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Tedizolid Phosphate: A New Antimicrobial Agent Against MRSA

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The incidence of drug resistance among gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) has reached a point in which new antimicrobials agents are urgently needed.[1] According to the Center for Disease Control (CDC), each year more than 2 million Americans develop infections from antibiotic-resistant bacteria.[2] The CDC has identified MRSA as a serious public health threat, and MRSA-related infections continue to be a major clinical and economic burden. Approximately 80,000 severe infections and 11,000 deaths are attributable to MRSA in the U.S. each year.[2] The direct healthcare cost of antibiotic resistance to the U.S. economy has been estimated to be as high as $20 billion annually with additional costs to society for lost productivity as high as $35 billion a year (2008 dollars).[2,3]

According to the Infectious Disease Society of America (IDSA) clinical practice guidelines, the currently preferred antimicrobials for the treatment of MRSA infections are clindamycin, daptomycin, linezolid, quinupristin-dalfopristin, rifampin, telavancin, tetracycline, trimethoprim-sulfamethoxazole (TMP-SMX), ceftaroline, dalbavancin, and vancomycin.[4] These agents are recommended by the IDSA to treat skin and soft tissue infections (SSTIs) and susceptible community-acquired MRSA (CA-MRSA) infections. Although some of these agents do not have U.S. Food and Drugs Administration (FDA)-approved indications for the treatment of MRSA-related infections, they are often used off-label for this type of treatment.[4] These agents are generally efficacious in treating MRSA-related infections, but they have drawbacks, including increasing emergence of non-susceptible isolates associated with treatment failure (e.g., with daptomycin, rifampin, vancomycin, and tetracycline); toxicities and adverse effects (e.g., linezolid and hematologic toxicity; quinupristin-dalfopristin and arthralgias/myalgias; clindamycin and higher rates of *Clostridium difficile* infections than other oral agents; TMP-SMX and hyperkalemia). Furthermore, these agents may not be suitable for certain patient populations (e.g., tetracyclines in younger children) or in certain types of infections (e.g., daptomycin in pneumonia).

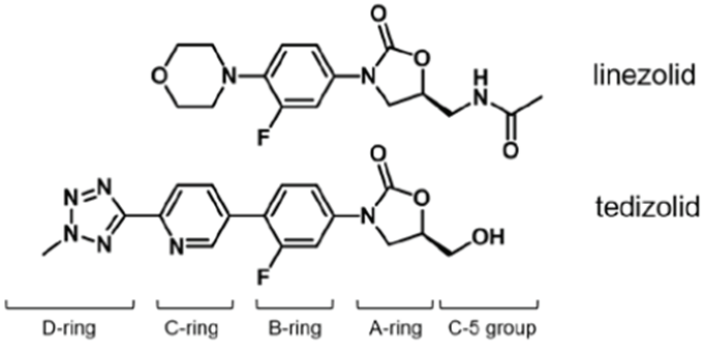

Figure | Linezolid and tedizolid molecular structures.[1,19]

Tedizolid phosphate (Sivextro™), developed by Cubist Pharmaceuticals, Inc. (Lexington, Massachusetts), is a new oxazolidinone antimicrobial being developed for the treatment of acute bacterial skin and skin structure infections (ABSSSI).[1,5] Tedizolid is the first oxazolidinone drug to be developed since linezolid in 2000. Like linezolid, tedizolid is available intravenously and orally allowing IV-to-PO conversion without needing a change of antibiotic.[1] Tedizolid was granted an FDA-approved indication for treatment of ABSSSI caused by susceptible bacteria on June 20, 2014.[5] The purpose of this article is to review the pharmacology, spectrum of activity, pharmacokinetics, drug-drug interactions, clinical trials and efficacy of tedizolid.

