Notes on the Design of Bioequivalence Study: Emtricitabine/Tenofovir Alafenamide

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Unit – Medicines Assessment Team (PQT/MED) are issued to aid manufacturers with the development of their product dossier. Deviations from the approach suggested below may be considered acceptable if justified by sound scientific evidence.

The current notes should be read and followed in line with the general guidelines on submission of documentation for WHO prequalification. In particular, please consult the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability" in: *Fifty-seventh report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations,* Geneva, World Health Organization, 2024. WHO Technical Report Series, No. 1052, Annex 8.

Below, additional specific guidance is provided on the invited immediate release products containing emtricitabine and tenofovir alafenamide (TAF).

Pharmacokinetics of emtricitabine and tenofovir alafenamide

Maximum emtricitabine plasma concentrations are observed within 0.5 to 3.0 hours of dosing in the fed state. TAF peak plasma concentrations are observed after about 1 hour after dosing in fed state.

The elimination half-lives of emtricitabine and TAF are 10 and 0.51 hours, respectively, following single doses.

Administration of emtricitabine with a high-fat meal does not affect systemic exposure ($AUC_{0\text{-}inf}$) of emtricitabine; therefore, emtricitabine may be administered with or without food.

Administration of TAF with a high-fat meal increased the systemic exposure of tenofovir alafenamide by 65%; therefore, TAF should be administered with food.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of emtricitabine and TAF, the following guidance with regard to the study design should be taken into account:

Design: A single-dose cross-over study is recommended.

Dose: The EoI includes emtricitabine/TAF 200mg/25mg and 200mg/10mg strengths. A single oral dose of one tablet of emtricitabine/tenofovir alafenamide 200/25mg should be employed in the BE study for this product. Similarly, a single oral dose of one tablet of emtricitabine/tenofovir alafenamide 200/10mg should be employed in the BE study for this product.

Fasted/fed: The bioequivalence study should be conducted in the fed state, as TAF should be taken with food, and emtricitabine can be taken with or without food.

Subjects: Healthy adult subjects should be recruited. It is not necessary to include patients in the bioequivalence study.

Parent or metabolite data for assessment of bioequivalence: The parent drug is considered to best reflect the biopharmaceutical quality of the product. The data for the parent compound should be used to assess bioequivalence of emtricitabine and TAF.

Sample size: Information currently available to PQT/MED indicates that the intra-subject variability for emtricitabine is around 20-25%, while the intra-subject variability for TAF C_{max} is reported to be approximately 36%. These data may facilitate the calculation of a sufficient sample size for the bioequivalence study.

Washout: Taking into account the elimination half-life of emtricitabine (10 hours) and TAF (0.51 hours) in healthy volunteers, a washout period of seven days is considered sufficient to prevent carry-over.

Blood sampling: The blood sampling should be intensive for the first three hours after administration to properly characterize the C_{max} of emtricitabine and TAF. For example, blood samples might be taken at pre-dose, 0,083, 0.17, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 24.00, 36.00, and 48.00 h after drug administration.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure emtricitabine and TAF in human plasma using LC-MS/MS analytical methodology. The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of the C_{max} in most profiles of each formulation (test or comparator). The bioanalytical method for each analyte should be validated in the presence of the other analyte (see ICH Harmonised Guideline M10 for more information).

Statistical considerations: The data for emtricitabine and TAF should meet the following bioequivalence standards in a single-dose crossover design study:

- The 90% confidence interval of the relative mean AUC_{0-t} of the test to reference product should be within 80.00–125.00%
- The 90% confidence interval of the relative mean C_{max} of the test to reference product should be within 80.00–125.00%.