Notes on the Design of Bioequivalence Study: Tenofovir

Notes on the design of bioequivalence studies with products invited to be submitted to the WHO Prequalification Team: medicines (PQTm) are issued to aid manufacturers with the development of their product dossier. Deviations from the approach suggested below can be considered acceptable if justified by sound scientific evidence.


Below, additional specific guidance is provided on the invited immediate release products containing tenofovir disoproxil fumarate.

**Pharmacokinetics of tenofovir**

Following oral administration of tenofovir disoproxil fumarate, tenofovir peak plasma concentrations are typically reached within one hour post-dose in the fasted state and within two hours post-following a standardized high fat meal. Relative to fasting conditions, the administration of a single dose of tenofovir with a standardized high-fat meal increases the tenofovir $C_{\text{max}}$ by 14% and the AUC by 40%. For this reason, tenofovir is can be administered without regard to food (according to the FDA label) or with a meal (according to the EU SmPC). Tenofovir displays linear pharmacokinetics. Tenofovir is excreted in urine predominantly unchanged. The mean terminal half-life of tenofovir is 12–18 hours.

**Guidance for the design of bioequivalence studies**

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

**Dose:** Tenofovir disoproxil fumarate is marketed in the strengths of 150 mg, 200 mg, 250 mg and 300 mg. The bioequivalence study should be conducted with the highest strength proposed in the application e.g., the 300 mg tablet strength. An additional strength biowaiver for the 150 mg, 200 mg and 250 mg strengths can be requested. Refer to Annex 7, TRS 992 for the requirements regarding this approach. A decision on the acceptability of the dose-strength biowaiver request, however, can only be made upon review of the data submitted in the application.

**Fasting/fed:** The bioequivalence study should be conducted in the fasted state.

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

**Analytical considerations:** Tenofovir should be the basis for the bioequivalence assessment. Assay sensitivity for tenofovir (limit of quantitation) is currently 5–10 ng/ml.
**Sample size:** Tenofovir is not a highly variable drug. Values for intra-subject %CV are generally 15–20% for Cmax and 10–15% for AUC. These data may facilitate the calculation of a sufficient sample size for the bioequivalence study. Sample sizes are generally between 24 and 32.

**Washout:** Taking into account the elimination half-life of tenofovir in the fasted state of 12–18 hours, a washout period of seven days is considered sufficient to prevent carry over.

**Blood sampling:** The blood sampling should be intensive during the first 1 hours after administration to properly characterize the Cmax of tenofovir. Considering the elimination half-life, it is sufficient to take blood samples up to 72 hours after administration for the characterization of tenofovir pharmacokinetics.

**Parent or metabolite data for assessment of bioequivalence:** Tablets contain tenofovir disoproxil fumarate, which is the water soluble diester prodrug of the active ingredient tenofovir. Following absorption, the prodrug is rapidly converted to tenofovir. Therefore, bioequivalence should be based on the determination of tenofovir.

**Statistical considerations:** The data for tenofovir should meet the following bioequivalence standards in a single-dose, crossover design study:

- The 90% confidence interval of the relative mean AUC0-t of the test to reference product should be within 80.00–125.00%
- The 90% confidence interval of the relative mean Cmax of the test to reference product should be within 80.00–125.00%.

**Biowaiver:** The European Medicines Agency indicates that tenofovir disoproxil fumarate is a high solubility and low permeability compound (BCS Class III),\(^1\) therefore a BCS based biowaiver could be feasible as described in Annex 7, TRS 992.

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