Pharmacology

Mechanism of Action

Tedizolid inhibits protein synthesis in the ribosome by binding to the peptidyl transferase center (PTC) of the 50S ribosomal subunit and inhibiting the initiation phase of translation.[6] Tedizolid exhibits higher potency than linezolid by having additional interactions with bacterial ribosomes as a consequence of the pyridine (C-ring) and tetrazole (D-ring) functional groups in tedizolid's molecular structure.[7] The **Figure** shows the additional D-ring in tedizolid's structure as well as the differences between the C and A rings. The higher potency of tedizolid results in a lower therapeutic dose and lower systemic exposure. Another unique characteristic of tedizolid's molecular structure is the hydroxymethyl functional group attached to the A-ring

of tedizolid. This group gives the molecule a smaller footprint, and therefore binding of tedizolid to the bacterial ribosome is not impacted by Cfr methylation.[7]

Spectrum of activity

The spectrum of activity is largely limited to Gram-positive organisms including methicillin-susceptible *Staph aureus* (MSSA) and MRSA, methicillin-susceptible and methicillin-resistant coagulase negative staphylococci, vancomycin-susceptible and vancomycin-resistant *Enterococcus faecalis*, penicillin-sensitive, penicillin-intermediate, and penicillin-resistant *Strep. pneumonia*.[1] The bacterial susceptibility to tedizolid was assessed using standard disk diffusion susceptibility testing methods and minimum inhibitory concentration (MIC).[1] The MIC is the lowest concentration of the antimicrobial being tested in which it inhibits the visible growth of bacteria after overnight incubation.[8] The disk diffusion susceptibility testing methods are subject to established Clinical and Laboratory Standards Institute (CLSI) quality control ranges for the reference strains.[1] **Table 1** shows the weighted average MIC values of tedizolid and linezolid calculated from multiple pre-clinical studies in *S. aureus* strains. The MIC_{90} for linezolid is 4- to 5-fold higher than the MIC_{90} of tedizolid, which means that tedizolid inhibits the growth of MSSA and MRSA at a much lower concentration *in vitro* than linezolid. The proposed tedizolid MIC breakpoints for *S. aureus* strains are ≤2 µg/mL for susceptible strains, 4 µg/mL for intermediate strains, and ≥8 µg/mL for resistant strains; however, no official breakpoints have been defined at the time of this writing. The linezolid breakpoint is ≤4 µg/mL for susceptible strains.[17]

Pharmacokinetics

Pharmacokinetic studies of tedizolid show an oral bioavailability of 90%, suggesting the same dose may be appropriate for both oral and IV administration.[9] In these studies, tedizolid showed linear kinetics with respect to mean plasma tedizolid concentration versus time among multiple doses (200 mg, 400 mg, 600 mg, 800 mg, and 1200 mg). Tedizolid is rapidly distributed into tissues, with a mean apparent volume of distribution at steady-state of approximately 108 to 117 L. Tedizolid demonstrated moderate protein binding in human plasma in the range of 86.1% to 91.9%.[11]

Studies have shown that tedizolid penetrates into interstitial space fluids of subcutaneous adipose and skeletal muscle tissue.[9] Tedizolid has also been shown to concentrate highly in pulmonary epithelial lining and alveolar macrophages by approximately 41-fold and 20-fold relative to free plasma concentrations.[11] These data suggest that tedizolid may be effective in the treatment of lung infections.

The primary elimination pathway of tedizolid is sulfation.[9] After the administration of oral tedizolid, about 80% of the dose is excreted as the sulfate conjugate of tedizolid, <3% of the conjugate is recovered in the feces, ~18% of the conjugate is recovered in urine, and <3% unchanged tedizolid is excreted in feces.[1] Thus, most of the elimination of tedizolid occurs in the liver.

The mean half-life of tedizolid is about 11.2 hours following a single 200 mg dose.[9] Tedizolid phosphate is a prodrug that is rapidly converted by phosphatases to tedizolid, the active form of the drug.[12] **Table 2** shows the mean pharmacokinetic parameters following the administration of 200 mg of tedizolid as a single dose or multiple doses in oral and intravenous dosage form. These data demonstrates that the same dose of tedizolid can be given either oral or IV.

