Tedizolid Population Pharmacokinetics, Exposure-Response, and Target Attainment

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BACKGROUND
Tedizolid is a novel antibiotic prodrg rapidly converted by hepatic enzymes to its active moiety tedizolid after administration. Tedizolid is a 4-fold more potent in vitro than linezolid against Gram-positive pathogens, including methicillin-resistant Staphylococcus aureus and strains resistant to linezolid or vancomycin1,2 and is rapidly bactericidal in vivo.3 Tedizolid is administered once daily (orally or IV at identical dosage).

In clinical studies, tedizolid has demonstrated a favorable pharmacokinetic (PK) profile in healthy volunteers, including a long half-life, minimal accumulation over time, and high bioavailability (>80%), and low interpatient variability in drug exposure levels.4

○ Once daily dosing regimens of 200, 300, or 400 mg resulted in similar PK efficacy outcomes in a Phase 3 study.5

○ In two recent Phase 3 trials, 4-6 daily doses of tedizolid phosphate 200 mg once daily were demonstrated as noninferior efficacy to a 10-day course of linezolid (600 mg twice/day for the treatment of acute bacterial skin and soft tissue infections [ABSSSIT]) with improved gastrointestinal tolerability and a reduced potential for hematologic toxicity.6,7

A population pharmacokinetic model was developed to evaluate the impact of covariates on oral safety, factors influencing PK and PK/pharmacodynamic (PD)/PK variability, and the probability of attaining the tedizolid PK target measure.

METHODS

○ Data were obtained from four densely sampled Phase 1 studies (PK data), one sparsely sampled Phase 1 study (PK and safety data), and two sparsely sampled Phase 3 studies (PK, safety, and efficacy data).

○ The following prospectively collected efficacy outcomes were utilized in the PK/PD analysis: early clinical response (with ≥20% decrease in lesion area) at the 48-72 h visit; clinical response [investigator assessed at the posttherapy evaluation (PET): 7-14 days after end-of-therapy]; and microbiological response at end-of-therapy and the PET. The PK/PD analysis was performed using NONMEM software.8

○ The following safety outcomes were utilized in the PK/PD analysis: treatment-emergent adverse events (TEAEs); TE gastrointestinal AE; changes in absolute neutrophil counts and in platelet counts.

○ The final PK model was based on data from the six clinical studies and included ideal bodyweight (BW) and total bilirubin as statistically significant covariates.

○ The model was used to generate empiric Bayesian estimates of AUC24h/MIC ratio, minimum observed drug concentration (Cmin), and maximum observed drug concentration (Cmax) at Day 1 and steady-state daily.

○ Logistic regression analysis was used to examine the effects of drug exposure on each of the efficacy and safety endpoints. The inference of covariates was to be evaluated only if an exposure-response relationship was identified.

○ The probability of attaining the PK/PD target measure (Day 1AUC24h/MIC ratio) associated with tedizolid efficacy was estimated from 100,000 simulated patients (100 trials of 1000 virtual patients each).

○ The MIC susceptibility breakpoint was defined as the highest clinically relevant MIC value with a 90% probability of PK/PD target attainment.

RESULTS

Table 1. Parameter Estimates From the Final Population Pharmacokinetic Model for Tedizolid

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical Value</th>
<th>% SEM</th>
<th>Min/Mean/Max</th>
<th>% SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>38.0</td>
<td>42</td>
<td>194.4 CV</td>
<td>11.0</td>
</tr>
<tr>
<td>CLR</td>
<td>14.0</td>
<td>0.5</td>
<td>3.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Power for the effect of BV on CLR</td>
<td>1.0</td>
<td>0.5</td>
<td>3.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Power for the effect of BV on Vc</td>
<td>2.0</td>
<td>0.5</td>
<td>3.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Vc</td>
<td>7.0</td>
<td>0.5</td>
<td>3.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Vp</td>
<td>1.0</td>
<td>0.5</td>
<td>3.9</td>
<td>2.8</td>
</tr>
<tr>
<td>F</td>
<td>0.85</td>
<td>0.2</td>
<td>3.9</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Figure 1. MIC Frequency Distribution (Bars) and Probability of PK/PD Target attainment for Tedizolid Phosphate at the AUC24h/MIC Ratio Breakpoints of 10 and 15

○ A 2-compartment model with sigmoidal absorption, absolute bioavailability, and log-linear disposition to its active moiety tedizolid was described. The data variability was low, with a 31% and 13.4% coefficient of variation for clearance and volume, respectively. Absolute bioavailability was high (80%).

○ Population parameter estimates for the final PK model are shown in Table 1.

○ No clinically relevant covariate effects on tedizolid PK were found (Table 2).

○ Exposure-response analyses based on data from the Phase 3 studies using 200 mg once/day showed no relationship between exposure and clinical or microbiologic response, representing the flat portion of the exposure-response relationship.

○ Safety analyses, including patients receiving up to 400 mg per day, showed a modest increase in the probability of experiencing an AE with increasing exposure. No such relationship was observed with the standard 200 mg dose that was evaluated in Phase 3 trials.

○ There were no trends in the plots of minimum or maximum decrease in neutrophil counts or platelet counts versus tedizolid exposure at 24-h monitoring time points, or steady-state exposure in Phase 3 trials.

○ The target attainment simulation indicated a high probability of attaining the PK/PD target mean (AUC24h/MIC ratio of 1.5 with a typical value of 0.85) with a susceptibility breakpoint of 0.5 µg/mL for 200 mg tedizolid phosphate (Figure 1). There was no apparent drop in microbial efficacy across a wide range of AUC/MIC ratios observed in the Phase 3 trials.

○ There was no relationship between tedizolid exposure and efficacy as all evaluated doses demonstrated similar efficacy results.

○ At 200 mg once/day, tedizolid phosphate did not appear to result in exposures associated with increased AEs, while slight increases in AEs (but not in hematologic changes) were seen with exposures resulting from higher doses.

○ The 200 mg dose had a high probability of attaining the PK/PD target mean (AUC24h/MIC ratio of 1.5) with a susceptibility breakpoint of 0.5 µg/mL.

○ No covariates exerted any clinically significant effect on tedizolid PK, suggesting that the 200 mg dose does not need to be adjusted for any patient subpopulation.

CONCLUSIONS

○ This population PK model supports the selection of 200 mg tedizolid phosphate once/day as the optimum dose for the treatment of Gram-positive infections.

○ There was no relationship between tedizolid exposure and efficacy as all evaluated doses demonstrated similar efficacy results.

REFERENCES


ACKNOWLEDGMENTS

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Figure 1. MIC Frequency Distribution (Bars) and Probability of PK/PD Target attainment for Tedizolid Phosphate at the AUC24h/MIC Ratio Breakpoints of 10 and 15 (Line)