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Tmax evaluation in the bioequivalence studies of generic modified release proton pump inhibitors

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Abstract

Purpose. In bioequivalence (BE) studies submitted to Abbreviated New Drug Applications (ANDAs), AUCt, AUCinf and Cmax are compared statistically to determine whether two products are bioequivalent. The FDA also qualitatively evaluates Tmax, to determine if any pronounced differences between test (T) and reference (R) are clinically significant. The purpose of this study was to use pharmacokinetic (PK), pharmacodynamic (PD), safety, simulated steady state, and clinical evaluation to determine whether differences in T and R Tmax values would affect therapeutic equivalence for modified-release proton pump inhibitors (PPIs).

Methods. We retrospectively collected Tmax data from 48 ANDAs containing total 113 BE studies including fasting, fed, and sprinkled BE studies for five modified-release PPI drug products. The Tmax T/R ratio distribution for each study was analyzed. For studies for which test and reference Tmax values appeared to be notably different, we performed simulations to predict steady-state PK profiles using nonparametric superposition. Additionally, we also conducted pair-wise statistical comparisons of the BE study adverse events (AEs) between the T and R products. We related the PK profiles in the BE studies to the known PK/PD relationships for PPIs. Finally, the clinical impact of the most pronounced Tmax differences on therapeutic equivalence was evaluated by FDA medical officers with expertise in treating GI disease.

Results. All studies met BE acceptance limits for AUC and Cmax. The distribution of the median Tmax T/R ratios from the 113 studies suggested that, in approximate 10% of studies, there was a possible pronounced difference in T and R Tmax values, primarily in the fasting studies. Simulation results indicated that differences in median R and T Tmax values were diminished at steady state. The distribution profile of adverse events for the test product was similar to that of the reference product. Finally, the clinical evaluation assessed PPI PK/PD and concluded that even the most pronounced Tmax differences were not expected to have an impact on safety and efficacy.

Conclusion. Our data analysis, PK/PD relationships, and clinical evaluation indicated that any Tmax differences between T and R in BE studies submitted from in-house applications for generic modified-release PPI drug products were unlikely to impact therapeutic equivalence