Pharmacokinetic population analyses of orally or IV administered tedizolid shows that in adolescents, the elderly, and subjects with advanced renal or moderate to severe hepatic impairment, small changes in volume of distribution and individual variability in clearance were observed.[1] Hemodialysis has no significant impact on the pharmacokinetics of tedizolid. Studies have not found any significant differences in pharmacokinetic parameters between sexes, races, patients with decline in renal or hepatic function, and patients with the presence of comorbidities. Therefore, no dosage adjustments are necessary for these populations. Women who were pregnant or lactating were excluded from the studies.

Drug-Drug Interactions

In vitro studies revealed no inhibition or induction of drug metabolizing enzymes with tedizolid phosphate and the active metabolite, tedizolid.[13] Tedizolid and linezolid reversibly inhibit MAO enzymes (MAO_A and MAO_B), which has the potential to increase the concentrations of circulating neurotransmitters. However, in phase I double-blind crossover clinical studies, tedizolid did not demonstrate any effect with MAO enzymes unlike linezolid.[13] Furthermore, in phase I clinical studies, tedizolid did not potentiate a rise in blood pressure associated with pseudoephedrine and tyramine.[13,14]

Clinical Trials

The major phase 2 study consisted of a randomized, double-blind, uncontrolled, dose-ranging study, comparing 200 mg, 300 mg, and 400 mg of tedizolid administered once daily for 5 to 7 days, and conducted at 12 sites in the United States.[15] Patients were eligible if they were adult (18-75 years) men or women receiving inpatient or outpatient care with a diagnosis of complicated skin and soft structure in-

Table 1 | Weighted average of MIC values for tedizolid and linezolid for MSSA and MRSA.[18]

Organism	Total No. Studies	N	Tedizolid MIC_{50}	Tedizolid MIC_{90}	Linezolid MIC_{50}	Linezolid MIC_{90}	Ratio MIC_{-90} Linezolid/Tedizolid
MSSA	6	1389	0.28	0.46	1.90	2.19	4.76
MRSA	10	1588	0.33	0.52	2.00	2.72	5.23

MIC_{50}-minimum inhibitory concentration against 50% of the isolates; MIC_{90}-minimum inhibitory concentration against 90% of the isolates; MSSA-methicillin-susceptible *S. aureus*; MRSA-methicillin- resistant *S. aureus*.

Table 2 | Selected pharmacokinetic parameters following single and multiple doses of 200 mg tedizolid in healthy individuals.[18]

	Oral		Intravenous	
Parameter	**Single Dose**	**Steady State**	**Single Dose**	**Steady State**
AUC[a] (μg·h/mL)	23.8 (6.8)	25.6 (8.4)	26.6 (5.2)	29.2 (6.2)
C_{max} (μg/mL)	2.0 (0.66)	2.2 (0.64)	2.3 (0.64)	3.0 (0.66)
C_{min} (μg/mL)	N/A	0.44 (0.19)	N/A	0.36 (0.09)
t_{max}[b] (h)	2.5 (1-8)	3.5 (1-6)	1.1 (0.9-1.5)	1.2 (0.9-1.5)
Clearance (L/h)	6.9 (1.7)	8.4 (2.1)	4.6 (1.2)	5.9 (1.4)

Data represent mean (SD) except where otherwise noted.
[a]AUC is $AUC_{0-\infty}$ for single administration and AUC_{0-24} for multiple administrations.
[b]Data are median (range).
C_{max} = maximum plasma concentration; **C_{min}** = minimum plasma concentration; **t_{max}** = time to maximum plasma concentration.

fection (cSSSI) caused by a suspected or confirmed Gram-positive pathogen. These infections consisted of abscesses (with ≥2 cm of surrounding induration or requiring incision and drainage), surgical or post-traumatic wounds, and deep, extensive cellulitis. The exclusion criteria were presence of diabetic foot infection, gangrene, necrotizing infection, ischemic ulcer, burn, perirectal abscess, infection at a central catheter site or metastatic infection. Patients were also excluded if they had the following lab values/conditions: estimated creatinine clearance of <52 mL/min; hepatic disease with aspartate transaminase (AST) or alanine aminontransferase (ALT) >3 times the upper limit of normal (ULN); bilirubin >1.5 times the ULN; alkaline phosphatase >3 times the ULN; HIV positive status with a CD4 count <200 cells/mL; neutropenia with absolute neutrophil count <1000 cells/mL, Bazett-corrected QT interval >450 ms in males or 470 ms in females; or, BMI >35 kg/m^2.

