

3) Tedizolid is a novel next generation oxazolidinone for the treatment of moderate and serious MRSA infections.

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Tedizolid (TZD) is a novel oxazolidinone with potency and clinical efficacy against MRSA infections. TZD is currently undergoing clinical development for the treatment of acute bacterial skin and skin structure infections (ABSSSI, also known as complicated skin and skin structure infections, cSSSI), hospital associated pneumonia (HAP) including ventilator associated pneumonia (VAP), and bacteremia. TZD is dosed at 200 mg once daily by IV or oral route.

TZD has a number of strong features for the treatment of MRSA and advantages over linezolid (LZD) the first generation oxazolidinone:

- TZD has a MIC₉₀ against MRSA of 0.5 mg/L, compared to 2 to 4 mg/L for LZD
- TZD retains activity against the cfr plasmid-mediated LZD resistant MRSA (MIC 0.5 mg/L compared to 16 mg/L for LZD)
- TZD is bactericidal in vivo while LZD is bacteriostatic
- TZD has a lower frequency of resistance and accumulates in phagocytes at higher concentrations than LZD
- TZD has less interaction with tyramine than LZD, leading to fewer drug-drug interactions
- TZD has more predictable Pharmacokinetics and less variability than LZD
- TZD showed less potential for myelosuppression than LZD in a phase 1 study
- TZD has a shorter course of therapy (6-7 days for ABSSSI and HAP/VAP respectively) compared to linezolid (10-14 days for ABSSSI and HAP/VAP)
- TZD is dosed once daily, while LZD is dosed twice daily

In a phase II trial for treatment of ABSSSI, TZD at 200, 300, and 400 mg once daily for 5-7 days showed $\geq 96\%$ clinical response with the majority of patients diagnosed with MRSA infection. In a phase III trial for treatment of ABSSSI, TZD 200 mg QD administered for 6 days, compared to LZD 600 mg BID administered for 10 days, met the non-inferiority margin with a 79.5% clinical response rate compared to a clinical response rate of 79.4% for LZD. This clinical response rate was based on the new FDA guidance for study of ABSSSI and was based on cessation of lesion spread and absence of fever. Clinical efficacy was consistent across subgroups and against patients infected with MRSA and non-MRSA pathogens. Patients in the TZD group had statistically fewer ($p=0.004$) gastrointestinal adverse events patients in the LZD group. TZD was well tolerated overall, and statistically fewer ($p = 0.038$) TZD patients yielded low platelets counts (below the lower limit of normal) compared to LZD patients. Low platelet counts are a biomarker for possible early myelosuppression.

TZD is under study in a second global phase III trials for ABSSSI, and an additional global phase III study in HAP and VAP is expected to start in 2013. In Japan, TZD will be studied in cSSSI, HAP, and bacteremia. The efficacy, safety, and biological characteristics of tedizolid are promising and suggest that this drug will have broad utility in the treatment of MRSA infections.