaired patients were essentially unchanged relative to the matched control group, and hemodialysis did not significantly extract tedizolid from the blood. Only 3 mild AEs (nausea, vomiting, and headache) related to tedizolid administration were reported in renally impaired subjects. The pharmacokinetic results from this study support the suggestion that no dose adjustments should be needed for tedizolid treated patients with severe renal impairment.

Hepatic Impairment

The phase 1 single-dose study of 200-mg oral tedizolid phosphate in subjects with moderate (Child-Pugh score of 7–9) or severe (Child-Pugh score of 10–15) hepatic impairment was recently reported [51]. The individual moderate and severe groups (n = 8 for each) were matched to a control population (n = 16) by age, sex, and body mass index. The overall tedizolid pharmacokinetic profile for patients with moderate and severe hepatic impairment was not markedly altered compared with the control population. The greatest changes observed were in AUC, with approximately 34% higher exposure in the severe hepatic impairment group compared with the control population. Tedizolid phosphate was well tolerated in hepatically impaired subjects, with 5 TEAEs reported by 8 subjects, including diarrhea (2 events), flatulence, transient flushing, and scalp hair growth. Overall the pharmacokinetic data suggest that dose adjustments are unlikely to be needed when treating hepatically impaired patients with tedizolid phosphate.

Adolescents

Tedizolid phosphate 200 mg once daily administered either intravenously or orally (n = 10 in each group) was also investigated by Muñoz and colleagues in adolescents aged 12–17 years [52]. Oral bioavailability of 200-mg tedizolid was 89%, and mean AUC values were within 10% of values previously observed for adults. Six patients experienced mild AEs; no serious AEs or changes in laboratory values were noted. Overall, 200-mg tedizolid was well tolerated in adolescents (aged 12–17 years) when administered intravenously or orally, with similar

pharmacokinetics to those observed in adult subjects. No dose adjustment is anticipated when treating adolescents with tedizolid.

SUMMARY

Based on available clinical and nonclinical data, tedizolid phosphate has revealed several potential clinical advantages over linezolid for the treatment of serious Gram-positive infections, including those caused by MRSA—notably, greater potency and potential clinical efficacy at lower once-daily doses. From a safety perspective, tedizolid phosphate achieves its clinical effects at lower daily doses (200 mg once daily) than are required for linezolid (600 mg twice daily). At the 200-mg dose, phase 1, 2, and 3 studies demonstrated no hematologic abnormalities over the anticipated 6 days of therapy, and out to 21 days of tedizolid phosphate treatment [18, 36, 39], an important distinction to the effect of 600-mg linezolid twice daily over the same time frame.

Tedizolid in circulation has lower potential for MAO inhibition than linezolid given its increased antimicrobial potency and favorable pharmacokinetic profile, and proactive testing demonstrated lack of MAO inhibition in clinical studies at the therapeutic dose of 200-mg tedizolid phosphate or in nonclinical studies at more than approximately 30-fold above the human equivalent therapeutic exposures [33]. Phase 2 and 3 trials are establishing a well-documented favorable overall safety profile for tedizolid phosphate in patients with ABSSSIs, including low AE rates, low probability of drug interactions, and little myelosuppression. For these reasons, tedizolid phosphate provides promising characteristics for the treatment of ABSSSIs encountered in the emergency department [4, 53], hospital [5], and outpatient settings [6] where oral dosing and minimal safety monitoring requirements are paramount for successful clinical outcomes.

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