Of the 192 enrolled patients between September 2008 and January of 2009, 188 received at least one dose of the tedizolid (n=63 in the 200 mg group; n=63 in the 300 mg group; n=62 in the 400 mg group).[15] Some of the relevant comorbid conditions in this patient population were diabetes mellitus (17.4%), prior skin infections at the same location of current infection (13.8%), hepatitis B positive (1.4%), hepatitis C positive (18.4%), failed prior cSSSI therapy (9%). Most common sites of the infections were in the limbs (52.6%), trunk (22.9%) and head/neck (11.7%). *Staphylococcus aureus* was the most common pathogen isolated, present in 90.3% of the patients; about 80.6% of these strains were MRSA. The clinical cure rate was similar across all dose groups. The clinical cure rate in patients with MRSA isolated at baseline was 96.8%.[15] All doses were generally well-tolerated, and as a result of this study, the 200 mg dose of tedizolid was selected as the lowest effective dose for further studies in ABSSSI.[1]

The phase 3 clinical trial, ESTABLISH-2, was a randomized, double-blind, multi-national, parallel-group non-inferiority trial, enrolling patients between September 2011 and January 2013, and involving 58 centers in nine countries (Argentina, Australia, Germany, New Zealand, Poland, Russia, South Africa, Spain and the U.S.).[16] The enrolled patients were ≥12 years of age, with ABSSSIs, consisting of cellulitis, erysipelas, major cutaneous abscess, or wound infection, with a ≥75 cm^2 minimum lesion area and with suspected or confirmed Gram positive pathogen. Patients also needed to have at least one systemic or regional sign of infection, such as lymphadenopathy, increase in body temperature, WBC ≥10,000 or <4,000 per μL, or >10% immature neutrophils. Excluded patients were those who had received antibiotics with Gram-positive activity in the last 96 hours or had failed antibiotic treatment for the primary site of ABSSSI; infections associated with prosthetic devices, vascular catheter sites, thrombophlebitis, diabetic foot infections, infected burns, chronic skin ulcers, septic-shock or severe sepsis; history of opportunistic infections with the underlying cause still active; receiving chronic immunosuppressive treatment or antipyretics drugs (other than aspirin <200 mg/day); or severe renal or hepatic disease.

Patients were randomly assigned in a 1:1 ratio to receive intravenous tedizolid 200 mg once daily for 6 days (n=332) or intravenous linezolid 600 mg twice daily for 10 days (n=334), with an option to orally step-down.[16] Randomization was stratified by geographic region and type of bacterial skin infection. Patients, investigators, and staff participating in patient care or clinical evaluations, and study sponsor, were masked to treatment assignment. A double-dummy design with placebo unique to each active treatment was used to maintain the blind. The primary endpoint was early clinical response 48 to 72 hours after the start of the treatment. Patients were classed as responders if they had a 20% or greater reduction in area of the primary lesion from the baseline; did not receive any systemic concomitant antibiotics with Gram-positive activity; and did not die from any cause within 72 hours of the first dose. Secondary endpoints chosen were response at day 7, end-of-treatment assessment, post-therapy assessment (7-14 days after end of treatment), and changes in patient-reported pain at predetermined time points throughout the study.

In the primary analysis, in which persons with missing data were considered non-responders, 283 of 332 (85%) tedizolid-treated patients achieved early clinical response, compared with 276 of 334 (83%) linezolid-treated patients.[16] These clinical response rates are based on objective assessments incorporating changes in lesion area at the 48-72 hours endpoint. **Table 3** summarizes the investigator-assessed clinical success rates for both treatments. These results show that tedizolid 200 mg given once daily is non-inferior to linezolid 600 mg given twice a day.

