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T_{max} evaluation in the bioequivalence studies of generic modified release proton pump inhibitors

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Purpose: In bioequivalence (BE) studies submitted to Abbreviated New Drug Applications (ANDAs), AUCt, AUCinf and C_{max} are compared statistically to determine whether two products are bioequivalent. The FDA also qualitatively evaluates T_{max}, 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 T_{max} values would affect therapeutic equivalence for modified-release proton pump inhibitors (PPIs).

Methods: We retrospectively collected T_{max} data from 48 ANDAs containing total 113 BE studies including fasting, fed, and sprinkled BE studies for five modified-release PPI drug products. The T_{max} T/R ratio distribution for each study was analyzed. For studies for which test and reference T_{max} 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 T_{max} 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 C_{max}. The distribution of the median T_{max} T/R ratios from the 113 studies suggested that, in approximate 10% of studies, there was a possible pronounced difference in T and R T_{max} values, primarily in the fasting studies. Simulation results indicated that differences in median R and T T_{max} 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 T_{max} 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 T_{max} 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

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