Table 3 | Investigator-assessed clinical success rates in phase 3 studies.[16]

Clinical Success	Tedizolid (N=332)	Linezolid (N=334)	Difference (95% CI)
48-72 hours[a]	304 (92%)	302 (90%)	1.2% (-3.3 to 5.6)
Day 7[a]	309 (93%)	308 (92%)	0.9% (-3.2 to 4.9
Day 11 (end of treatment)[b]	304 (92%)	301 (90%)	1.4% (-3.0 to 5.9)
Day 7 to 14 (post-therapy assessment)[b]	292 (88%)	293 (88%)	0.3% (-4.8 to 5.3)

[a]Clinical success defined as overall improvement of clinical status of ABSSSI compatible with study.
[b]Clinical success defined as resolution or near resolution of disease-specific signs and symptoms, absence or near resolution of baseline systemic signs and infections, no further antimicrobial treatment required.

Adverse Events

The most common adverse events that occurred in patients taking tedizolid and linezolid during the phase 3 clinical trials were headache, nausea, vomiting and diarrhea. The most common adverse events that lead to the discontinuation of both treatments were gastrointestinal disorders. **Table 4** shows the frequency of each adverse event for tedizolid and linezolid groups.

Summary

Antimicrobial-resistant infections continue to be a clinical and economic burden in the US. Hence, the need for new antimicrobial agents with activity against these pathogens is substantial. Tedizolid is a new oxazolidinone antimicrobial expected to be granted an approved indication by the FDA for the treatment of ABSSSI. Compared with current agents, this agent has enhanced potency, low adverse event rates, low probability for drug interactions, and little myelosuppresion.[14] Phase 2 and 3 clinical trials demonstrated that this treatment is well-tolerated and efficacious across several patient populations.[15,16] With its recent approval, tedizolid represents a new and effective alternative to current treatments for ABSSSIs caused by Gram-positive bacteria, especially MRSA-related infections.

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Table 4 | Adverse events of tedizolid phosphate and linezolid in phase 3 studies.[1,16]

Adverse Events	Tedizolid 200 mg once daily (N=331)	Linezolid 600 mg twice daily (N=327)
GI disorders	53 (16)	67 (20.5)
Headache	20 (6)	22 (7)
Nausea	26 (8)	36 (11)
Diarrhea	11 (3)	17 (5)
Vomiting	10 (3.0)	17 (5)

Data represent n (%).

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Coming Soon—Personalized Medicine Corner

Did you know that nearly 25% of outpatients are taking a drug that includes pharmacogenomic information in the FDA label?[1] Beginning in October, a new recurring *PharmaNote* column will answer questions and provide tips about how to use these and other personalized medicine data to optimize drug therapy. The *Personalized Medicine Corner* will appear quarterly and will be provided by the UF Health Personalized Medicine Program. To find out more or submit a question, email Miguel Ramos, PharmD, at mramos@cop.ufl.edu.

1. Frueh FW et al. Pharmacotherapy. 2008;28:992.

Hydrocodone Becoming Schedule II Federally Controlled Substance

If you are currently registered with the Drug Enforcement Administration (DEA) please take a few minutes to note an important regulatory change it has made.

On Friday, August 22, 2014, the DEA published in the Federal Register a final rule (21 CFR Part 1308; Docket No. DEA-389) to transfer hydrocodone combination products (HCPs) from schedule III to schedule II. HCPs have been controlled in schedule III since enactment of the Controlled Substances Act in 1971. HCPs are the most frequently prescribed opioid in the United States: nearly 137 million prescriptions for HCPs were dispensed in 2013.

This final rule will go into effect on **October 6, 2014**, **wherein HCPs will be controlled as schedule II substances under the Controlled Substances Act**. The DEA is permitting **legitimate HCP prescriptions issued before October 6, 2014 to be refilled until April 8, 2015**, if the prescription authorizes refills.

For more information, please visit the DEA website at www.deadiversion.usdoj.gov.

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